VIDEOCONFERENCE MEETING

STATE OF CALIFORNIA

ENVIRONMENTAL PROTECTION AGENCY

OFFICE OF ENVIRONMENTAL HEALTH HAZARD ASSESSMENT

PROPOSITION 65

CARCINOGEN IDENTIFICATION COMMITTEE

GOTOWEBINAR PLATFORM

TUESDAY, NOVEMBER 17, 2020

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JAMES F. PETERS, CSR
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APPEARANCES

COMMITTEE MEMBERS:

Thomas M. Mack, MD, MPH, Chairperson

Jason Bush, PhD

Catherine Crespi, PhD

David A. Eastmond, PhD

Thomas McDonald, PhD, MPH

Michelle La Merrill, PhD

Joseph Landolph, PhD

Dana Loomis, PhD

Peggy Reynolds, PhD

Mariana Stern, PhD

Luoping Zhang, PhD

STAFF:

Dr. Lauren Zeise, Director

Ms. Carol Monahan Cummings, Chief Counsel

Mr. Julian Leichty, Proposition 65 Implementation Program

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

Dr. Meng Sun, Chief, Cancer Toxicology and Epidemiology Section, Reproductive and Cancer Hazard Assessment Branch

APPEARANCES CONTINUED

ALSO PRESENT:

Steve Hentges, American Chemistry Council

Tracy Heinzman, Methyl Bromide Industry Panel

Steve Risotto, American Chemistry Council

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PROCEEDINGS

DIRECTOR ZEISE: Good morning, everyone. I'd like to welcome you all to this November 2020 meeting of the Proposition 65 Carcinogen Identification Committee. I'm Lauren Zeise, Director of the Office of Environmental Health Hazard Assessment, also called OEHHA within the California Environmental Protection Agency. We really appreciate the Committee taking this valuable time to provide us advice and consultation today. We have one main item on the agenda and that's prioritizing seven chemicals for possible consideration by the Committee at a later meeting. So listing won't be done today, but we will -- the main item is around -- is prioritization.

So I also want to welcome the audience. Appreciate your participation in this Proposition 65 meeting. We're really glad we're able to hold this meeting during the COVID State of Emergency. We've engaged GoToWebinar specialist Clara Robinson of LogMeInInc to assist us in this meeting. And she's now going to give the audience some instructions on how to participate in this virtual meeting. And also, this meeting does have closed captioning and so Clara will also point out how to access the closed captioning as well.

So, Clara.

(Thereupon a slide presentation.)

MS. ROBINSON: Great. Thank you so much, Director Zeise. So I'm going to go ahead and go over a few items, so you know how to participate in today's meeting. For participants viewing the meeting through the webcast at http://video.calepa.ca.gov, if you would like to provide public comment you will need to join the webinar at https://bit.ly/meetcic. And I can post that into the chat link in a few minutes.

Participants joining the webinar will have the opportunity to provide public comment during today's meeting by clicking on the hand raise icon on the left tab of your GoToWebinar control panel, when the meeting Chair indicates that he is ready for public comment on that item. Each commenter will be limited to five minutes. A voluntary online speaker card can be found at https://bit.ly/oehhacic. And again, I will post that shortly into the chat functionality for you. So we invite you to click on that link, if you plan to make a public comment. This will help us to ensure that we have heard from everyone who intends to comment.

If you would like to present slides and have not previously sent them to OEHHA, please email them to p65public.comments@oehha.ca.gov now. We will show your slides when it is your turn to speak. Just tell us next slide to advance to the next slide.

If you have a question regarding logistics for example about getting a speaker card or presenting your slides, you may type your question into the questions pane of the control panel at any time during the meeting. Please be advised that this is to assist us with issues that may arise in the virtual meeting process, but is not a mechanism for providing public comment.

Closed captioning for this meeting can be accessed at https://bit.ly/ciccaptions. And again, I will post that into the chat functionality very shortly.

And now I'll turn the meeting back over to Director Zeise.

DIRECTOR ZEISE: Okay. Thank you, Clara. And again the meeting is being recorded and transcribed and the transcript will be posted on OEHHA's website. So before getting into the substance of the meeting, I'd like to introduce the Committee. And if you could just wave as I walk through different members.

So first Dr. Jason Bush, professor of cancer biology and Chair of the Department of Biology, California State University, Fresno.

And then Dr. Catherine Crespi, professor-in-residence of Biostatistics at the University of California, Los Angeles Fielding School of Public Health. Welcome to the Committee, Dr. Crespi. This is

Dr. Crespi's first meeting, so welcome.

Then there's Dr. David Eastmond, emeritus professor Cell biology in the University of California, Riverside, Department of Molecular, Cell and Systems Biology.

Then Dr. Michele La Merrill, associate professor in the University of California at Davis, Department of Environmental Toxicology.

Dr. Joseph Landolph, associate professor molecular microbiology and immunology at the University of Southern California, Keck School of Medicine.

Dr. Dana Loomis, professor of environmental health at the University of Nevada, Reno, School of Community Health Sciences. Welcome to the Committee. Dr. Loomis, this is also his first meeting.

And Dr. Thomas Mack, professor of preventive medicine at the University of Southern California, Keck School of Medicine. Dr. Tom McDonald, Research Fellow, Global Stewardship at the Clorox Corporation.

And Dr. Peggy Reynolds adjunct professor at the University of California, San Francisco, Helen Diller Comprehensive Cancer Center in the Department of Epidemiology and Biostatistics.

And Dr. Mariana Stern who's professor of clinical preventive medicine in urology and the Ira Goodman Chair

in Cancer Research at the University of Southern California Keck School of Medicine.

Dr. Luoping Zhang, adjunct professor of toxicology at the University of California, Berkeley School of Public Health.

So welcome, Committee. And again, we really appreciate you taking the time to provide your advice at this meeting.

I will note that Dr. Loomis will be chairing the meeting today on behalf of Dr. Mack.

Now, I'll introduce OEHHA's staff. And OEHHA staff, if you could just turn on and off your cameras as you're being introduced. So Allan Hirsch, Chief Deputy Director; Carol Monahan Cummings, our Chief Counsel; Sam Delson, Deputy Director for External and Legislative Affairs; Dr. Vince Cogliano, Deputy Director for Scientific Programs. This is also -- I think maybe for some of you Dr. Mack -- Dr. Cogliano -- this is Dr. Cogliano's first meeting. And he comes to OEHHA with a wealth of experience from U.S. EPA and the International Agency for Research on Cancer. And he is our Deputy Director for Scientific Programs. So welcome, Vince.

And then from the Reproductive and Cancer Hazard Assessment Branch, Dr. Martha Sandy, the Branch Chief. Dr. Meng Sun, she's our new Section Chief of the Cancer

Toxicology and Epidemiology Section. And from the Proposition 65 Implementation Program, Julian Leichty, Special Assistant for Programs and Legislation.

Now I'll ask Carol Monahan, our Chief Counsel, for some introductory remarks or this meeting.

Carol.

CHIEF COUNSEL MONAHAN CUMMINGS: Okay. Good morning. It's a little strange having you all look like Hollywood Squares up here, but we'll do our best to make this work.

The staff is only going to be showing cameras when they're speaking. So if you need to speak to one of us, then just say that and we'll go ahead and get on camera and unmute.

As you know, today's meeting concerns the prioritization of chemicals for future potential listing discussions. No chemical listings will be considered at the meeting today. Your discussion and recommendations concerning priority will be informed -- will inform OEHHA's decisions concerning potentially bringing a given chemical to this Committee for consideration at a future meeting.

Your advice is not binding on OEHHA, but is very helpful to us in planning for future meetings. Our scientific staff will explain the prioritization process

in more detail shortly. OEHHA takes no position regarding whether a chemical should be prioritized or what priority that may be, though our staff are available to answer questions or locate information if you need it.

The Governor appointed you because of your scientific expertise to be the State's qualified experts on the carcinogenicity of chemicals and there's no need for you to feel compelled to go outside that charge. This Committee can consider human, animal, mechanistic or other data when making a recommendation to OEHHA on priority. You can also consider exposure potential for a chemical, but you don't need to consider whether or not the current levels of exposure are sufficient to cause any harm. So what you're looking at is whether or not there's potential for exposure in California or the U.S.

Feel free to ask clarifying questions of me or any of the other staff during the meeting. If we don't know the answer to your question, we'll do our best to find and report it back to you. Please also remember that all discussions and deliberations need to be during the meeting, not during breaks, lunch or with individual members on or offline.

I also wanted to let you know that Mario Fernandez on my staff - he's a Senior Staff Counsel - may need to cover for me at some point during the meeting.

He's very qualified and can answer your questions and he can also reach me, if necessary.

I just want to remind you that you do need to mute when you're not talking. This is a public meeting and everyone can hear what you're saying.

So any questions?

No. Okay. Thank you.

DIRECTOR ZEISE: Okay. Thank you, Carol.

And now, I'll turn the meeting over to Dr. Dana Loomis today's meeting Chair.

COMMITTEE MEMBER LOOMIS: Thank you, Lauren. Good morning, everyone and thank you for joining us under these rather strange circumstances. I'm very happy that we can still meet virtually in spite of the current pandemic. As you heard earlier, this is my first meeting and so I'm -- not only have I not been to one of these meetings before, I haven't chaired one. So if I get things wrong, I will ask fellow members of the Committee or the staff to help me out.

I also point out that we do have a scheduled lunch break around noon. When the time comes, I'll announce that in between discussion of some of the items on the agenda. And we'll also try to take a short break about every hour for five or ten minutes.

So again, thanks everyone for joining us. As

you've heard before, we have one principal agenda item and that is the prioritization process where we, the Committee, are asked to advise OEHHA on the priority of seven chemicals for future consideration for listing.

And so we'll turn to that agenda item in just a moment. But before we do that, I'll ask Dr. Martha Sandy for -- to open the presentation of the process by the staff.

DR. SANDY: Thank you, Dr. Loomis. And welcome CIC members. Usually for prioritization, I'm the one that gives a background presentation on the prioritization process, but I'm pleased to tell you that today I'm going to ask Dr. Meng Sun, who is the new Section Chief of the Cancer Toxicology and Epidemiology Section to give that presentation. So I'll turn it over to Dr. Sun.

DR. SUN: Thank you, Dr. Sandy. Good morning. Clara, could you show my slides, please?

(Thereupon a slide presentation.)

DR. SUN: Thank you.

So the main item that we're going to discuss today is the prioritization of chemicals for possible future CIC review and listing consideration under Proposition 65.

As several of our CIC members have joined the Committee after 2016, which was the most recent year we

brought chemicals for prioritization ranking, I'm going to give a brief overview of this prioritization process.

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DR. SUN: The purpose of the prioritization process is to identify chemicals for evaluation of cancer hazard by the CIC. Specifically, we track chemicals that we think have some evidence of carcinogenicity and we then prioritize among this large group of chemicals. The goal is to identify chemicals that the CIC should evaluate. We want to focus your attention on chemicals that are relevant for Californians. So we look at chemicals that we think have apparent exposure in California and then we look at chemicals with the most information that suggests that they might be carcinogenic.

I want to emphasize that prioritization is a preliminary appraisal of the evidence of hazard. It is not a thorough comprehensive review, like we do when we write the hazard identification document. The prioritization process is meant to be a quick screen of readily available data relevant to carcinogenicity for a large number, hundreds, of chemicals.

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DR. SUN: Here is a schematic of the

prioritization process we follow, based on the top portion of figure one in OEHHA's 2004 prioritization process document, which has been provided to you as part of this meeting's materials. Let me walk you through this slide.

We maintain a chemical tracking database shown at the top of this slide and among the chemicals that are tracked, we identify those that have apparent exposure in California and some evidence suggestive of carcinogenicity.

This subset of tracked chemicals are called candidate chemicals. We apply a focused data screen to those candidate chemicals. By that, I mean that we conduct focused literature reviews to identify chemicals that report positive findings in cancer epidemiological studies in humans and thus pass our human data screen and to identify chemicals that have certain types of positive tumor findings in studies in animals, and thus pass our animal data screen.

Chemicals that pass either one or both of these data screens continue further in the prioritization process. They're subjected to a preliminary toxicological evaluation of the overall evidence of carcinogenicity, taking into account additional information such as studies on key characteristics of carcinogens, metabolism and pharmacokinetics.

Chemicals for which this preliminary evaluation indicates carcinogenicity may be a concern are proposed to you for consideration. And we consult with you in a meeting like we're doing today.

After the meeting, we will consider your advice and OEHHA will select chemicals for preparation of hazard identification documents.

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DR. SUN: Here is a recap of our past and present prioritization efforts. Between 2009 and 2011, we applied the human and animal data screens to more than 380 chemicals. For chemicals that pass either one of those data screens, we looked at the overall evidence by conducting a preliminary toxicological evaluation and identified those with the most compelling Evidence to bring to the CIC for consultation.

Over the course of those three years, we brought 104 chemicals to this Committee asking the Committee to rank each chemical in terms of priority as either high, medium, low or no priority. On an ongoing basis, we continue to look for new information on tracked chemicals and on those identified as candidate chemicals by conducting updated literature searches. And as new chemicals are added to our tracking database, we screen

them for exposure in California and evidence suggestive of carcinogenicity.

For all chemicals newly identified as candidate chemicals, we applied the human and animal data screens. Also on an ongoing basis, as we identify chemicals that pass the human and/or animal data screens, we conduct a preliminary evaluation of the overall evidence and identify those with the most compelling evidence as chemicals to bring to you for consultation.

In 2016, we brought five chemicals to your Committee for consultation and prioritization ranking. And now in 2020, we are bringing seven chemicals to you.

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DR. SUN: Now, we'd like to focus specifically on the part of the prioritization process shown here on the slide, where candidate chemicals are screened first by applying a human data screen to the results of a focused literature review and then by applying an animal data screen to an appropriately focused literature review.

For chemicals that pass either of these screens, we proceed to step 3, as shown on the slide, in which we conduct a preliminary toxicological evaluation of the chemical. That entails consideration of the overall evidence from readily available information relevant to

carcinogenicity, including findings from human and animal studies, and mechanistic and other relevant data.

Based on these preliminary evaluations, we identify chemicals with the most compelling data as chemicals to bring to you for consideration, consultation and ranking.

Next slide, please.

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DR. SUN: This slide summarizes the human data screen that we apply. It is meant to be quick tool to identify candidate chemicals with some positive findings of carcinogenicity that have been reported in humans. We look for cancer epidemiological studies that report a positive association between exposure to the chemical of interest and increased cancer risk. More weight is given to analytical studies and less weight to descriptive studies and case reports.

In addition, studies reporting positive associations are reviewed to determine whether the cancer effect might be attributed to the chemical with some confidence. If so, the chemical passes the human data screen.

Next slide, please.

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DR. SUN: This slide summarizes the animal data

screen that we apply. As with the human data screen, this screen was designed as a quick tool to identify candidate chemicals with a certain minimum amount of positive findings in animal studies in order to distinguish from those that do not have that minimum level positive findings in animals.

And for the newer members of the CIC, I will note that back in 2008, as we developed the animal data screen, we consulted with a committee on the design and content of this screen. As shown here, there are several ways in which a chemical can pass the animal data screen. The first is if a chemical has two or more positive animal cancer bioassays. And I should point out that for purposes of this screen, we have defined a positive animal cancer bioassay as one in which an increased incidence of a malignant or combined malignant and benign tumors is observed.

Other ways in which a chemical can pass animal data screens is if there is one positive study in which the tumors occurred to an unusual degree with regard to incidence, site, or type of tumor, or age at onset, or if there are findings of tumors at multiple sites in that single positive study or if, in addition to that one single positive study, there is a second animal study reporting an increase in benign tumors known to progress

to malignancy.

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DR. SUN: This slide highlights where we are today in the prioritization process. We are at the stage where we're consulting with the CIC on the seven chemicals that we have proposed for Committee consideration.

Next slide, please.

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DR. SUN: Your Committee in the past has asked us to put the table together like this, where we have characterized each of the chemicals in terms of exposure and we have -- where we have identified the types of studies available for each chemical. With regard to exposure characteristics, chemicals may be identified as being widespread or -- and/or high in frequent consumers, or as having limited exposure perhaps only in occupational settings, or as being high in infrequent consumers.

In terms of the types of studies that are available for each chemical for the different types of data, human, animal and other relevant data, we are indicating with a check mark the types of studies that are available.

For example, a check mark in the analytical human data column indicates that there is at least one

analytical human study on the chemical. Such a check mark does not indicate whether there are any analytical epidemiological studies with positive findings however. It merely indicates that there is an analytical epidemiological study on that chemical.

Among the seven chemicals included here in this table, decaBDE and PFOS were brought to the CIC in 2010 and they were ranked at that time as medium priority. Bisphenol A and trifluralin were bought to the CIC in 2011 and they were also ranked, at that time, as medium priority. Since that time, significant new data have been identified for all four of these chemicals, so we're bringing them to you again today.

This is the first time that chlorpyrifos, coal dust, and methyl bromide have been brought to the CIC for consultation.

I'd like to explain that under the structural similarity with Proposition 65 carcinogens column, we have check marks for five chemicals. In our prioritization document, we inadvertently missed specifying the names of these carcinogens for two chemicals. For bisphenol A, it is similar to the carcinogen tetrabromobisphenol A. And for PFOS, we applied the structural activity relationship broadly to fluorinated chemicals such as tetrafluoroethylene.

I also wanted to point out that PFOS is structurally similar to PFOA or perfluorooctanoic acid. PFOA is currently ranked as a high priority chemical.

Next slide, please.

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DR. SUN: Today, we are asking you to recommend rankings for these seven chemicals in terms of priority for preparation of hazard identification materials for possible future CIC review and possible listing under Proposition 65. You will notice that we are asking you to rank these chemicals as either high, medium or no priority.

And now I will turn this over to OEHHA's Deputy Director Dr. Vince Cogliano to say a bit more about these three priority categories.

DR. COGLIANO: Thank you very much Meng. And good morning everybody. So those of you who have been to more prioritization meetings than I've been will remember that in the past you've been asked to rank chemicals as high, medium or low, or no priority. And in going over the materials, we realized that saying that we should consider a chemical was low priority is a bit of a mixed message. That it's really saying it's not much of a priority at all. So to be totally transparent and clear, we had decided to -- not to use that category going

forward and to just ask you to recommend -- make your recommendations be high priority, medium priority, or not a priority. So that's the change we're making for this meeting compared to meetings in past years.

And so with that, that's all I have to say at this time. Thank you.

DR. SUN: Thank you, Dr. Cogliano. That concludes our presentation today. And I will now turn it over to Dr. Loomis.

COMMITTEE MEMBER LOOMIS: Very good. Thank you, Meng and Vince.

So we're -- in just a moment we'll begin the Committee discussion phase of this meeting. I'll take a minute to explain how this will work. So we have seven chemicals on the agenda today. For each one, two or three members of the Committee have been designated as lead discussants. So I'll call on each of the lead discussants by name and ask them to give their views of the chemical and a preliminary suggestion about whether it warrants priority for further consideration.

We'll then call on other members of the Committee if they would like to make any remarks. And then having done that, we'll have time for public discussion. Public discussion will be limited to five minutes per speaker. And at this point, I'll ask our facilitator, Clara

Robinson, to explain the mechanics of that process.

MS. ROBINSON: Okay. Thank you. So I'm just moving to the next slide here. So for the public comments, if you wish to provide a public comment, please use the hand raise feature that is located on the left tab of your GoToWebinar control panel. We will see your hand raise and we'll ask you -- and we will unmute you so that you can ask your question.

Again, if -- we do request that you fill out a speaker card. And I put the link into the questions pane earlier, where you can fill that out. And again, if you would like to present slides and you have not already sent them to OEHHA, please send them to the email that is located on the slide that you are viewing right now.

And if you need any assistance during the virtual meeting, you can submit questions to the questions pane in the control panel.

Before we get started with that, Dr. Loomis, I just wanted to see if we wanted to take a quick break just to verify the recording situation.

COMMITTEE MEMBER LOOMIS: Sure. If we need to do that, let's take five minutes, is that enough?

MS. ROBINSON: Hopefully, yes.

COMMITTEE MEMBER LOOMIS: Okay. I have one more point to make about the discussion process and then I'll

call for a break, if that works for you.

MS. ROBINSON: Sure.

COMMITTEE MEMBER LOOMIS: Okay. So we've heard about the public comment process. Then having heard from all those members of the public who wish to speak, I'll come back to the Committee and ask for further discussion and a vote on priority, calling on each member of the Committee to give their opinion.

So if there's nothing further, we need to discuss about the process at this point, let's take five minutes for a technical break.

(Off record: 10:36 a.m.)

(Thereupon a recess was taken.)

(On record: 10:44 a.m.)

DIRECTOR ZEISE: Okay. I think we can get started, Dana. I think we can start back up.

COMMITTEE MEMBER LOOMIS: Okay. Very good. So if everyone is here - I think I see all the Committee members - then let's get started with the scientific portion of the meeting. That means we begin with the first chemical bisphenol A. So for this substance, Joe Landolph, Michele La Merrill and Peggy Reynolds are the designated lead discussants.

So Dr. Reynolds, let's begin with you.

COMMITTEE MEMBER REYNOLDS: Okay. So as has been

nicely outlined by the OEHHA staff and -- as well as from public comments from the American Chemistry Council. BPA is something that's been used since the 1950s to make highly durable plastics and it's been common used in food packaging. Exposure in humans is ubiquitous, but BPA has been subject to extensive negative press and recently been discontinued from use in many a food and beverage packing products. As has been illustrated on the BPA free notation seen on many products.

So while I defer to my colleagues on the toxicology and mechanisms of BPA, there does appear to be good evidence for xenoestrogenic properties that raise concerns about carcinogenic potential, particularly for hormonally mediated tumors. An NIH EPA expert panel review in 2007 documented that endocrine disrupting properties had been demonstrated in several in vivo studies and that BPA should be considered to be a xenoestrogen. A 2016 update further reinforced that conclusion. And panel members concluded that BPA may be reasonably considered to be a human carcinogen for breast cancer.

There's also some epi evidence that BPA may be associated with greater mammographic density, which is well known as a risk factor for breast cancer. But, in fact, the epidemiologic evidence was then and still is

pretty sparse.

So one of the biggest challenges for human health studies of this nature is exposure assessment. The most common method for assessing exposure in humans is from measuring metabolites in urine. Assessing BPA in blood is less desirable as detection levels tend to be low and less informative. And roughly half of the few epi studies to date have relied on urine samples.

It's only a small smattering of studies. There were 13 studies presented to us for this initial review. Most of them were breast cancer, seven of the 13 studies. And of those, four had exposures for urine samples. Generally, the breast cancer literature has been quite null, as has been the one study on endometrial cancer, which was the study based on blood samples.

It's not surprising that so many of these studies were breast cancer, because of the endocrine disrupting and estrogenic activity of BPA. But despite various approaches to exposure measurements, they, along with that one endometrial cancer study, haven't really observed elevated risks, while there appear to be positive results for a few other miscellaneous cancers.

This could be in part because the animal evidence for in utero BPA-related epigenetic reprogramming suggests that the design of most current epi studies may have been

looking at the wrong window of exposure. This is a general problem for studies of breast cancer.

So although there are relatively few epidemiologic studies of BPA in cancer risk, and only a few of those are positive, the laboratory evidence, in my mind, continues to suggest potential risk relationships for humans, particularly for those endocrine related cancers.

So because of the extensiveness of BPA exposure in the population and high public interest in human health risks, I would classify this as a high priority for CIC review.

COMMITTEE MEMBER LOOMIS: Good. Thanks, Dr. Reynolds.

COMMITTEE MEMBER REYNOLDS: And i'll pass it on.

COMMITTEE MEMBER LOOMIS: Okay. Let's go on to Dr. Landolph then.

CHIEF COUNSEL MONAHAN CUMMINGS: I'm sorry, Dr. Landolph, if I could just interrupt quickly. I'm not seeing everybody's cameras on for the Committee. Could you check and make sure all of you that you have your cameras on, in particular Dr. Reynolds. Okay. Yeah. We just need Dr. Reynolds I think.

There you are. Okay. Thank you.

COMMITTEE MEMBER LANDOLPH: Okay. So, yeah, I

agree with Peggy. It certainly is a high exposure chemical to humans. And to make a long story short, the last time we looked at it, I voted medium on it, but there's been a lot of data that's in on it since, so I'm going to shift my vote to high.

I'm looking at the two hydroxyl groups on the there. It looks like potential for the possibility of oxidation to quinones and that you could generate oxygen radicals off this.

So I'm going to turn to the animal studies that I'm more conversant with. And let's see here. Table three is male Fisher rats -- 344 rats exposed bisphenol in feed for 103 weeks. And the hematopoietic system looking at leukemias they got 13, 12 and 23 at the 0, a 1,000 and 2,000 parts per million doses. The trend test was P equals 0.021. So that's good. The mammary gland they looked at the fibroadenoma, 0, 0 and 4. And the trend test was P equals 0.0114. And the testes they looked interstitial tumors and they got 35, 48 and 46 roughly out of 50. And the trend test there was good at P is less than 0.001. So that was hematopoietic system and mammary gland.

In Table 4, the results were not quite as striking. The hematopoietic system was 2 out of 50, at 0 at the median dose, it was 8 out of 50, and a the high

dose of 10,000, it was 3 out of 50. So it was a rise, but it was not significant.

For the chromophobe carcinoma and the pituitary gland, it went 0 tumors at 0 dose, 0 tumors at 5,000, then it jumped to 3, so the P equals 0. -- less than 0.05. So that's positive.

There was a positive test for tumor incidence in female F1 Sprague-Dawley rats exposed during gestation. And the numbers were low, but there was a P test of P equals less than 0.05. So that's positive as well.

And there was a whole set of lymphomas arising in different organs, liver, prostate, bone marrow, spleen, kidney and systemic in male F1 Sprague-Dawley rats exposed to bisphenol A during gestation. And the trend test was pretty good for all of them. It was less tan 0.01, except for one which is -- was less than 0 -- P equals 0.002.

So I'm going to skip over a lot of this and say I see a lot of positivity in the animal studies. So basically, I'm going to stick with high.

And I want to turn just real briefly to the in vivo studies. And you get DNA adducts in CD1 male rat liver is positive. And in vitro, you get Formation of DNA adducts to the N7 of guanine. So that's positive. And DNA accounts in cultured Syrian hamster embryo cells positive. So that indicates that you're getting DNA

adducts formed from the metabolism of this compound.

Then in genotoxicity you get DNA double strand breaks, meiotic aneuploidy in females. In vitro, you get K-ras mutations, HGPRT mutations in V79 cells was negative however, you get micronucleus formation, you get aneuploidy, you get chromosomal abnormalities, and DNA double strand breaks in a number of different systems.

So I would say, since we last met, this compound is much more positive. It induces chronic inflammation. And it does cell transformation in Syrian hamster embryo cells. So I'm going to go along with Dr. Reynolds and say that my recommendation is we move this one up to high, both because of the wide spread exposure and large number of positivities in the animal studies.

COMMITTEE MEMBER LOOMIS: Okay. Thanks, Dr. Landolph. Let's go on to Dr. La Merrill.

COMMITTEE MEMBER LA MERRILL: Good morning. I'll give you my overall impression and dive a little into it further. I noticed in humans and rodents there are reports of mammary cancers and prostate cancer or neoplasia that are consistent with interactions of multiple nuclear receptors. Primarily, those of estrogen and further evidence of those estrogen receptor interactions have pretty nicely elucidated epigenetic gene regulatory mechanisms associated with them. And there's

evidence that there's estrogen receptor-dependent proliferation. And these combined with reduced apoptosis and elevated genotoxicities make me think that this should be a high priority.

When I looked at the human data, I only looked at the case controls, I noted there were no cohort studies. We heard from Dr. Reynolds how the exposure assessment is problematic, both in terms of this being a short lived, in terms of half-life, but also windows susceptibility issues. Despite those practical difficulties in conducting this research among case control studies, two out of four had elevated odds of breast cancer and two out of four were null. For other sites, there was only one representative case control study that I observed and they had elevated odds for lung cancer, prostate cancer, meningioma, breast -- excuse me, brain cancer, in addition to osteosarcoma and a gene interaction with lysyl oxidase, LOX genotype.

And the animal studies, as you heard from Dr. Landolph, there are extensive sites that were targeted mostly at hematopoietic and endocrine reproductive axis in both male and female rodents. And this was across government and academic labs at least. And this included both rats and mice involving primary exposures, co-exposures, and xenograft approaches. And these sites

and lesions included pituitary carcinomas, mammary carcinomas, hepatic adenoma - excuse me - carci -- and carcinoma combined, lymphomas in multiple sites, prostate neoplasias, or often known as PINs, and adenocarcinomas.

So there were numerous demonstrations of Dose response trends, but also sometimes those only were pairwise. And you heard a lot about the genotoxicity from Dr. Landolph. I mentioned there's quite a bit known on epigenetic effects of BPA that are primarily associated with histone modifications in the estrogen receptor. There is a study of chronic inflammation in rabbits.

The estrogen receptor that is targeted is not just nuclear alpha and beta, but also the membrane G-protein coupled estrogen receptor. And this has been demonstrated in a number of different species and with selective antagonists to have dependence for downstream effects, including neoplastic transformation of human breast cancer -- breast epithelial cells. There is some evidence of immortalization by transformation of hamster embryo cells as well.

And with that, I think I'll stop and just reiterate that I would recommend this as high priority based on that weight of evidence.

COMMITTEE MEMBER LOOMIS: Okay. Great. Thanks to all the discussants. And now let's see whether other

members of the Committee have anything that they'd like to add to what we've already heard. The process for this, as I understand it, is going to be since I can see all of you, you physically raise your hand and I'll call on you. So, Dr. Eastmond, you have your hand up, go ahead, please.

COMMITTEE MEMBER EASTMOND: Thank you. I have kind of a different take certainly on the animal studies. I didn't review this chemical in great detail, but I did notice that the NCI NTP chronic bioassays results, although they noticed these various trends, they recognized most of these were associated with old age, and so they concluded there was no clear evidence. This is from the 1992 one I believe, or '82, I can't remember.

And then the more recent Clarity study, which was done by NCTR, although there's some controversy, overall it's pretty negative in the animal studies, like overwhelmingly negative, and positive results were seen in many different endpoints, as far as estrogenic activity, et cetera.

But as far as cancer itself, I didn't see the evidence for that. I'm not familiar with it. I do recognize it is an estrogenic compound. It's about one -- it's not nearly as potent as estrogen. It's -- I think it's a hundred-fold or a thousand-fold less potent. So at high doses you will see effects, but when you get to the

low dose is where most people are exposed. It's really questionable whether you see those effects or not.

Anyway, I do realize this is a high profile compound. There's a lot of concern about it. There's certainly mechanistic information. So, you know, I would tend to put it more in the medium category, but that's my -- the main thing for me is I don't really mind going through it, but there's a huge amount of work involved with the OEHHA staff, so that's kind of my thinking about this compound.

COMMITTEE MEMBER LOOMIS: Okay. Thanks.

Dr. Mack, I think you had your hand up as well.

COMMITTEE MEMBER LOOMIS: It looks like you're on mute.

CHAIRPERSON MACK: Yes. I have a completely different reason for wanting to put it in a high priority. Although, I think it could be just on the basis of its universal exposure and the relatively minimal animal data.

But there's -- I -- my attention was caught by the Chinese study of what they initially said was non-small cell lung cancer. This is something that an epidemiologist probably wouldn't do initially, because non-small cell lung cancer puts together two cancers which have completely different etiologies, the standard, most -- formally most common kind of lung cancer, which is

very much tobacco related and adenocarcinoma of the lung, which is a very different entity. The standard kind of lung cancer is decreasing in frequency because of the decreased number of people that are still smoking. And it is most common in Black men and Black women and then on Whites after that.

But adenocarcinoma is very different. It not only is -- it is most common in Black men, but it's most common in White women, and it's a very striking difference. And it's also not decreasing in frequency as the other lung cancers which are related to tobacco are. It's increasing. And it's increasing in both men and women.

And because that study in China was, in fact, basically a study of adenocarcinoma, because it's by far the most common non-small cell lung cancer in China, and the numbers were fairly large and the result was fairly positive. So because of the fact that White women may have a different kind of exposure than Black men and because this tumor is increasing, I think it warrants a high criteria as well.

COMMITTEE MEMBER LOOMIS: Thanks for that interesting observation. That's worth keeping in mind.

Let's see. Would any of the other members like to make a comment at this point? Let's see, Dr. Eastmond.

Any other hands. Let's go to Dr. McDonald, first, then we'll come back to you, Dr. Eastmond, since you've already spoken once. Go ahead, Dr. McDonald.

COMMITTEE MEMBER McDONALD: Yes. Thank you, and hello, everybody.

Yeah, I also, like Dr. Eastmond, I wasn't as compelled with the animal evidence. You know, the 1982 NTP study did have some suggested findings, particularly the rare mammary gland fibroadenoma in the high dose males. But overall, those early studies showed maybe some suggestions by trend test in the mice, but not by pairwise. And then the later studies by NTP in 2018, generally I view those as negative. There's some suggestions maybe that there's a U-shaped dose response curve or something like that going on, but, you know, you just don't responses in the higher dose groups.

Clearly, there's lots of mechanistic evidence on this compound. I think the only other thing I'd like to add is on the epi studies, I'm a little worried that in nearly all the studies, exposure assignment is (inaudible) by a single urinary sample, you know, for a chronic endpoint. And so that's one area of concern which I find is a little bit of a weakness in the human data, but I'll let the epi folks speak to that.

Thank you.

COMMITTEE MEMBER LOOMIS: Okay. Dr. Eastmond, did you want to say something else?

COMMITTEE MEMBER EASTMOND: Oh, this was just to follow up with Dr. Mack's comment. I thought the shift in tumor types and lung cancer had to do with the reduction in the coal tar, the PAH, and the increase in nitrosamines in cigarettes and that's why there was a shift in once cancer being seen. That's just a follow-up to your specific comment.

COMMITTEE MEMBER LOOMIS: Okay. Dr. La Merrill wants to say something else.

So go ahead, please.

COMMITTEE MEMBER LA MERRILL: Yes. Thank you. So to speak to the comments about the NTP studies, I am a little perplexed about the conclusion that there's not really anything going on in the 1982 study. The trends are significant which means that there is a linear dose response associated with that. I heard also that there was not a pairwise association, but, in fact, at the higher doses, it was observed. And I see that in particular that there was a trend significance for hematopoietic with leukemias, the fibroadenoma of the mammary gland, as well as the interstitial cell testes tumor.

And with respect to the point-wise doses, there

was significantly elevated leukemias and testes tumors in the 2,000 ppm dose compared to the control and for the testes in the 1,000 group.

You know, I also heard mentioned that there was sometimes a non-monotonic. I think it's confusing to me to hear you on one side saying, Dr. McDonald, that we shouldn't be too interested in the trend test and on the other hand you're saying that the non-monotonic and not much effect at the higher dose is to be dismissed. I'm not really sure what type of pattern of significance it is that you find remarkable.

But I want to point that regardless of our interpretations of the statistical significance that was actually reported, that across multiple models we have in multiple species, rats and mice, and both males and females, carcinomas in one, two, three, four -- at least four different sites. And so based on the criteria that we're supposed to be thinking about elevated concern for animal studies, I think this is kind of more than adequate to consider this worth a full review to look more carefully at some of these studies that are being brought up.

COMMITTEE MEMBER LOOMIS: Okay. Thanks.

Dr. Bush.

COMMITTEE MEMBER BUSH: Thank you. Yeah, just a

matter of procedure. And perhaps Dr. Zeise or Sandy could answer this. Do we know whether DART is evaluating this particular chemical?

DR. SANDY: Hello. This is Martha Sandy. Yes, I can tell you that actually bisphenol A has been listed by the DART IC Committee. They considered it just for one endpoint, the female reproductive endpoint and it was placed on the list based on that. And you'll be hearing at the end of the meeting about a court case where we had proposed listing BPA based on developmental toxicity and through the authoritative bodies mechanism. And that case is winding its way through the process, so we'll update you on that at that time.

COMMITTEE MEMBER BUSH: Thank you.

COMMITTEE MEMBER LOOMIS: Good. Are there any other preliminary comments from the other members of the Committee who haven't spoken yet?

I don't see any hands raise, so I'll add mine really briefly. The -- I agree that the epidemiologic evidence of carcinogenicity is inconsistent. I would call it limited in IARC terminology. But nevertheless, there is a concern about widespread exposure to this chemical and its high public profile. I also noted that there's evidence that it induced oxidative stress and chronic inflammation in two studies of exposed humans, which I

don't think was mentioned in earlier comments. So for me, it would merit high priority for further consideration.

So unless there are any further -- oh, last thoughts, there's Dr. Stern. Go ahead, please.

You're on mute.

COMMITTEE MEMBER STERN: I don't want to take too much time, but I just want to add my thoughts. I agree that the epidemiological evidence is consistent with limited based on lack of findings for some cancer types, primarily for breast cancer, were based on the mechanisms one would expect to see strong associations.

But I want to echo what Dr. Reynolds said that based on the mechanistic evidence, it suggests that the impact of these compounds might be during development. And there are no studies that have looked at cohorts to see whether young women exposed during childhood development are impacted by these, so -- but the mechanistic evidence to me is compelling in that direction.

And they are some cancers like lung, and prostate, and meningiomas, and bone cancer for which there are positive associations. So putting it all together, I think that it merits further evaluation and it's a high impact, based on the concern of potential impact it might have on young women during development.

COMMITTEE MEMBER LOOMIS: Okay. Thanks. Any final comments before we invite the public to speak?

Dr. Landolph, one more comment.

COMMITTEE MEMBER LANDOLPH: Yeah. I'm going to agree with Dr. Stern, and Dr. La Merrill. When I looked at this, there is positivity in the animal database. I don't think you can just put a zero coefficient in front of that. I Don't agree with that.

Secondly, the key characteristics of carcinogens is met in a few areas here. It forms DNA adducts in vivo, and in vitro, and it's genotoxic. And it causes aneuploid in SHE cells. So there's a lot of classical contributions of the principles of carcinogenesis to this compound.

I ask myself could I say that this compound is not carcinogenic? And I would have to reject that hypothesis straight out of hand, due to the large amount of evidence that I see presented here. So I disagree with some of the other speakers.

COMMITTEE MEMBER LOOMIS: Okay. Thank you.

Let's go now to public comments. The Committee will have a chance for further discussion after that. And I see that Mr. Hentges has his hand up. And so I think we need our facilitator to call on him to speak.

MS. ROBINSON: All right. Mr. Hentges, I have -- I have unmuted you from our end, but you are currently

self-muted. You should see an icon of a microphone on the top left corner of your control panel. Please click on that to unmute yourself from your end. There you go. Hi, Steve. Can you hear us?

DR. HENTGES: Hello. Can you hear me now? I should be coming through.

MS. ROBINSON: We can. You are.

DR. HENTGES: Okay. Thank you.

I sent in written comments before and probably you have those and you've looked at those. So what I intend to do is to provide a hopefully brief synopsis of some of the key points from the written comments, hopefully within the five minute timeline.

So first, what is BPA? It's an industrial chemical. It's primarily used to make polycarbonate plastics and epoxy resins. About 75 percent of BPA is used to make polycarbonate, about 20 percent for epoxy. Small amounts are used to make specialty plastics and resins. Only trace levels BPA -- residual BPA remain in the finished materials, typically less than a hundred ppm.

Human exposure is -- has limited potential from the use of polycarbonate and epoxy products. The -- human exposure in general has been well studied with biomonitoring studies that consistently show exposure is very low, typically less than a hundred nanograms per

kilogram per day from all sources. It does not distinguish between one source versus another.

And those exposures are well under TDIs that have been set worldwide. Those are in the range of 4 to 50 micrograms per kilogram per day. So human exposure is well below the TDI levels.

As far as metabolism and pharmacokinetics, BPA has also been well studied. It is efficiently metabolized and rapidly eliminated from the human body in urine. After exposure, metabolism converts BPA to biologically inactive and non-estrogenic conjugates, mostly that means BPA glucuronide, and lower amounts of BPA sulfate. Those are the things that are found in urine in biomonitoring studies. It's reported as BPA, but those are what's actually present.

Unconjugated BPA in urine is typically one percent of the administered dose, administered meaning the doses in pharmacokinetic studies. Consistent results from several human pharmacokinetic studies and numerous animal studies have been found. These results indicate that BPA is very unlikely to cause health effects at any foreseeable exposure level.

BPA has been comprehensively reviewed by agencies and organizations around the world. There are no -- those consistently find that there is little concern for

carcinogenicity and there's no different conclusion from government agencies or Proposition 65 authoritative bodies.

Reviews of BPA have been conducted around the world, but in the U.S. that principally includes the U.S. Food and Drug Administration, but also Europe, Japan, and some years ago there was a joint extra meeting that was sponsored by FAO and WHO. All of use reviews, or most of them, also conclude that BPA is not mutagenic.

The -- mentioned earlier were the NTP studies that were conduct -- conducted, the bioassays on BPA that were conducted on rats and mice, so I consider to be the seminal studies, there was no evidence for carcinogenicity in female rats and male and female mice, and equivocal evidence in male rats.

More recently, this was also mentioned, FDA was subjected to a two-year toxicology study by the FDA in the so-called Clarity Core study. That study began exposure during gestation and exposure ranged over a wide range from low to much higher doses of BPA.

There was little evidence in that study that BPA could be carcinogenic, carcinogenic. BPA also has been subjected to numerous in vitro and in vivo genotoxicity assays. The weight of evidence from those assays indicate that BPA is not genotoxic, especially that would be true

even though it's relevant in in vivo studies.

So in conclusion, based on the extensive scientific database available for BPA, we recommended that BPA be designated as low priority. And I realize now that you've actually eliminated that categorization. And so maybe no priority or medium would be the correct recommendation on that. So we recommend basically that it's not the highest priority for your further consideration.

So hopefully I finished in five minutes. I'll stoop there and we can go to the next commenter.

COMMITTEE MEMBER LOOMIS: Okay. Thank you very much and thanks for staying within the time limit. I understand that there may be another member of the public who wants to speak, but I don't see another hand raised, so -- okay. So Clara is indicating there is no other public comment.

So if that is the case, then we go back to the Committee for final discussion and a vote on priority for this chemical. Any further thoughts about BPA from the Committee?

Okay. I don't see any other comments, so I'm going to call for a vote on priority for bisphenol A in the order in which I see you on the screen.

Dr. La Merrill?

COMMITTEE MEMBER LA MERRILL: Sorry. I had to navigate to my mute button.

I vote for high, please.

COMMITTEE MEMBER LOOMIS: Thanks.

Dr. Crespi?

COMMITTEE MEMBER CRESPI: High.

COMMITTEE MEMBER LOOMIS: Dr. Bush?

COMMITTEE MEMBER BUSH: High.

COMMITTEE MEMBER LOOMIS: Dr. McDonald?

COMMITTEE MEMBER McDONALD: Medium.

COMMITTEE MEMBER LOOMIS: Dr. Stern?

COMMITTEE MEMBER STERN: High.

COMMITTEE MEMBER LOOMIS: I vote high.

Dr. Zhang?

COMMITTEE MEMBER ZHANG: High.

COMMITTEE MEMBER LOOMIS: Dr. Mack?

I see you speaking, but I don't hear you.

COMMITTEE MEMBER McDONALD: High.

COMMITTEE MEMBER LOOMIS: Heard it that time.

Dr. Eastmond?

COMMITTEE MEMBER EASTMOND: Medium.

COMMITTEE MEMBER LOOMIS: Dr. Landolph?

COMMITTEE MEMBER LANDOLPH: High.

COMMITTEE MEMBER LOOMIS: Dr. Reynolds?

COMMITTEE MEMBER REYNOLDS: High.

COMMITTEE MEMBER LOOMIS: Okay. I don't think I've missed anybody, but if I did, please shout.

It sounds like the majority say high.

So let's move on to the next chemical, and that is chlorpyrifos. And we'll do this one in the same way. I'll call on the lead discussants first.

Dr. Crespi, first you, and then we'll go to Dr. La Merrill.

COMMITTEE MEMBER CRESPI: Sure. Thank you.

So chlorpyrifos is an organophosphate pesticide. As far as exposure goes, the State Department of Pesticide Regulation is banning all agricultural use in California at the end of this year, based on findings of developmental neurological effects in children at small doses and other top health effect issues.

So it's expected that exposure to the general public after the end of the year would primarily come from -- from residues on food that are -- food that's grown out of state. So that would be the primary mechanism -- primary route of exposure after the end of this year for folks in California.

I was focusing on the epidemiological evidence, which is more in my wheelhouse. Most of the literature -- published literature comes from a particular prospective cohort study, the Agricultural Health Study, which was a

study of over 8,000 farmers and pesticide applicators and their spouses in Iowa and North Carolina. And that study enrolled folks starting in 1993 to '97. And it collected exposure data to about 50 pesticides prospectively through self-report, through questionnaires, which is a strength of this study with the prospective exposure data collection. And the incident cancers were identified by linkage to the State Cancer Registry.

So it's a very large prospective cohort study with a number of strengths. So I think relatively low risk of bias for this type of study.

And that study has been pretty well mined in terms of looking at multiple different types of cancer and whether risk is associated with it -- with the various pesticides and classes of pesticides for which exposure data was collected using various different exposure metrics.

There were shorter term studies that were published in the mid-2000s and then some longer term with longer term follow up published more recently with about 15, 20 years of follow up.

So most of -- most of the human analytic data comes from this particular study. And then there are some various case control studies which have looked at this chemical, most of which are relatively small.

So I think as I mentioned, the Agricultural Health Study, especially looked at a lot of different cancers. And I think that the most noteworthy positive results found are for breast cancer and kidney cancer.

So there was an earlier study with shorter follow-up that found some evidence of elevated risk of breast cancer among -- principally among the spouses. Although, some of the spouses applied the chemicals directly, so there was husbands' use and then also direct use among this -- the female part of the cohort.

And so the -- this is looking at like 30,000 women and over 10 -- over a thousand breast cancer cases, and they did find elevated hazard ratios on the order of 1.5 statistically significant. And then there was also another study that looked more closely in terms of tumor type and found a positive association with estrogen receptor, negative -- PR negative tumors in post-menopausal women with a risk ratio of about 2.3, and that was statistically significant.

So those are, I think, some notable positive findings for breast cancer. And I think also supporting a concern for breast cancer would be a case control study that was -- a population-based case control study that was conducted in the Central Valley of California. It was relatively small with 155 cases and 150 controls. The

exposure assessment was done using historical pesticide application data and geolocated -- location histories for the subjects. And it did find odds ratios on the order of three and four for breast cancer. So I think, taken together, those are a cause of concern for a risk of breast cancer associated with chlorpyrifos.

Also, for the Agricultural Health Study, there was a very recent study published on renal cell carcinoma with 20 years of follow-up. And they found an elevated risk of 1.7 and there was a very clear exposure response gradient.

So I found that in terms of the epi evidence, those were two of the more compelling associations with cancers. And then there were scattering, sort of more limited evidence for some other cancers, such as non-Hodgkin's lymphoma. There was positive association, but in a study with very few exposed cases, seven exposed cases, similar for brain cancer glioma, a case control study a with only ten exposed cases, but found an odds ratio of 23. So I did find that there was some noteworthy positive associations in the epidemiological literature.

And I think I'll end and I'll leave it to my colleagues to discuss the more mechanistic and animal study literature.

COMMITTEE MEMBER LOOMIS: Okay. Do you have a

preliminary suggestion about priority at this point?

COMMITTEE MEMBER CRESPI: Well, I think that there's very concerning evidence in the literature. However, it looks likes the risk of exposure after this year would -- the levels of exposure would be relatively low. So I -- I think I'm going to go with medium.

COMMITTEE MEMBER LOOMIS: Good. Thanks.

Let's go on to Dr. La Merrill now.

COMMITTEE MEMBER LA MERRILL: Hi. Thanks. Good morning, again.

So my overall impression is that pesticide exposure assessment in humans can be quite difficult to do, because most of the studies are, you know, occupational. In AHS, there's a lot of co-exposures and they can be quite high. And so, you know, residual confounding is something I was mindful of and really looking for that evidence to kind of integrate with the charges I had, which were to focus on the animals and the mechanism. And, you know, I do agree that there was some increased breast cancer hinted at. There was a couple of studies in AHS that it seemed like it depended on what year they published it. And so I think it might need to be a looked at further, but we have already heard that from our epidemiology expert.

And I did note, however, that in addition to that

work, there was evidence in the mechanistic literature for ER agonists across various experimental assays, including MCS -- MCF7 human breast cancer cell effects that were ablated by ER selective antagonist. And it was positive for ER expression or activity in seven ToxCast and Tox21 assays.

There's also evidence of progesterone receptor binding. That literature has been less investigated, so I think elucidating whether or not the signals are ER in nature or PR in nature. If that was causally related to breast cancer I don't believe is addressed in the literature at this time.

But actually what caught my attention even more so was because of the way that there will be co-exposures among ag workers, I particularly was interested in the epidemiology where we were looking at the effects in the highest quartile of exposure. And what I saw was that although, as we heard the kidney was a significant elevated risk for kidney cancer, the effect size was under two-fold increased risk, which is often kind of a rule of thumb for potential uncontrolled confounding.

However, with rectal cancer, the risk of that was estimated to be 2.7 relative risk, in addition to having a trend in the AHS. And when I looked in the mechanistic literature, there was a study that indicated human

colorectal adenocarcinoma cells had increased proliferation when exposed to chlorpyrifos. And so I thought that that was a bit revealing and potentially worth factoring into our assessment.

As far as the animal literature goes, I would say that it's generally null. There were five studies and there was only one of those studies that was positive, but it was weak, in that they had increased lung adenomas in the mid-dose group, but there wasn't a significant trend. And the study data appeared to be reported a bit thinly, in terms of there was no report of tumor incidence. So I thought the animal data was pretty underwhelming.

As far as more depth on the mechanism, there is some mixed evidence for genotoxicity. There were both positive, and negative, and slash null reports. And I think it -- it would really require a more in-depth study of the quality of these investigations to decide where the weight of the evidence would land. But I would say based on my cursory review, that it appeared to be more often positive.

There -- for the key characteristics of epigenetics, it's not been investigated very much. There were two studies with DNA methylation. They were both null. There was one study of histomodifications and there was positive associations with having chlorpyrifos

exposure in HDAC changes and this is, you know, a key histone modification and epigenetics in general.

Oxidative stress, key characteristic was, I think, observed in all four of the models that were examined that I looked at. And that included human and rat cells. I already mentioned the receptor points previously, so I won't get back into that.

And the last one that I saw evidence for was the human colorectal proliferation that I also mentioned, so I think I'll stop there.

And I just wanted to seek clarification for OEHHA to make sure I didn't misunderstand the directive here. So our goal is evaluate hazard right, and not take into account exposure levels?

CHIEF COUNSEL MONAHAN CUMMINGS: Yeah. This is Carol. You're correct. You can -- what you want to look at is if there's any exposure potential from whatever source, you know, if it's residue or otherwise. But we would look at levels at a much later part of the process.

COMMITTEE MEMBER LA MERRILL: Okay. Because although Professor Crespi acknowledged that the -- it would be mostly out of state, you know, the -- the rules and regulations, and what happens elsewhere, and even here, are not things this group has control over. And so I would say that based on the colorectal cancer

association with the high relative risk and the high exposure -- the highest exposed of the age as cohort in addition to the colorectal cancer cell proliferation as well as the hinting at the human breast cancer association with some of the ER and PR evidence out there that I'm leaning towards high as the initial recommendation. I -- I don't feel as strong about it, so I'm really looking forward to discussing that with the rest of you.

COMMITTEE MEMBER LOOMIS: Okay. Thanks.

Now, let's go around to the rest of the Committee and see if there are any initial thoughts having heard from the two lead discussants.

I don't see -- okay. There's Dr. Eastmond with his hand up.

COMMITTEE MEMBER EASTMOND: I can't speak much to the epidemiology. Whereas, mechanistically, maybe there are off-target effects, but the primary effect of this is inhibition of acetylcholinesterase. And there's no reason you'd expect that to do the same sort of damage to occur to DNA or to be carcinogenic. Certainly genotoxic. And apparently the animal evidence doesn't indicate really evidence for carcinogenicity.

So it doesn't seem like a real strong concern for me. I'm not familiar with the epi studies, so I can't really comment much about those.

COMMITTEE MEMBER LOOMIS: Anyone else?

Dr. Mack.

CHAIRPERSON MACK: Of course, these all have to be evaluated at some point, but we're talking about prioritization for the Committee, which only does a couple every year. So in terms of prioritization, I think the neurologic damage that this compound does trumps cancer to some extent. And the relative infrequency of exposure makes it go into a low priority for me.

COMMITTEE MEMBER LOOMIS: Thanks. I heard from Dr. Sandy who wants to clarify a point about exposure. So go ahead, please, Martha.

DR. SANDY: Yes. Thank you. In prioritization -- so what Carol just told you is very -- is accurate and correct for listing. You consider the toxicological and epidemiology data. And you're thinking of hazard for listing consideration. For prioritization, you may decide to use -- to take into account the exposure information as well in how you prioritize it. I just wanted to comment on that.

Thank you.

COMMITTEE MEMBER LOOMIS: Thanks for that clarification. Now, back to the Committee. Any other initial comments?

Not seeing any hands raised, I'll give my comment

really briefly. I put this one in medium priority. You know, I echo the comments about the Agricultural Health Study. It's a well done study. It's large. But they've examined a large number of compounds in multiple publications over time, so it really has to be looked at pretty carefully to sort out, you know, what is the -- the most recent and relevant finding for any particular compound?

It's really true that the epidemiology of pesticide exposure is exquisitely complicated. And unfortunately, as is often the case for this particular chemical, I've found the epidemiologic evidence to be inconsistent and kind of equivocal.

I also didn't see any strong evidence of the key characteristics of carcinogens in exposed humans. So medium priority is where I came down.

Anyone else before we see if there's a public comment?

Okay. Not seeing any hands. Clara, I don't see any hands raised, but are you aware of anyone else who wants to speak about this chemical?

MS. ROBINSON: I do not see any hands raised at this time. But just as a reminder, if you would like to provide a verbal public comment on this item, please raise your hand by clicking on the hand-raising icon on the left

tab of your GoToWebinar control panel, whether or not you have submitted a speaker card. And also as a reminder, if you need assistance with the virtual meeting, you can submit questions through the questions pane in your attendee control panel. And at this time, I still do not see any hands raised.

COMMITTEE MEMBER LOOMIS: Okay. Thanks, Clara.

So let's go around to the Committee and we'll -- since there wasn't any discussion following the discussants and comments we've already heard, unless there's something else to be said, let's go ahead and poll everyone for their final views on chlorpyrifos.

Okay. Seeing no other hands raised, we'll go in the same order.

Dr. La Merrill?

COMMITTEE MEMBER LA MERRILL: Medium.

COMMITTEE MEMBER LOOMIS: Dr. Crespi?

COMMITTEE MEMBER CRESPI: Medium.

COMMITTEE MEMBER LOOMIS: Dr. Bush?

COMMITTEE MEMBER BUSH: Medium.

COMMITTEE MEMBER LOOMIS: Dr. McDonald?

COMMITTEE MEMBER McDONALD: Medium.

COMMITTEE MEMBER LOOMIS: Dr. Stern?

COMMITTEE MEMBER STERN: Medium.

COMMITTEE MEMBER LOOMIS: I said medium.

Dr. Zhang?

COMMITTEE MEMBER ZHANG: Medium.

COMMITTEE MEMBER LOOMIS: Dr. Mack?

CHAIRPERSON MACK: Low.

COMMITTEE MEMBER LOOMIS: We're not using low. Would you like "medium" or "no"?

Sorry, Dr. Mack, we're not using low priority for this particular meeting, so would you prefer to characterize this as "medium" or "no priority".

You're on mute. Can't hear you. You're on mute.

CHAIRPERSON MACK: We're ranking them in terms of the order in which we take them up. And there is so many others that I believe have a higher priority, based on the fact that there's already evidence that this stuff is dangerous, and it's relatively low frequency of exposure. So on those two grounds, I consider it to be less emergent.

COMMITTEE MEMBER LOOMIS: So would you like to call that "medium priority" or "no priority". Those are the possibilities, if you don't think it's high.

CHAIRPERSON MACK: I thought we had three alternatives, high, medium and low. So I'm choosing low. If you want to get rid of that, then I go back to medium.

COMMITTEE MEMBER LOOMIS: Okay. So the three alternatives we were given are high, medium and no, N-o.

So I think you said medium, if you can't have low, is that right?

CHAIRPERSON MACK: I'm saying low, but if you want to call it medium --

COMMITTEE MEMBER LOOMIS: Okay.

CHAIRPERSON MACK: -- I don't think it makes any difference, because there's going to be a lot of mediums and some of them are going to wind up being low.

COMMITTEE MEMBER LOOMIS: Right. Okay. That's what we'll call it.

Dr. Eastmond.

COMMITTEE MEMBER EASTMOND: By the time OEHHA would do this evaluation, the compound will be banned and not used in California. It doesn't persist, so for me it's a low -- it's a no priority.

COMMITTEE MEMBER LOOMIS: No priority.

Dr. Landolph?

COMMITTEE MEMBER LANDOLPH: Can you hear me?

COMMITTEE MEMBER LOOMIS: Yes.

COMMITTEE MEMBER LANDOLPH: Yeah, I'll give it a medium.

COMMITTEE MEMBER LOOMIS: Dr. Reynolds?

COMMITTEE MEMBER REYNOLDS: Medium.

COMMITTEE MEMBER LOOMIS: Okay. Very good.

Now, next compound up -- Dr. Zhang would like to

say something.

Go ahead, please.

COMMITTEE MEMBER ZHANG: Yes. Since we're discussing about the low, the previous low priority was no. You know at the beginning, I think Dr. Vincent was explain it to us. But I want to make a point is even though if we say no, N-o, I think maybe we should add it it's no for now. It's not no forever, because, you know, sometimes, you know, the chemicals made currently for our Committee members were thinking is maybe very low or no priority. But I just think we should make that clear unless if I misunderstood something.

COMMITTEE MEMBER LOOMIS: Let's see if the staff would like to speak to that comment.

DR. SANDY: Yes. This is Martha Sandy. I'll say that, yes, as we heard in the presentation that began from Dr. Sun, we do continually monitor the literature. And when there is new compelling information for a chemical that you've ranked, or maybe we haven't even brought it to you, we bring them back, if there's something we think you should look at, if it's compelling.

So you may say no, now, but if there's new information, we may bring that chemical back to you for ranking and consultation.

COMMITTEE MEMBER LOOMIS: Okay. Good.

Thanks. So we've done two chemicals. We are at 11:43. So according to the agenda, we were supposed to do coal dust before lunch. I'm wondering if that's okay to do that. If the Committee would like to take a quick break, or break for lunch now, so three options. Let me ask, first, does anyone object to doing coal dust now and then breaking for lunch?

I see no objections, so let's go ahead with coal dust. I'm actually one of the lead discussants for this compound, this substance, so I'm going to go ahead and give my summary then.

So coal dust was reviewed by IARC in 1997. And at that time, it was put in Group 3 with inadequate evidence in humans and animals. So, you know, coal dust is an interesting substance. I'm going to focus on the epidemiologic studies, since that's my expertise.

It's been studied, exposures to coal -- of coal -- to coal dust have been studied quite a lot over a long time period, but mostly not with a focus on cancer. So it's relatively recently that cancer has become a topic of interest here.

Some older studies did report excess mortality from lung and stomach cancers among coal miners. But even in the more recent literature, most of the data available are on non-malignant respiratory disease and injuries not

surprisingly.

So now turning to recent studies, there are two large studies of occupational cohorts of coal miners in the U.S. and the United Kingdom that are notable, because they feature long-term follow-up and quantitative assessment of exposure to coal dust. But there's a complication here, in fact, through all of these studies, whether epidemiologic or toxicologic, and that is that coal dust isn't a pure substance. It tends to be mixed in reality with a smaller or larger amount of crystalline quartz, which is a Group 1 carcinogen that causes lung cancer.

So in both of these cohort studies, there were, in addition to their quantitative assessments of dust exposure, efforts to control for potential effects of the admixture of silica dust of quartz in the coal dust. In the U.S. study, the most recent analysis of that that reports data for lung cancer did show a statistically significant increase in lung cancer mortality with increasing dust exposure after controlling for silica.

So that is a exposure response trend. However, the UK study didn't find any notable excess of lung cancer or any trend, again after controlling for silica.

Those studies also looked at stomach cancer. In the U.S. study, the most recent publication didn't report

any data, but in the prior publication there was no notable excess of lung cancer and no trend, likewise in the UK study no notable excess and no trend.

Those studies, although they're quite large, didn't report data for other cancers. So for that, we have to look at case control studies. There are quite a number of those from different countries. I'll just highlight a few.

Case control study of lung cancer in Polish women only did find a significant excess of lung cancer with self-reported excess -- self-reported exposure to coal dust. A similar study in the U.S. that included men and women found a significant excess in men, but not in women.

A few other studies looked at coal dust exposure in connection with cancers of the larynx and pharynx. One notable study was a case control study in France that found a positive association with cancer of the larynx, and a stronger statistically significant association with cancer of the hypopharynx. Another large multi-center study of -- in Eastern Europe also found similar exposures that were positive and statistically significant.

Both of those studies were notable, because exposure was assessed by experts based on complete occupational questionnaires. So, the exposure data are a bit better than simple self-report. And earlier French

study also found an excess of combined cancer of the larynx and hypopharynx. And one other study in Serbia looked at cancer of the oropharynx, but found no association.

A few other cancers have been looked at in case control studies. I note significant excesses of multiple myeloma and acute myeloid leukemia in one study each.

I'll just briefly mention the studies in animals, but defer to the experts in that area. It looks like there has been, since the IARC evaluation, one long-term carcinogenicity bioassay, which found no lung tumors in animals treated with coal dust and none in the control group. Coal dust used in that experiment had a very low silica content of less than 0.1 percent.

The second animal study doesn't appear to be a true cancer bioassay and had kind of a strange design because the coal dust involved various mixtures of silica, and there was a significant difference in the incidence of lung tumors between the treated animals and the control animals, but it didn't seem to be related to the mixture of silica.

So moving on to the mechanistic data. Just really briefly, I didn't see any genotoxicity data in exposed humans, but there are positive findings of chromosome aberrations and sister chromatid exchanges in

human and mammalian cells in vitro and mixed findings in some mutagenicity studies involving other test systems.

I noted evidence of oxidative stress in exposed humans and increases in TNF alpha in bronchoalveolar lavage fluid from treated rats. So, for me, this one with kind of equivocal epidemiologic evidence and not compelling mechanistic evidence, and limited potential for exposure in California falls into the medium priority category.

Now, we can move to the second discussant, Dr. Landolph.

COMMITTEE MEMBER LANDOLPH: Thank you. Can you hear me okay?

COMMITTEE MEMBER LOOMIS: Yes.

COMMITTEE MEMBER LANDOLPH: Okay. Good. Thank you.

Yeah, it's interesting. I would have expected more than that for such a mixture of substances. I was thinking of benzpyrene when I looked at this, but I agree with your assessment of the epidemiological data. And the animal data is really somewhat sparse. There was that one table of data, Table 9, and it showed they just looked at the percent of animals with tumors. And it was benign, malignant and total. And they do have benign and malignant tumors. The highest goes up to 72.7 percent of

malignant tumors 66.7. The others go down from that towards zero eventually. So that is not a dose response or anything like that. And they didn't report the tumors, so they can't do good statistics on it. So it's really a -- I would say that's a positive. There's only like a one point set of data. It's not very good.

The other data, yes, it's genotoxic. It induces chromosomal aberrations and SCEs in human lymphocytes. It induces sister chromatid exchange in Chinese hamster ovary cells. If you nitrosate the extracts of this coal dust, then you get positive in three Ames strains. It induces oxidative stress. Long lives radicals in coal dust recovered from the coal miners' lungs and lymph nodes, which was interesting and they find higher 7-hydro-8-oxo-deoxyguanosine, so it's another marker of oxidative stress, as was previously mentioned.

And it induces chronic inflammation. They say it causes immortalization, but that's -- that's a misprint. It really induces they say cell transformation, which means a morphologic transformation, which is a surrogate for carcinogenesis in vitro.

So I would say, yeah, it's kind of medium to no. Probably medium, I guess. It's just a very sparse database and not that much has been done on it yet. I'd hate to see OEHHA go through and make a huge hazard ID

document on this with such a paucity of data. So I'm probably leaning toward probably no at this point.

Thank you.

COMMITTEE MEMBER LOOMIS: Other comments from the Committee. Dr. McDonald, are you trying to say something?

COMMITTEE MEMBER McDONALD: Yes. Thank you. The lead discussants, I didn't hear any discussion about exposure potential in California. I did see from the OEHHA document that there could be some occupational exposures from rail transport and shipping. I guess there's one coal plant in the state, but I'm not aware of any active coal mines. So did any of the lead discussants find much on exposure in California?

Thank you.

COMMITTEE MEMBER LOOMIS: I did not. I presume it's quite limited. And, of course, you know, the use of coal is declining, probably not fast enough.

Other comments from the Committee?

Dr. Mack.

CHAIRPERSON MACK: For the record, I actually -- just as I did last time, this stuff causes pulmonary infla -- pulmonary -- I'm sorry I'm blocking on the word -- inflammation and a bad disease. And the exposure is relatively small. So I actually think this one deserves low priority for formal evaluation. Of course, again, it

will have to be done sometime, but there's so many others with higher priority.

COMMITTEE MEMBER LOOMIS: Thank you for that, Dr. Mack.

Other comments.

All right. It looks like there are none. So let's proceed to poll the Committee on coal dust. We'll go in the same order.

Dr. La Merrill?

COMMITTEE MEMBER LA MERRILL: No.

COMMITTEE MEMBER LOOMIS: Dr. Crespi?

COMMITTEE MEMBER CRESPI: I'm also going to go with no.

COMMITTEE MEMBER LOOMIS: Dr. Bush?

COMMITTEE MEMBER BUSH: No.

COMMITTEE MEMBER LOOMIS: Dr. McDonald?

COMMITTEE MEMBER McDONALD: No.

COMMITTEE MEMBER LOOMIS: Dr. Stern?

COMMITTEE MEMBER STERN: No.

COMMITTEE MEMBER LOOMIS: Dr. Zhang?

COMMITTEE MEMBER ZHANG: No.

COMMITTEE MEMBER LOOMIS: Dr. Eastmond?

You're on mute.

Mute.

COMMITTEE MEMBER EASTMOND: I go with medium. I

Interesting. Although, I don't think there's too much data out there, but it will interesting.

COMMITTEE MEMBER LOOMIS: Dr. Landolph?

Can't hear you.

You're muted.

Still muted.

Can't hear you?

COMMITTEE MEMBER LANDOLPH: Medium.

COMMITTEE MEMBER LOOMIS: Medium.

Okay. Dr. Reynolds?

COMMITTEE MEMBER REYNOLDS: No.

COMMITTEE MEMBER LOOMIS: Dr. Mack, I think you already said no. Do you stay with that?

CHAIRPERSON MACK: Yes.

COMMITTEE MEMBER LOOMIS: Okay. And I was on medium. So I think the noes have it.

All right. We are caught up on the agenda, so I think this is a good place to stop for a lunch break. So let's reconvene at 1:00 o'clock.

(Off record: 11:57 a.m.)

(Thereupon a lunch break was taken.)

AFTERNOON SESSION

(On record: 1:01 p.m.)

COMMITTEE MEMBER LOOMIS: So let's go ahead then with the -- we reconvene the second part of the scientific discussion. Welcome back, everybody I had you had -- hope you had a good break.

Before we start with next the substance, I'll just remind the Committee that we have written comments on all of the substances on the schedule for this afternoon, which you may want to look at.

Having said that, let's go ahead with decaBDE. So for that -- Dr. Eastmond.

COMMITTEE MEMBER EASTMOND: I need to recuse myself from this particular chemical, because of a potential conflict of interest, so I'll be sitting in, but won't be making comments or voting.

COMMITTEE MEMBER LOOMIS: Okay. I won't call on you.

Any other business before we go ahead with this discussion?

Nope. Okay. So lead discussant, Dr. McDonald please go ahead.

COMMITTEE MEMBER McDONALD: Yeah. Thank you. Thank OEHHA for pulling together all of the papers and the nice discussion. I also want to thank the public

commenter for presenting written comments on decabromodiphenyl ether, which is a part of the class of the PBDEs, the polybrominated diphenyl ethers. This is the fully brominated version of that class.

It's a flame retardant used in plastics and high impact polystyrene, also in rubber. So it's in lots of electronics, textiles, building materials. It's found in human breast milk and blood as part of the California Biomonitoring Program. Detected in about up to 40 percent of people, depending on the study. Most cases the levels would be considered very low, in the low nanogram per gram lipid. But some populations, such as firefighters, have been shown to have somewhat higher concentrations up near a hundred nanogram per gram.

DecaBDE is found in house dust and in foods. So exposure is very low, but widespread, and it's likely decreasing over time. As you probably read, it's being phased -- it was phased out of production in the U.S. in 2013. There's still some TSCA reporting for current -- current years. Some public comments from the American Chemistry Council's North American Flame Retardant Alliance was kind enough to indicate that some of the releases out of 2018 were actually transfers to landfill.

And OEHHA was nice to provide us with a proposed rule from U.S. EPA in 2019 that's proposed a prohibition

of deca, except in some very critical products, such as aircraft, hospital curtains and plastics recycling. I'm not sure what the status of that proposal is.

This compound does breakdown in the environment to some of the lower brominated congeners of the PBDE class, but it's not clear what -- what percentage of the lower brominated are in -- are measured in people come from deca or come from use of other flame retardant mixtures. Half-life in people is about 15 days.

I won't focus too much on the epidemiology. I'll leave that to Dr. Stern, but there were three human studies. One on papillary thyroid cancer in some gene variants showed rela -- very high odds ratios. I would note in that case control study, it was -- exposure was based on house dust and blood-paired samples. But if you look at the distributions of those concentrations versus cases of controls, those distributions overlap quite significantly, so there was ability to compare high and low exposures, but they're not that far away from each other.

The same with the other hospital case control out of China, 14 PBDEs were measured. And I'll let Dr. Stern get into the details. But in that case as well, the blood levels of PBDEs among cases of controls, those distributions overlapped quite substantially.

With respect to animal carcinogenicity, just for completeness, I'd say that there's an early cancer bioassay that wasn't in the prioritization document back in 1975. Kociba dosed decaBDE up to just one mg per kg for two years, finding no tumors. This actually studies actually the basis of U.S. EPA's oral reference dose for this compound.

But as you'll see in the later NTP 1986 studies, the doses that were used there were over 2,000 times higher. So you can see why the Kociba study should be discounted.

There were four cancer studies of deca reported by the U.S. National Toxicology Program in 1986, one in male rats, and one in female rats, and then, of course, male and female mice. DecaPBDE is not acutely toxic and it's well tolerated to very high dose. And that's probably because only about one percent is actually believed to be absorbed according to the NTP in those studies.

The doses given to the animals in the -- in the NTP studies were extremely high in the male rats, for example up to 6,650 mg per kg, females 7,780 mg per kg. And then the -- excuse me that was mice. And then rats were 2,240 mg per kg and 2,500 mg per kg as the top dose. Those are very high, but -- and would kind of exceed EPA's

current carcinogenicity test guidance that indicates quote "The highest dose tested need not exceed 1,000 mg per kg per day", unquote.

By nonetheless, in the male rats, there was some hepatocellular adenomas, benign tumor, that was increased in the dose response fashion to both doses and by trend test, but there was no corresponding increase in carcinoma. There was also pancreatic and acinar cell adenomas also benign tumor in the high dose. Female rats survival was not appreciably different from controls.

Again, there were statistically dose-related increases of adenomas. There were two carcinomas in the mid-dose, but none in the high dose, and thus the malignant tumors did not show a dose-related trend.

In the male mice, survival of the males really was quite decreased early on in the control group due to fighting. But by the end, survival was pretty good and not statistically different from controls at the end.

There were increases of both benign and malignant tumors. However, the incidences only reached statistical significance in the mid-dose group for the hepatocellular adenomas and carcinomas combined. And benign, malignant -- and benign and malignant combined were only -- were not significant by trend test. There also was suggested increases of thyroid cell adenomas and

carcinomas combined with an incidence of 0 of 50 in the control group versus 4 of 50 and 3 of 50. Female mice showed no increases in cancer relative to controls.

With respect to other information, the lower brominated PBDEs, specifically the technical grade pentaPBDE mixture is on the Prop 65 list. As I said earlier, it's unclear if deca is metabolized to the same congeners in the PBDE product that was tested for carcinogenicity. And there's also some breakdown of deca in the environment to lower brominated species, but that's really not a basis for prioritization. The penta group -- the penta PBDE, the listed carcinogen also, it caused liver adenoma and carcinoma combined in both rats and mice in both sexes, as well as some thyroid adenoma and pituitary gland adenoma in the male rat.

Genetox, it's not mutagenic in bacteria and mammalian cells, but there is mixed results from mammalian cell clastogenetic -- clastogenic effects. But generally negative, but there are a few positive findings in there.

There's a number of studies on receptor mediated effects, such as PXR. Also, thyroid hormone disruption studies in mice at high doses. And then also some other receptor cell modifications with estradiol antagonistic effects.

Okay. So I'll leave it there. And I would say

overall I would characterize and prioritize this as medium.

COMMITTEE MEMBER LOOMIS: Okay. Thanks.

Dr. Stern, on to you.

COMMITTEE MEMBER STERN: Thank you for that introduction that provided all the background information. So I'm going to add that what struck me with this chemical is that the home environment is one of the main sources of exposure, mostly indoor dust. And that there's studies that have shown a good correlation between household dust and biomarkers of exposure in humans. So that means that the exposure is pretty ubiquitous.

At the same time, it means that the assessment in epidemiological studies is challenging, because of where you find this chemical and also because the short life is relatively short -- the half-life is relatively short.

What I want to emphasize is that some of the biological studies have highlighted that one of the potential mechanisms that -- the impact that it could have in humans is by disrupting thyroid hormones. And this seems to be one of the main concerns from a human perspective.

So as it has been mentioned, there's been four epidemiological studies that have been done, so the literature is very scarce in terms of the human effects.

Of these four studies that have been done since 2017, so the literature is pretty recent for these compounds, they're all case control studies. There are no cohort studies that have been done. One of the studies is population based and three are hospital based. Two of the studies are focused on thyroid cancer in the U.S., one on breast cancer in China and one on pediatric acute lymphoblastic leukemia in California.

Of the four studies, two reported positive associations. And I'll go into a bit more detail, one in thyroid cancer and one in breast. One reported an unexpected inverse association and the other a nul association. And so the data is fairly limited.

And part of -- I think part of the concern is the exposure assessment. So some of the studies use household dust and some of the studies look at serum -- serum detection of this compound.

So as mentioned before, there's one study that show a positive association. This was a study done in North Carolina looking at papillary thyroid cancer. And they used both. They used household dust and they used serum measurements. Now, they did not detect the BDE-209 compound in the serum, so they did not provide data for association with the serum sample, but they did provide data for the household dust sample. And they found a

significant positive association showing that individuals who had high levels of exposure had almost two times -- more than two times the risk of developing papillary thyroid cancer.

The downside is that this was a fairly small study. There were 70 cases and 70 controls. They did some subanalysis looking at specific mutation in the tumors and they found that the association was higher -- was stronger among those that did not have a mutation in the BRAF gene.

So the other positive study was in breast cancer. As mentioned before, this was done in China. This was a larger study with 209 cases. This was a hospital-based study. And here what they did is they measured adipose tissue. So in the cases, mostly it was breast tissue. And in the controls, it was a mixture of breast and abdomen tissue. And they found that there was good correlation in other studies between the abdomen -- the amount present in abdomen fat tissue and breast.

Here they did see a dose response, between -- across different tertiles for exposure and with a significant trend. And then they did analysis adjusting for other BDEs and they -- the positive trend remained. So -- so this study is supportive of an effect or there's an association between this compound and cancer risk.

The other good thing about this study is that they use adipose tissue, which is able to capture a longer period of exposure than the serum samples or the dust.

Now, there were two other studies, one in thyroid cancer done here in the U.S. in Connecticut that did not find a positive association. What they mention in that study -- this study did not look at dust samples. They look at serum measurements. And one of the things that the authors mention is that because of this short half-life of the compound, the serum measurements are done at one point in time and they'll be sufficient to capture the exposure.

The other thing they noted is that among the participants, which were all women, in Connecticut, the levels were significantly lower than the rest of the country. And they did not have a fairly wide range of exposure, so that may explain why they were unable to find an association. The study done in California for pediatric ALL did use household dust samples. And this study was negative.

So what I found compelling about this compound is that -- particularly the biological effects on the thyroid hormones is because we do see rising rates of thyroid cancer here in California. That was among females, which started going up in the 2000 and have pretty much peaked

around 2011. In California, as a whole, they have stayed the same. But if you look at data for the Bay Area, the rates keep going up. So the finding of that one study on thyroid cancer I thought was intriguing. However, there are no other studies, so the evidence is limited for humans.

Now, as mentioned before, the animal evidence seems -- is also limited. Mostly suggestive of a potential effect in hepatocellular adenomas. There's no animal studies that support that rule for thyroid. There's just a few studies. What drew my attention was that in looking at the mechanistic evidence, there is -- there are some studies that support that this compound may modulate effects via the thyroid hormone. So that goes along the lines with the epidemiological study found.

So overall, I think based on the limited evidence for humans and the limited but suggestive evidence for the mechanistic studies on animal studies, I would say that the priority is medium for this compound.

COMMITTEE MEMBER LOOMIS: Well, thanks for that. This is Dana Loomis. I'll back. I don't know if anyone noticed, but I disappeared. But the power went out where I am. And so I'm just on the phone right now and I can't see any of you. So not being able to see, I won't know if anyone raises their hand to comment. So I think what I'll

doing is just go down the list.

I'll call on each of you in turn --

DIRECTOR ZEISE: Dana.

COMMITTEE MEMBER LOOMIS: Yes.

DIRECTOR ZEISE: Hi, Dana.

COMMITTEE MEMBER LOOMIS: Yes.

DIRECTOR ZEISE: Hello, Dana. This is Lauren Zeise. I'd be happy to assist you letting you know whose hands are up --

COMMITTEE MEMBER LOOMIS: Great. That would be perfect.

DIRECTOR ZEISE: -- if you'd like.

COMMITTEE MEMBER LOOMIS: So is anyone's hand up?

DIRECTOR ZEISE: I don't see anyone's hand right now.

Okay. Joe Landolph.

COMMITTEE MEMBER LANDOLPH: Yeah, there you go. Okay. Can you hear me now?

COMMITTEE MEMBER McDONALD: (Hand raised.)

COMMITTEE MEMBER LOOMIS: Yes.

COMMITTEE MEMBER LANDOLPH: Yeah. Okay. This sounds pretty similar to TCDD. It binds to the AH receptor. It's not really very genotoxic. Maybe a little bit of oxygen radicals produced. I agree with Mariana. I would mechanistically put it in the TCDD-like class and

give it a medium priority. I think that's a reasonable thing to do for this compound.

DIRECTOR ZEISE: Okay. Dana, Dr. Mack's hand is up.

COMMITTEE MEMBER LOOMIS: Okay. Dr. Mack, please go ahead.

DIRECTOR ZEISE: Dr. Mack, you need -- could you please turn on your speaker?

CHAIRPERSON MACK: How's that. I'll go along with medium also. But with thyroid cancer, you would have to worry about the effect of ultrasound examinations in doctors' offices, as a lot of evidence with the increasing risk in California, as well as in Korea and Japan is due to the high prevalence of doctor's examinations, finding very small tumors that are unlikely to actually progress. But given the evidence and given the interaction with genetics, I'll go for medium also.

DIRECTOR ZEISE: Okay.

COMMITTEE MEMBER LOOMIS: Thank you.

So anyone else?

DIRECTOR ZEISE: I don't see any other hands, Dana.

COMMITTEE MEMBER LOOMIS: Okay. I also would put it in medium. Now, I found the human evidence less than compelling, but exposure is widespread. And, you know, I

noted also their structural similarity to several other carcinogens, which elevates it for me.

As far as I know, we don't have anyone from the public who's requested to speak, but perhaps Clara could verify that.

MS. ROBINSON: That is correct. At this time, there are no hand raised. But just a quick reminder, if you would like to make a public comment, please go ahead and raise your hand at this point.

And there are still no hands raised at this point, Dr. Loomis.

COMMITTEE MEMBER LOOMIS: Okay. Good. So we'll just go down the list then and complete the roll call. I know some of you have already spoken, but I may have missed part of it. So I'll just call on everyone.

Dr. Bush, where do you put it?

COMMITTEE MEMBER BUSH: Medium.

COMMITTEE MEMBER LOOMIS: Okay.

Dr. Crespi?

COMMITTEE MEMBER CRESPI: Medium.

COMMITTEE MEMBER LOOMIS: Okay.

Dr. Eastmond?

COMMITTEE MEMBER EASTMOND: I've recuse myself.

COMMITTEE MEMBER LOOMIS: That's right. Forgot. Thank you.

Dr. La Merrill?
COMMITTEE MEMBER LA MERRILL: Medium.
COMMITTEE MEMBER LOOMIS: Dr. Landolph?
COMMITTEE MEMBER LANDOLPH: Medium.
COMMITTEE MEMBER LOOMIS: I said medium.
Dr. Mack?
CHAIRPERSON MACK: Medium.
COMMITTEE MEMBER LOOMIS: He said Medium. Okay.
Dr. McDonald?
COMMITTEE MEMBER McDONALD: Medium.
COMMITTEE MEMBER LOOMIS: All right.
Dr. Reynolds?
COMMITTEE MEMBER REYNOLDS: Medium.
COMMITTEE MEMBER LOOMIS: Dr. Stern, I think you said medium. Are you still there?
COMMITTEE MEMBER STERN: Medium. Yeah, medium.
COMMITTEE MEMBER LOOMIS: Okay.
And Dr. Zhang?
COMMITTEE MEMBER ZHANG: Medium.
COMMITTEE MEMBER LOOMIS: Okay. Very good. I think we have consensus on medium.
So let's move on down to methyl bromide. The lead discussants are Dr. Eastmond and Dr. Reynolds.
So, Dr. Eastmond, let's go ahead with you.
COMMITTEE MEMBER EASTMOND: Okay. Thank you. I

didn't realize OEHHA had summarized things for us, so I went through and did my own summaries, so this is pretty independent evaluation.

The first thing I'd indicate that methyl bromide was a fumigant was used pretty extensively in California, but was phased out -- began to be phased out in 2005 I believe because of concern about ozone depletion. It was allowed with exceptional authorizations, but I believe those have also been phased out in California, so its use is probably very little or none at all.

It is a moderate to highly toxic chemical. It's an alkylating agent, methylating agent. And it's structurally similar to bromoethane, and possibly other haloalkane carcinogens.

As far as genotoxicity and mutagenicity, it's pretty consistently positive. In in vitro studies it causes DNA binding, DNA adducts, mutations in bacteria, and different types of damage in mammalian cells.

It becomes -- when you go In vivo, it's not nearly as clear cut. There is DNA binding that's been seeing adduct formation. However, there was not an increase in mutation seen in transgenic mice assays, which is one would have expected. It's kind of unusual. It's shown some mixed results in the NTP studies. The short-term studies show positives. But the longer term

studies, no increase was seen for both micronuclei and sister chromatid exchanges.

And there was one study, in which a non-significant increase in HPRT variance and oral micronuclei was seen in one small human study, but did not achieve statistical significance.

Things become much more cloudy when we get to the animal studies. There are -- first of all, let me -- well, let me -- there are two quality rat studies and two quality mouse studies. It was negative at all sites in the male -- male and female mice studies.

It was negative at all sites in the two female rat studies, negative at all sites in one male rat study, and positive for pituitary gland adenomas but negative at all other sites in the other study.

Now, that's -- those -- the one study wasn't in the materials that was given to us, but it was outlined in the IARC evaluation that took place in, I believe, 1999. Let me respond. In the document we received, they highlight some -- a report from Danse et al. in 1984, in which increases in forestomach tumors were reported in a 90-day study. High incidence, these are like 60 and 70 percent of the animals were reported to have forestomach tumors.

This would be very unusual, because it was only a

90-day study. And we all know tumors generally take a long time to develop. This was questioned. The pathologist from the National Toxicology Program went out, reevaluated the slides, and concluded these with hyperplasias. So in my mind, both biologically it doesn't make any sense, and the follow-up study indicated that that study is not really credible. And there was a follow-up study that went for about a year and didn't see any tumors in the forestomach. They didn't see hyperplasias on oral administration.

The other studies were inhalation studies. So in general, the animal studies are largely negative and considered that way.

The human epidemiology, Dr. Reynolds will probably do a better job of this than I. But let me start with -- since she actually did some of these studies, I understand. But I'll give you my sort of summary.

There are two studies of childhood cancers Dr. Reynolds was involved in. One of them is an ecologic study, one of them is a case control study. Both did not see any increases in combined childhood cancers, Leukemia or brain cancer. There are other reports of sort of increases. Most of these are not statistically significant or they don't have dose responses or other things in testicular cancer, gastric cancer, breast

cancer, renal cancer. And I can go through them if you'd like in more detail. The one that's particularly interesting -- or most interesting is the prostate cancer.

The initial results from an Agricultural Health Study, which reported a significant increase in exposure related associations between methyl bromide exposure and prostate cancer. However -- and that was followed up by some other studies from Mills and Yang that saw a modest increase, particularly -- although these again are sort of not statistically significant, but suggestive of trend, I believe. And there was an increase seen by Cockburn et al. and saw a significant increase, but there was no -- the trend was not significant.

The Agricultural Health Study and the follow-up, which was published in 2012 by Barry et al., the original association between methyl bromide and prostate cancer did not persist in the follow-up study, so it was -- they did not see sort of a significant trend there.

There was a study which was done by a group called Budnik et al., and they looked at a meta-analysis of the three earlier positive studies, and they reported a meta-odds ratio of 1.2, which was not quite statistically significant, a P value of 0.076. But since the one study would be replaced by the more recent Barry study, it's likely that association would undoubtedly be weakened.

I guess, so -- you know, overall my assessment of that, I put this as a medium concern. It's clearly mechanistically of a concern, because the alkylating properties in the adducts. But the animal studies certainly don't seem to be very strong and the human studies are mixed suggestive, but I don't think any of them in and of themselves are particularly strong either. But I'll look for Peggy to kind of correct me on the epi studies.

Thanks.

COMMITTEE MEMBER LOOMIS: Okay. Thanks, Dr. Eastmond. So let's go on to Dr. Reynolds then for her comment.

COMMITTEE MEMBER REYNOLDS: Okay. Thank you. You did most of my work for me by going through the epi studies. And I appreciate that. I'll try and be brief. My view of the epi literature is there's really two main sources of epi evidence for cancer risk associated with methyl bromide, the federally-sponsored multi-agency very large Agricultural Health Study, which is something that was initiated back in 1993 with follow-ups through 2015, and then several studies from California spanning the '90s up until just 2019, that you have gone through in some detail.

So Dr. Crespi did a lovely job of telling us some

detail about the Agricultural Health Study. Just briefly, it was a large carefully designed prospective cohort study, which is considered to be one of the great advantages for epidemiologic studies.

It was a cohort study of farmers and pesticide applicators and their spouses in both Iowa and North Carolina. And although pesticide use was initially based on questionnaires, the cohort members were actually selected based on applications for restricted-use pesticides in each of those states, and given their occupations, are likely to have been able to fairly well report their use of these -- of this particular pesticide, not to mention all of the other ones that were studied.

So with nearly 90,000 participants, active follow-up through 2015, extensive covariate information, and several intermediate nested studies, the AHS has been a really valuable source of information for many pesticide-associated health risks.

For methyl bromide, they reported significantly elevated cancer risk for two cancers, as I think you mentioned, stomach cancer with evidence of dose response with a relative risk of 3 for the highest quartile, but based only on 15 exposed cases, and prostate cancer in the highest categories of use, which were based on six and five cases respectively in the fourth and fifth quartiles

of use, and evidence of dose response.

They looked, but did not find, higher cancer incidence for several other cancers including kidney, NHL, leukemia, Hodgkin's Lymphoma, oral cavity, rectum, lung, bladder or melanoma, nor in fact for prostate cancer in the follow-up study. Although, they did report suggestively elevated risk among those with a family history of prostate cancer.

Analyses of cancers among the spouses, which is an interesting group did not report specifically on methyl bromide, although they did find elevated breast cancers with chlorpyrifos, which we already talked about.

So there were these small nested case control studies in the Central Valley. A couple of the UFW farm workers cohorts, which found no cancer associations for methyl bromide use on prostate cancer, but a suggestive elevation for stomach cancer at the highest level.

And then you mentioned some of the geographic information studies. These were based on California's very unique Pesticide Use Reporting system and residential patterns in California. And these studies found very mixed results for people living in areas of high methyl bromide use. So they found a higher incidence of prostate cancer for residents at diagnosis. I think this was the Cockburn study, and no elevation in breast cancer risk.

And as you mentioned my own studies of childhood cancer using the PUR database found no elevation associated with maternal residence at birth or the child's residence at diagnosis. So, in general, human health studies have had the opportunity to study risk in cohorts within areas of high agricultural pesticide use, but with mixed results, due in part probably to small sample sizes, as is the case for the UFW studies or indirect measurements is the case for population studies using those indirect exposure estimates based on nearby pesticide use.

So I think the most robust evidence really does come from the large Agricultural Health Study. Granted, as the exponent reviewers pointed out in public commentary, the relatively small proportion of applicators reporting methyl bromide use, which was just under 15 percent, and the small number of specific cancers of interest, could result in what they refer to as sparse data bias. But there -- and in addition there are always problems of multiple testing in these kinds of studies. And the Agricultural Health Study looked at many cancers and many pesticides over time.

There does remain nonetheless some evidence for elevated risk of specific cancers among pesticide applicators. And those are the kind of people for whom

exposures may still persist under the EPA critical uses criteria.

So while there's some human health evidence for cancer risk, hopefully the phase-out in 2016 and continuation of that from the Montreal Protocol and the Clean Air Act will result in future declining population exposures for Californians. And I would agree with you, I would classify this as medium for CIC review. I was going to say medium to low, but we don't have low anymore. So I'll go with medium.

Thank you.

COMMITTEE MEMBER LOOMIS: Okay. Thanks a lot. Now, Lauren, if you can help me identify anybody else from the Committee who'd like to speak now.

DIRECTOR ZEISE: Yes. Dr. La Merrill.

COMMITTEE MEMBER LA MERRILL: Yeah. I just wanted to point out that when I looked for tissue-specific mechanisms based on the AHS evidence, I did find that there was on DNA adducts found in stomachs - I believe it was rats - methylguanine, but I haven't see anything for the prostate that's been evaluated positive or negative mechanistically.

COMMITTEE MEMBER LOOMIS: Thanks.

Anyone else?

DIRECTOR ZEISE: Tom McDonald. Dr. McDonald.

COMMITTEE MEMBER McDONALD: Yeah. I just had a question for Dr. Eastmond. I noticed in the methyl bromide industry panel comments, there was another set of bioassays that were done about the ministry -- a Japanese Ministry of Labor in 1992 that were also negative. Were those summarized in your analysis?

COMMITTEE MEMBER EASTMOND: They were. I didn't have access to those actual studies, but they're summarized in the IARC evaluation. So they are the ones which were negative. It was an inhalation study in mice and they were both negative in male and female mice. In the rats, they were -- the females were negative, the males were negative except for an increase in basically pituitary glad adenomas.

And so I think the idea was because there was a similar study done out of a Dutch health ministry in rats and that didn't see an increase. So you've got two high quality inhalation rat studies, one saw an increase, the other didn't, so they tended down, dismiss those results. But there was -- and IARC reported an increase in one of the tumor sites.

COMMITTEE MEMBER McDONALD: Thank you.

COMMITTEE MEMBER LOOMIS: Anyone else?

DIRECTOR ZEISE: Dr. Stern.

COMMITTEE MEMBER STERN: I just wanted to add two

comments that caught my attention when we reviewing the epidemiological in case they are helpful.

I was puzzled by the finding from the Agricultural Health Study for prostate cancer, because they had a decent size in their 2003 study, where they found dose response with a positive significant trend. And then with they added more -- more men to their study with their -- the Barry 2012 study, then the study was null. It was nothing.

So I -- you know, that kind of caught my attention. But then I look at the comments that were offered by the investigators. And one hypothesis that they suggest was that the men that were added -- the new cases that were added in the newer study had less -- had used less of the methyl bromide, because it was starting to being phased out or for some other reason. So they speculate that perhaps with the addition of the new cases, there could have been kind of a dilution effect of the association, because these men were not as exposed as the previous study with the men that were diagnosed earlier in the cohort. So I just wanted to add that comment.

And the other comment is that the positive study by Cockburn, which was done using the GIS database that Dr. Reynolds explained, they did find a positive association when using residential exposure, but then they

also did a cell analysis where they look at the exposure at the address of where the men were living when they were diagnosed, because some of them may have moved after diagnosis. And when they did that did, they did find a dose response with a significant trend.

So I agree with Dr. Reynolds that there's some challenge with these type of assessment is not as accurate as what the Agricultural Health Study uses. But I just wanted to add that comment that it's a little bit of, you know, concern about the potential effect on prostate.

COMMITTEE MEMBER LOOMIS: Thank you.

Anyone else?

DIRECTOR ZEISE: Dr. Landolph.

Hi. Your mic is not on, Dr. Landolph.

COMMITTEE MEMBER LANDOLPH: Okay. Yeah. I think -- yeah, there's some epi data here. There's far less animal data, but not that many tests have been done. There a reasonable amount of genetox data. And I have to point out that carcinogenesis, if you look at the slopes in the dose response curves, it spans them full. So this might fall toward the weaker end. I think we need more data on it, but I'd be comfortable with a medium at this point, mainly because they're an alkylating agent and there are two alkylating agents on there already.

COMMITTEE MEMBER LOOMIS: Other comments?

DIRECTOR ZEISE: No other -- oh, Dr. Reynolds.

COMMITTEE MEMBER REYNOLDS: Oh, never mind. I was just going to comment in that there was an indication that Dr. Sandy might have wanted to make a comment in response to my comment about declining exposure.

DR. SANDY: Sure. Thank you very much. This is Dr. Sandy. Just a really quick -- just to follow up on what Dr. Reynolds had said about exposure as was discussed in the summary. The critical uses exemption and the quarantine and pre-shipment uses are still operative right now. So for the most recent use -- year of use 2017, we have data suggesting 1.8 million pounds were used in California for pre-planting soil fumigation, and post-harvest fumigation of commodities, and for treatment of certain plants and trees.

Thank you.

COMMITTEE MEMBER LOOMIS: Thanks for that information. That's very helpful. I just have a brief comment. I largely find the epidemiologic evidence inadequate with just one indication of positive association of stomach cancer in the AHS and one or two positive associations with prostate cancer, depending on how you interpret the change in the results of the AHS. The animal data appeared inadequate to me too.

So in spite of the agent being genotoxic, I would

have put it in low priority, if we had low priority. So I guess at the moment, I'll probably stay with medium.

So would any other members of the Committee would like to speak before we check on public comments?

Sounds like there's no one.

So if that's correct, I understand that there is one member of the public whose asked to speak. Clara, if you could verify that and allow that person to speak, if they're there --

MS. ROBINSON: Absolutely.

COMMITTEE MEMBER LOOMIS: -- that would be great.

MS. ROBINSON: Yes. We have a Tracy Heinzman, who has their hand raised. So Tracy, I'm going to go ahead and unmute you from my end. You are -- there you go. Go ahead Tracy.

MS. HEINZMAN: Hi.

COMMITTEE MEMBER LOOMIS: Let me remind you -- before you start -- sorry -- let me remind you that your comment is limited to five minutes.

MS. HEINZMAN: Yes. Thank you, Dr. Loomis. Understood.

My name is Tracy Heinzman. I'm the Executive Director of the Methyl Bromide Industry Panel. We submitted public comments, which it appears that several of the Committee members have reviewed. I just want to

make a couple of points given the discussion.

I do want to make it clear that in terms of exposure, the critical use exemptions, they were eliminated or basically phased out in 2015. The last year that the United States applied for critical use exemptions through the Environmental Protection Agency and the State Department was 2015. They have not solicited any critical use exemption request from the applicator or user community since then and there is no indication that they would start those again.

The only uses which continue are, what we call, quarantine and pre-shipment uses, which were allowed under the protocol. The vast majority of those uses are in post-harvest fumigation in industrial settings, primarily in ports when commodities are coming in or they're being exported out. There's a very limited pre-plant soil quarantine use for nursery stock. And that is primarily concentrated in Siskiyou County in California where strawberry nursery plants are grown in greenhouses.

The -- I do note that from Dr. Sun's earlier presentation in her chart, when you look at the exposure column, it's -- she indicates that, you know, occupational exposure it says very limited and that there is really no general public, consumer, residential type exposure at this point, given the limited uses of the chemical.

The other -- you know, we would recommend that this have no priority. We understand that there -- you know, there is some concerns or some points were made about animal data here and also about the epi studies. But there is one important point I wanted to make that was not included in any of the discussion, including the OEHHA document, is -- and that is the Environmental Protection Agency's Office of Pesticide Programs, which is recognized as an authoritative body for purposes of the -- OEHHA's 2004 policy on prioritization.

And methyl bromide was evaluated for registration review. It had a complete human health risk assessment done in December of 2018. And then in September of this year, the EPA put out its -- what it's called its interim decision on registration review.

In both the risk assessment and in the recent September document, EPA concluded it was not likely to be carcinogenic based on the long-term in vivo studies that Dr. Eastmond mentioned. And also EPA's review included review of epidemiological data. There were 44 studies that were reviewed. Some of them are part of the analysis that was done by the OEHHA staff and EPA found that those studies were not -- did not show us a sufficient association to change its view that there was no evidence that methyl bromide causes cancer.

So I just wanted to point that that, because in the 2004 policy document, it does make a comment that when there is a recently reviewed determination by an authoritative body, and that body finds insufficient evidence of carcinogenicity, the document does say it's unlikely that a chemical in that category would be proposed for the CIC review.

So I don't know if it was so new that the staff wasn't aware of it and it may be didn't show up in some of the other reviews that were done, but I wanted to point that out.

And then my only last comment would be that I appre -- we do appreciate the opportunity to submit our written comments and we're glad that the panel reviewed them. And also, we would like to thank you for your service on the Committee. You know, it is time-consuming, and we appreciate that you are devoting your time to this, and that you all have the highest credentials for reviewing toxicology and epidemiology data.

And with that, I will take any other questions that anybody might have. I do believe that this is a chemical that has very low exposure potential.

COMMITTEE MEMBER LOOMIS: I'm sorry your time is up.

MS. HEINZMAN: Okay. Thank you.

COMMITTEE MEMBER LOOMIS: Okay. Thanks. Thanks for your comment.

Is there any other public comment?

MS. ROBINSON: There is no other public comment at this time.

COMMITTEE MEMBER LOOMIS: Okay.

DR. SANDY: Dr. Loomis.

DIRECTOR ZEISE: Sorry for interrupting, Martha Sandy is available to make a comment on --

COMMITTEE MEMBER LOOMIS: Yeah, I was going to ask if she wanted to address that.

DR. SANDY: Yes, thank you.

The U.S. EPA's document review of methyl bromide, there are actually two documents, one is proposed and one is draft. And so for authoritative bodies, we are looking for final documents from authoritative bodies.

COMMITTEE MEMBER LOOMIS: Okay. Thanks for that clarification. So we have time for more discussion by the Committee. And again, Lauren, if you can help me identify if anybody would like to speak, that would be appreciated.

DIRECTOR ZEISE: Okay. Sure. Dr. Eastmond's hand is up.

COMMITTEE MEMBER EASTMOND: I have a question --

COMMITTEE MEMBER LOOMIS: Go ahead, please.

COMMITTEE MEMBER EASTMOND: -- what we addressed

to Martha Sandy -- Dr. Sandy. It seems to me that was helpful to know how the OEHHA dealt with sort of authoritative body determinations from EPA. Let's say that the Committee goes forward and gives this some ranking, either medium, or high, or whatever. If the EPA finalizes their document subsequently, would you use that information to revise your priority or would you just go forward on strictly what the Committee has recommended?

DR. SANDY: We do take into account new information as it becomes available on chemicals, even after they've been -- after we've consulted with you and they've been ranked.

COMMITTEE MEMBER LOOMIS: Okay. Thanks.

Other comments from the Committee, further discussion?

DIRECTOR ZEISE: Not seeing any raised hands.

COMMITTEE MEMBER LOOMIS: All right. Let's go ahead and poll the Committee then, if there's no further discussion.

Dr. Bush?

COMMITTEE MEMBER BUSH: Thank you. Medium.

COMMITTEE MEMBER McDONALD: Medium -- medium to low. Medium

COMMITTEE MEMBER LOOMIS: Sorry, who was the second speaker there. I'm sorry, I can't see you.

COMMITTEE MEMBER EASTMOND: That was Dr. Mack.
DIRECTOR ZEISE: Dr. Mack.
COMMITTEE MEMBER LOOMIS: Okay. Mack. Okay. So medium, medium
Dr. Crespi?
COMMITTEE MEMBER CRESPI: Medium.
COMMITTEE MEMBER LOOMIS: Medium.
Dr. Eastmond?
COMMITTEE MEMBER EASTMOND: Medium.
COMMITTEE MEMBER LOOMIS: Dr. La Merrill?
COMMITTEE MEMBER LA MERRILL: Medium.
COMMITTEE MEMBER LOOMIS: Dr. Landolph?
COMMITTEE MEMBER LANDOLPH: Medium.
COMMITTEE MEMBER LOOMIS: All right. Dr. McDonald?
COMMITTEE MEMBER McDONALD: Medium.
COMMITTEE MEMBER LOOMIS: Thank you.
Dr. Reynolds?
COMMITTEE MEMBER REYNOLDS: Medium.
COMMITTEE MEMBER LOOMIS: Dr. Stern?
COMMITTEE MEMBER STERN: Medium.
COMMITTEE MEMBER LOOMIS: Dr. Zhang?
COMMITTEE MEMBER ZHANG: Medium.
COMMITTEE MEMBER LOOMIS: And I said medium.
So that finishes that compound.

I see we've been going for about an hour. We have two substances left plus some remaining business, which looks like it would not take very much time.

I'm wondering if this would be a good time to take a short break, before we finish up the rest of the business. Would anyone object to taking about a five-minute break?

DIRECTOR ZEISE: We're seeing thumbs up across the Committee.

COMMITTEE MEMBER LOOMIS: Okay. And with luck, maybe the power will come back on here, but I'm not counting on it. We're having a bit of a storm up here. So we'll come back at about 2:03.

Thank you.

(Off record: 1:58 p.m.)

(Thereupon a recess was taken.)

(On record: 2:05 p.m.)

COMMITTEE MEMBER LOOMIS: Maybe we could go ahead with the first discussant for PFOS and it's Dr. Stern. So if you would please go ahead and give us your summary comments on PFOS.

COMMITTEE MEMBER STERN: Sure. I'll go ahead. So just a bit of background, PFOS are industrial -- are present in industrial and household products, including firefighting foams, stain or water resistant coatings for

cookware, fabrics, leather, food packaging and paper products.

These type of chemicals are extensively used as processing aids in the manufacture of fluoropolymers to produce items such as non-stick surfaces and the other compounds that I just -- the other products that I just mentioned, so they're present in many things that we are exposed on a daily basis.

In the U.S., produce was phased in early 2000, but they're still made elsewhere in the world. And with import of products, that means that we're continue -- we continue to be exposed.

There is also production still of chemicals that can be transformed or degraded to release PFOS. One of them is a ethylperfluorooctane sulfonamide acetic acid, which I will refer to a EtFOSAA, which is a biological metabolite of the raw material EtFOSE, which is used in the manufacture of packaging and paper products.

This compound is a precursor that eventually leads to PFOS, which PFOS itself is highly stable. So it's a persistent product that is not further metabolized. There's also another compound called PF -- PFOSA, which is used to repel grease and water for packing along with other applications. And this one can breakdown to PFOS.

So the routes of exposure are several. It can be

inhaled, it can enter through mouth, it can enter through dermal absorption. It is readily absorbed into other organisms, so it's present in fish and other foods, as well as drinking water.

Studies in different places including L.A. County have found that it's detectable in human specimens. The half-life in humans has been estimated between four to five years and in water it can be more than 92 years.

In terms of the biological effects, I will not go into detail. I will let my colleague Dr. Zhang summarize that evidence, but I just want to highlight a few things.

One is that PFOS are members of the PFAS family, which are environmental endocrine disruptive chemicals, which means that they can alter normal patterns of tissue organization and interfere with stromal-epithelial interactions. There's a whole host of potential biological effects that can be induced by these type of chemicals.

It seems that for PFOS the main target might be the liver, based on animal studies, where it can alter metabolic processes including a reduction or alterations of cholesterol levels. The other studies that have shown that it can be linked to mammary carcinogenesis.

So I will focus mostly on the epidemiological evidence. So there were a total of 90 studies that were

provided to us by OEHHA. So thank you for those materials, and these included studies that cover about nine different cancer types. And I will give you more details.

Now, two of the studies actually reported on patients that had been included in a prior study, so there were actually 17 unique studies that we can comment on.

The studies including both case control studies that were nested in prospective cohorts, as well as regular case control studies, and a few cross-sectional studies. There were three cohorts that contributed data. One is an occupational cohort in Alabama that contributed data to -- for several cancers. Then there's also the Danish birth cohort and the Child Health and Developmental Studies Pregnancy cohort that contributed data for breast.

So overall, the big picture for the epidemiological evidence is that two of the 17 studies show evidence of positive associations between PFOS and breast cancer. And I'll give you a bit more detail about that. There were five studies of the 17 that show some suggestive evidence with findings that were either only significant among some subgroups or they were not significant for PFOS, but they were significant for the precursors.

There were five studies that showed evidence of

positive associations, but they were not significant, and four studies that showed no evidence of association and one study that actually showed an inverse association. That was significant. All studies except one use blood measurements of PFOS over the precursors, and the Alabama occupational cohort used job descriptions.

So I will focus mostly on the breast cancer studies for which there were some significant findings. There were seven studies that look at breast cancer. One is a nested case control study that was done in France. And it was done in a cohort of women involved in education, called the E3N cohort of about a hundred thousand women. And when they look at all the cases, include all the tumor types combined, they do see -- they did see some evidence of significant associations that were only significant for one of the quartiles, but not dose response trends.

However, when they divided the women based on the estrogen receptor status. They found that among women who that estrogen receptive positive tumors, there were significant associations and they saw significant trends. Similar for women that had positive progesterone receptor status.

The numbers for estrogen receptor negative and progesterone negative tumors were very small, so the

confidence intervals were very wide. So I think those data were very unreliable.

The other study was a study done in Greenland among Inuit participants. And one of them -- the motivations to do the study is because of the high exposure based on high intake of marine mammals, which are -- may have high concentrations of PFOS. So in this study, they did see dose response with significant associations with the highest tertile with an odds ratio of five. Most of the women in this study were post-menopausal.

So those were the two positive studies. Then there were four additional studies on breast, one case control and three nested case control studies that did not really find strong evidence for an association with PFOS itself, but they did find when they did subgroups. For example, one case control study done in Taiwan found positive associations when taking into account age at diagnosis, but not really when looking at all women combined.

Then there was another study that was done as a nested case control study within a pregnancy cohort. And here what they did is they looked at the daughters of the women that were in the cohort, so these are fairly young diagnosis. And what they did here is they did not really

find associations with PFOS. They didn't report data for PFOS alone. They look at it in combination with interactions with cholesterol. They didn't see any evidence of association with PFOS, regardless of cholesterol levels, but they did see a positive association with the precursor EtFOSAA when cholesterol was high, but not when cholesterol was low.

So another study that was done also show a similar pattern. This was a nested case control study in the Danish birth cohort. They didn't see much evidence or association with PFOS, but they did see association with PFOSA, which is a precursor. And then finally, there was another study where that follow-up on that study where they look at some interactions with metabolism enzymes and they found some evidence of interaction for PFOSA and for PFOS with two metabolic enzymes, but so not really supporting association with the compound itself, but supporting that there could be some Susceptibility in the population.

Finally, the Alabama occupational cohort did look at breast cancer and they did find elevated standardized mortality ratios for breast cancer, but there were only two -- two individuals that were diagnosed in the cohort. So very -- very, very wide confidence interval for that.

So in conclusion for breast, there's some

suggestive evidence that there might be associations, but only among estrogen receptor or progesterone receptor positive cases and some positive associations mostly with the precursors but not with PFOS itself.

There were some additional studies -- two additional studies in bladder. One was a case cohort study, the other one was a cohort study with the Alabama cohort. No real evidence of association there.

For prostate cancer, the Denmark cohort, they did a case cohort study and they did find elevated odds ratios, but no real evidence of dose response.

And then finally there were study on pancreas cancer that didn't find any association.

Liver cancer the same. There were only two studies. One was from the Denmark cohort, one from the Alabama. The Alabama cohort, again they found some evidence of elevated mortality ratios, but there were only two deaths reported of liver cancer in the cohort. So very, very low power to be detect a significant increase.

There were multiple other cancers that were examined in the Alabama cohort, like esophagus and melanoma, both of which they found elevated mortality ratios, but again very wide confidence intervals because of very small numbers.

As I mentioned, there was one study done in

cross-section -- it was a cross-sectional study that reported inverse associations with colorectal cancer. And they couldn't quite explain these. And there was another cross-sectional study done in Greece that did not find evidence of association.

So pretty much the available evidence seems to support some potential effect for breast cancer, potentially estrogen receptor and progesterone receptor -- tumors and no real evidence for other cancers.

So I won't go into the details of the animal studies. I will let Dr. Zhang do that. However, just briefly, there's some evidence of association with mostly adenomas, but not carcinomas, no studies that support an association with breast. Only one -- only four studies were reported, one actually considered PFOS as a promoter and not as an initiation agent.

In terms of genotoxicity of the 18 studies that I read in the documents, only 11 were positive. There's some evidence that it may induce epigenetic alteration, some evidence of oxidative stress. So that's some supportive evidence that it may have carcinogen activity.

The intriguing part is that there are 10 studies that support some -- 10 studies that investigated whether it could modulate receptor-mediated effects. And seven of those studies were positive and they showed data that is

consistent with mechanism through the estrogen and the androgen pathways, which is compatible and consistent with the findings from the epidemiological literature.

There are also three studies that support effects on proliferation and anti-apoptotic activity. Some studies support chronic inflammation and two studies that support it may have immortalization effects.

So overall, my reading of the evidence is that the mechanistic effects are consistent with alterations of estrogen and androgen pathways with some carcinogenic processes. The epidemiological evidence has two studies that support a possible association with breast cancer, particularly estrogen -- positive estrogen receptor, positive cancer and progester -- progesterone re -- positive cancers, and very limited and weaker evidence for prostate.

So based on all these my -- I'm kind of in between a medium and a high. I think based on the evidence, it feels like more of a medium to me. But because there is still potential exposure through imported goods and because of the potential role it my have on disrupting estrogen, and androgen pathways, and the evidence for breast cancer, I think I'm going to start with a high and I'm going to welcome comments from the panel before I make my final -- my final vote.

And I want to stop here.

COMMITTEE MEMBER LOOMIS: Thank you very much. Okay. Thanks. Thanks a lot.

Dr. Zhang, you're the next discussant.

COMMITTEE MEMBER ZHANG: Yes.

COMMITTEE MEMBER LOOMIS: It looks like you're on mute.

COMMITTEE MEMBER ZHANG: Hi. Can you hear me?

COMMITTEE MEMBER LOOMIS: Yeah.

COMMITTEE MEMBER ZHANG: Okay. Good.

Yes. I want to thank you, Dr. Stern and give us a pretty good re -- overview on the epi study and the general exposure as well.

And so I think one thing I wanted to just put here, because this -- we're actually reviewing not just one chemical, not just the PFOS, but also including PFOS -- the salts of the PFOS, you know, for example PFOSA and the other types. So this is one. And also including some precursors. You know some chemicals can, you know -- being metabolized too the P -- PFOS. And also PFOS is a major chemical in this PFAS. This is much bigger, you know, including maybe thousands of different PFAS family. But I think PFOS is actually major one -- one of the major PFOA and the PFOS, it's two major ones in the PFAS family. I just want to put this ahead.

And also, I'd like to thank OEHHA staff to actually put this review together. And one other thing is all the other exposure on PFOS is from I believe it's from NHANES study that have -- see widespread exposure. And also, the PFOS has been detected in 98 percent of blood sample screened, so that's exposure right there.

And from what Dr. Stern already reviewed in human studies to me looks like the breast cancer incidence related with PFOS exposure it seems more stand up than other type of cancers.

So my review is going to be majorly focused on animal carcinogenicity data and the findings and the potential mechanisms. So this is a two part.

For the animal cancer incidence studies, so they have long term, that's including two years, exposure or I would say medium or shorter term is only like about one year, 52. So -- and I think -- I mostly agreed with what OEHHA staff documents have been pulled together.

So to me, the increase -- the incidence of liver adenoma in rats is -- has been, you know, tested and reported in quite a few different studies. And the -- the P value is, you know, about 0.01 or 0.05.

So -- and -- so the liver adenoma in comparison with other type of cancer, such as -- also, we see the increase -- is it, by the way, I just want to put it here,

my power in the house is shaking. My light is turning on and off, okay, just in case if I'm off. I'm just trying -- I have no idea why I think its -- it's the weather here. So my lights is on and off.

Let me back to the animal data. So for the thyroid follicular cell adenoma, also they did see some increase the incidence on that, but mostly at the highest dose tested. That's -- oh, second highest dose tested, and -- but not at the highest dose somehow. So overall, for the thyroid adenoma didn't see the -- you know, it's not statistically significant.

But for the short-term studies, the one-year study and the data see thyroid follicular cell adenoma in male rats, you know, but that's only what they see. They had only at the highest dose, 20 ppm PFOS.

So anyway, overall, I see the animal studies still kind of limited, but the data showing clearly the liver adenomas seems -- it's pretty real. And another in vitro -- oh, no, that's a study on the tumor promotion study in the rainbow trout, also whether they have using -- using the -- using the 10 ppm, aflatoxin B1 as an initiator and then treat the trout for six months at the -- you know, for the 100 ppm, it's pretty high PFOS. But what they didn't see is the increase -- increase the liver cancer in the trout, so -- and that's very

significant.

So it looks like what they're showing is a PFOS in that system is acting as a tumor promoter. But if there is no initiator they didn't see increase the liver cancer. So that's what I see -- I sort of see the animal data looks like.

So the next I would like to focus on the potential mechanism. So here, OEHHA has used the key characteristics approach, which was, you know, promoted by Smith 2016 paper. So, so far, it's about four or five year, this approach has been use -- applied by IARC and also some NTP and EPA studies as well.

So I -- what I'm just trying to -- here to look at what the -- what the -- what so far the PFOS cases reviewed by OEHHA is it looks like it had 8 out of the 10 key characteristics of carcinogens it seems reported some kind of studies or positive or potentially positive.

So that's 10 of them, except the KC1 and 3, that's -- so I would go into a little bit detail of them just telling you how I am trying to analyze the data.

So first, see that OEHHA data, but also for the -- using the KC approach, the Environmental Working Group has also reviewed PFAS, including PFOS and other PFAS chemicals. And they look at the each KCs from 1 to 10. So basically trying to compare not just taking the

OEHHA documents, but -- but also looking at the Environmental Working Group's report and then having -- I have analyzed -- I have also analyzed the -- particularly on the two immunotoxicity KCs, that's including KC6, KC7 as chronic inflammation and immunosuppression, so -- and using the knowledge we have. So this is basically the approach I'm trying to pull ahead. How do I analyze this potential mechanism data.

So in general, there are, I think, four KCs has a little discrepancy between different -- different reports or different reviews, my personal opinions.

First is the KC2, genotoxicity. Looks like there are some studies we forwarded positive findings in micronuclei induction and DNA strand breaks by comet and also some mutations. And so that's -- that's what -- what we see.

But, to me, the data is still pretty weak and the Environmental Working Group actually concluded this genotoxicity is actually null. No genotoxicity. My -- in my opinion would be either weak or weak genotoxic -- genotoxicants. So that's a -- that's for the KC2.

For the KC 4 epigenetics, there is some strongly suggestive studies. So this KC4 actually I think both OEHHA and Environmental Working Group had put in as suggestive positive. And they base it on, you know, kind

of a global hypomethylation using line 1 and some specific gene methylations. But I still think -- I would still think the -- even though the epigenetic has been reviewed all in human studies, animal studies and in vitro study, I still think we need more data to really describe detail of how PFOS can, you know, generate the epigenetic effect.

So KC9 immortalization, this is only looks like very limited studies. And there's two reviewed by OEHHA, but Environmental Working Group actually thought it's not sufficient. So I'm just trying to put this discrepancy mechanism first. And KC 10 cell growth and the death is -- most of the studies it looks very positive. But the only problem is all -- almost in in vitro studies. So that's no in vivo studies to support.

So now, what we have now is a major or strong KCs, so that's a KCs 5 to 8. And in two of the KC actually is basically -- is a no -- no data at all or very limited data. That's KC1 and 3, so we don't have to talk about.

So the oxidative stress, that's a -- that's a KC 5 and it looks like very strong evidence in multiple studies. And or -- crossing all three systems in human study, animal studies and in vitro has been seen the reactive oxidate -- oxidative species increase and lipid peroxidation increase the 8-hydroxyguanosine and also

gluta -- gluta -- glutathione and glutathione peroxidase, you know, the glutathione depletion.

So oxidative stress I think that also could be a way we -- for us to -- for -- you know, to see some weak genotoxicity could also caused by oxidative stress. But, to me, the PFOS itself it may not be a very strong genotoxicant. It could -- you know, after we have more data we -- I think the ep -- though an epigenetic mechanism could be stronger than the genotoxic mechanism. So that's one point I want to put in there.

The second is I also want to make sure here we -- I have independently reviewed the NTP 2016, the report on immunotoxicity and which include inflammation and immunosuppression of the PFOA and PFOA -- PFOS. So -- so -- and also, recently, we have using -- we have systematically reviewed these two immunotoxicity involved KCs in benzene, you know, and benzene induced the cancers. And also, we currently review the PFAS, including PFOS. So -- and I just look at a little bit more details about where PFOS, and the PFOS salts, and other related chemicals can cause immunotoxicity. So, to me, actually, I think the measure and also pretty strong mechanism is through the immunotoxic mechanism.

So what -- what are we seeing is increase the cytokine productions, or cytokine activities, ex --

especially in the interleukin 6 and also the pro-inflammatory cytokine the, TNF alpha. I mean, this is the two major ones, because that's already reported by multiple different studies.

But of course, they are many other cytokines -- increase cytokine production mechanism interleukin 1 alpha, interleukin 1 beta, and interleukin 8 or 10, et cetera. So that's to me is enough to see PFOS related or induce the chronic inflammation.

For the immunosuppression KC 7, what actually most the data showing is a decrease that natural killer cells in multiple studies and also across most three -- you know, in vitro and in vivo as well. So here, not only natural killer cells decrease, but also other type of white blood cells, particularly CD 4, CD 8, T-cells, and interferon gamma, et cetera. And so that's -- that's why I actually think PFOS induced the immunotoxicity could be a major one as well.

The last I think it's also the most important is the KC 8 is the receptor-mediated effect. If we -- if you remember what Dr. Stern also summarized from the human study, you know, for the breast cancer, and, you know, potential estrogen kind of related cancers, so from this specific key characteristics, what do they have -- whatever reported is PPAR-alpha, PPAR-gamma, all the --

and ER, AR and other type of receptors that all see they are related with PFOS exposure.

And particularly again, this receptor-involved effect has been seen again in the human exposed studies, animal, in vivo and in vitro studies. But, of course, there are still a couple of negative studies, but I see the most evidence is still in the positive studies.

So here really make me really thinking is PFOS -- if PFOS may act as the estrogen disruptor chemicals. So I think it may -- you know, Michele -- Michele La Merrill could, you know, tell us even more since that's her field.

But again, I'm not -- I don't remember if Dr. Stern mentioned this, but I think this is -- Celik studies involved in the estrogen metabolized genes. They also see some of the, you know, polymorphous associations. So that's all chemical supportive.

So overall, in summary, I think based on the data reviewed so far, the breast cancer incidence are -- associated with the exposure in humans and the liver adenoma incidence in rats, and I would say strong evidence in the key characteristics, 5 to 8, that's including oxidative stress, immunotoxicity, and the receptor-mediated effect in PPAR, et cetera.

I would recommend the PFOS and its related chemicals to be high prioritized.

Thank you.

COMMITTEE MEMBER LOOMIS: Okay. Thank you very much. Let's see if there are comments from the rest of the committee.

Dr. La Merrill, I see your hand.

COMMITTEE MEMBER LA MERRILL: Hi. Yeah. So to address what Professor Zhang just said, you know, my take on the estrogen receptor data is that it's kind of mixed. It's difficult to understand exactly what's going on without reading the papers in depth to understand what were the differences, because it wasn't always the same reaction that there were a few -- two null studies saying that ER activity was not modulated by PFOS. One was in -- one supposedly looked at several human cell lines and one was at yeast-two hybrid assay. But then there was a couple that did. Obviously, selective estrogen receptor modulation is real, because we talk about that with the chemotherapy tamoxifen.

And so, you know, there could be some contextual biologically plausible explanations for those differences. And I would really kind of need to look at it more carefully. But certainly in combination with all of the breast cancer studies, it kind of raises my eyebrows so to speak in terms of being interested in looking at the full data more in depth across the different study types.

And Professor Stern, I actually had a question for you -- or maybe a couple. I noticed when I looked through the epi that it was the birth cohort in particular where they did not find P-F-O-S, PFOS, significant, but in both of those birth cohorts they instead named the upstream precursor. And one it was PFOSA and the other one it was EtFOSA. And I was just wondering if that was your impression and kind of what was your take? Like, do you think there's anything significant about that? I thought it was interesting that those were the only 2 birth studies, in that the PFOS was not significantly -- wasn't positively associated, excuse me, not insignificant.

And the other question I had for you was the Taiwan Hospital study. Because I know there was a lot of subgroup analyses and the Taiwan one was looking saying PFOS was positively associated with breast cancer in young women 50 years and younger. And I was just wondering was that the nature of their study design or did they have older women as well and just kind of arbitrarily used that division rather than, for example, menopause status?

COMMITTEE MEMBER STERN: Yeah. To answer that last question first and then I'll go to the birth cohort study. So I don't know -- I don't recall the motivation for why they stratified by age and not just menopausal

status. I noticed that 46 percent of the participants were menopausal -- post-menopausal women.

So they had half and half of the women were pre- and post-menopausal. But you're correct, when they -- when they look at all the women combined, they don't see evidence of association with PFOS, but when they stratify based on age, they notice that there was a positive association among the younger women, those diagnosed before age 50.

And then they did an additional subanalysis combining the age with the estrogen receptor status, and they found that among women that had estrogen-receptor positive tumors and were younger than 50, then it was a positive association that was not observed among the other comparison groups.

But the rationale for why they stratified by young diagnosis, I don't recall -- I don't remember if they mentioned something. I do remember that they mentioned some concern about increasing rates of breast cancer in Taiwan. So maybe they are seeing higher rates with potentially some increasing numbers of younger diagnosis. And maybe that's why they wanted to do that. I would have to pull the paper and look at it again.

And then your second comment was for the birth cohort, the Danish birth cohort. And, yes, you are

correct they did not see an association with PFOS, but they did -- they saw an association with PFOSA, which is considered to be a precursor, with an association with the highest quintile.

Let me see what else. In this -- in this particular cohort, most of the women that were studied, were premenopausal. Was that the study you referred to?

COMMITTEE MEMBER LA MERRILL: Yeah. I just -- it was that one and CHDS. I was just curious, you know, if anybody in general thought that there might be a reason why the precursor -- I just thought it was strange that the only studies that had precursors that were significant were the two birth cohorts. If we -- can't

COMMITTEE MEMBER STERN: Yeah, so there was a study -- or, sorry. Go ahead.

COMMITTEE MEMBER LA MERRILL: That's okay.

COMMITTEE MEMBER STERN: I was going to offer an explanation, but go ahead follow-up on your thought, and then I'll answer that.

COMMITTEE MEMBER LA MERRILL: No. No. No. It's fine. I just -- you know, it could be due to chance. It's not a large N of a cluster. It's -- I just thought well is this something we need to consider?

COMMITTEE MEMBER STERN: One of the studies, because I think there's several studies that were done

with -- so they're independent studies, not all done with the same cohort. There are a few independent studies that have the same pattern, no association with PFOS, but association with the precursors. So one of the studies which was the pregnancy cohort done in California, which look at the daughters of the women involved in the cohort, they offer a potential explanation. You, know in none of the studies I saw that they could understand why they see the association with the precursor but not with the actual compound.

But one explanation that they offer is that maybe there's faster metabolism of the -- of the PFOS and that's why it's -- it's harder to detect it, but maybe the precursor that has a different metabolism and maybe that's why it's easier to detect it, and that's why we tend to see the positive association.

But I was curious the to the fact that there are several studies that have that finding of not having an association with PFOS, but having an association with a precursor.

COMMITTEE MEMBER LA MERRILL: And I'm saying, just to clarify it, all of the experimental work was done with PFOS not the precursors, correct, all the cases? It seemed like it was all PFOS when I looked.

COMMITTEE MEMBER STERN: I think so. I'm going

to let Dr. Zhang confirm.

COMMITTEE MEMBER ZHANG: Yes.

COMMITTEE MEMBER STERN: My understanding is, yeah, they all look at -- at least the ones that we were provided, they all were based on PFOS and not the precursors.

COMMITTEE MEMBER ZHANG: Yeah.

COMMITTEE MEMBER STERN: One thing I want to mention that was not part of the materials that we were given, but this is something that I found that was interesting is that there is some growing literature showing that PFOS may -- or PFOS in general -- or perhaps PFOS, they may have a relationship with nonalcoholic fatty liver disease, which as we know is a precursor of liver cancer. So this is something to consider that might be interesting to look at in more detail if we move forward with evaluation of this carcinogen later on, because of the rising trends of liver cancer among Hispanics here in California and the relationship with nonalcoholic fatty liver disease.

COMMITTEE MEMBER LOOMIS: Okay. Let's take a note of that and see whether any other members of the Committee have preliminary comments. Anything to add?

Not seeing any hands raised at this point.

I believe we have one person who's asked to make

a public comment. So, Clara, if you could allow that, please.

MS. ROBINSON: Absolutely. It looks like we have Steve Risotto with his hand raised. And, Steve, I've unmuted you, so go ahead.

MR. RISOTTO: All right. Thank you very much. Can you hear me okay?

MS. ROBINSON: We can.

MR. RISOTTO: Okay. Awesome.

Good afternoon, Dr. Loomis and Committee members. I'm Steve Risotto, and I am a Senior Director at the American Chemistry Council. I'm here to comment on the Committee's consideration of Perfluorooctane sulfonate, or PFOS.

ACC has submitted written comments and I'd like to briefly summarize those comments for you now. For starters, PFOS does not appear to meet the screening criteria for consideration by the Committee laid out by OEHHA staff this morning.

Referring to the information in Table 2 of page six of the prioritization document prepared by the staff, we note that there is only one animal cancer bioassay available for PFOS. And the results of that study do not report evidence for tumors at multiple sites associated with PFOS exposure.

In addition, OEHHA staff have provided minimal evidence of tumor promotion for PFOS. And finally, PFOS is not structurally similar to any chemicals that have been identified as carcinogens under Prop 65.

In response to Dr. Sun's earlier remarks perfluorooctanoic acid, or PFOA, has not been identified as a carcinogen under Prop 65. And a look at the structure of tetrafluoroethylene and the fact that it is readily metabolized reveals little similarity to PFOS.

As noted in the staff summary, the epidemiological evidence for PFOS is generally negative. However, recent case control studies have suggested an association with hormone receptor status among women with breast cancer in France and Taiwan. In both cases, the association with estrogen receptor -- was with estrogen receptor positive tumors, the most commonly diagnosed tumor type, while the association of overall breast cancer incidents was less clear.

Both studies were based on a single blood sample, which in the case of the study among French women may have been taken several years before diagnosis and the concentrations reported very significantly between the two studies.

In addition, while the increase was observed among older women in the French study, there was no

similarly observed increase among women over 50 years old in the study in Taiwan.

Regarding the single cancer bioassay in rats, the reported increase in liver adenomas and carcinomas was accompanied by an increase in the incidence of the liver cell necrosis and hypertrophy similar to that reported in short-term studies of PFOS.

As a result, the authors concluded that the liver effects were consistent with activation by nuclear receptor for PPAR-alpha and CAR PXR and that the available data do not provide support for cancer risk for an exposure to PFOS.

The other tumor types reported in the bioassay a lack dose response and had a comparable incidence across dose groups, including among the control animals.

Based on negative results of a large series of in vitro and in vivo short-term tests of genes, chromosomes or DNA repair, PFOS and its salts are not considered to be genotoxic. However, the prioritization document provides information on studies examining the effects of PFOS on six other characteristics that have been associated with carcinogenic potential.

While the application of these characteristics may be useful for identifying and organizing relevant data, it is critical that they be combined with an

understanding of the plausibility and causal linkages of the key events and biological responses involved in carcinogenicity -- carcinogenesis.

Without a critical evaluation and integration of the mechanistic evidence, application of the identified characteristics is of limited potential, limited value in supporting the scientific defense of a conclusion of carcinogenic potential.

Given the limited animal and human evidence and the uncertainty about the significance of mechanistic information, ACC recommends that PFOS remain a medium priority for consideration as a Proposition 65 carcinogen.

Thank you, and I'd be happy to answer any questions.

COMMITTEE MEMBER LOOMIS: Thank you for that comment and for staying within your time limit.

Let's go back to the Committee now and see if there's any further discussion on PFOS. I see several hands. Let's go to Dr. McDonald who hasn't spoken yet.

COMMITTEE MEMBER McDONALD: Yeah. I just wanted to make a point that, you know, the nature of PFOS is -- in the body is very, very long lived. And so a single measurement can serve as an integrated measure of years of exposure. So I just wanted to add that point.

COMMITTEE MEMBER LOOMIS: Okay. Thanks. I saw

Dr. Zhang had her hand up again. Go ahead, please.

COMMITTEE MEMBER ZHANG: Yes. I support what Tom McDonald just said. And not only PFOS has a long half-life time and also is not only persistent in the body, it's also persistent in the environment as well.

One other comment I may want to ask OEHHA staff, I -- somehow I heard from Dr. Sun is PFOA -- P-F-O-A, PFOA has already been listed as a high priority. Is that -- is that the case? Because PFOA and PFOS is the two measured compounds in the PFOS. So I just want to make sure, is that -- is that true, PFOA has already been listed as a high priority, and, if yes, when? That's just my question.

COMMITTEE MEMBER LOOMIS: You're on mute.

DR. SUN: Sorry. Yeah, to answer your question, Dr. Zhang, PFOA is currently a high priority chemical and we can look up the year that it was ranked by your Committee and get back to you. But currently it's high.

COMMITTEE MEMBER LOOMIS: Okay. Other comments?

Dr. La Merrill.

COMMITTEE MEMBER LA MERRILL: Yeah. I just want to briefly point out that PPAR-alpha is found and modulated in its activity when it's the human form as well as the mouse form by PFOS. That's been published. And so there has been some -- I think earlier on in the

literature there was some questioning on whether or not the peroxisom proliferation was relevant to humans by the PFOA and PFOS. And I think that with PFOA, which is very chemically similar, they have found that you get a very similar profile, even when you use a humanized PPAR-alpha in a mouse. And it's been shown that PFOS can bind the humanized one, so to take note of that.

And also although there was a number of subgroup analyses that kind of dampened my enthusiasm about the breast cancer in humans somewhat, I will -- I would like to point out that people in the breast cancer community really feel that each of the breast cancer subtypes are really distinct diseases. So to look at ER positive and PR positive breast cancer as a -- as a subgroup, I think is -- is like saying that in contrast we should just combine all hematopoietic cancers. And we know that's not appropriate either. And so I do feel that that wasn't kind of overly cherry-picking in that context.

COMMITTEE MEMBER LOOMIS: Okay. Thanks. I'm going to add a comment myself. You know, I was also struck by the epidemiologic data. And while acknowledging that there are a number of puzzling findings and -- that some of the results come from subgroup analysis, you know, having looked at a lot of putative endocrine disruptors with an eye to these endocrine-related tumors, we don't

often see this kind of vindication of an association. So although I still wouldn't call this sufficient evidence of carcinogenicity, I do think it's -- it is kind of compelling.

Go ahead, Mariana.

COMMITTEE MEMBER STERN: Oh, sorry. I didn't hear you.

I just want to add one comment in response to the comment from the public comments that we heard regarding the epidemiological study from the cohort study which is, in my view, is I think the strongest evidence that we have from all the epidemiological studies that we were. That we reviewed.

This is the France study which is a nested case control study in a cohort. This is a large cohort of a hundred thousand women. And in the public comment we heard concern about the fact that the measurement was done years before the cancer developed, but I want to highlight that from my perspective that's the strength of this data, because typically we want to measure the exposure before the disease developed, so that we can eliminate any potential concern about reverse causation bias. So I think that adds strength to the study that the samples were obtained before the women were on -- went on to develop breast cancer, which we know may take many years

to develop. So I just wanted to add that perspective to the study.

And I agree with -- with the comment made by Dr. La Merrill that I think looking at epidemiological studies of breast cancer, looking at associations, stratifying by estrogen or progesterone receptor is pretty much expected. We always do that, because we do consider that the risk factors can be different for these two subtypes of diseases.

COMMITTEE MEMBER LOOMIS: Thanks. That's a very good comment about the exposure assessment. I had the same observation and I agree with it.

Let's see, Dr. Zhang another quick comment.

COMMITTEE MEMBER ZHANG: Sorry. Yeah. A quick comment. Also, I think the breast cancer studies, Dr. Stern, you know, reminds us. But also I see -- I see the -- generally, for the stratified exposure different category and they see kind of a P trend, positive P trend, you know, in this epi of human studies. It's difficult, but I think you'll hear for the breast cancer they -- a couple of the studies they did show the significant P trend. I think that's also convince -- and make me convinced that, you know, the -- the cancer incidence related with exposure is right there. Just want to make that point.

COMMITTEE MEMBER LOOMIS: Thank you. Let's see if there's any more discussion from the Committee before we go around and take a vote.

I'm not seeing any other hands.

So unless anybody wants to jump in really quickly, let's go ahead in the order in which I see you on the screen.

Dr. Bush?

COMMITTEE MEMBER BUSH: I'm going to say high.

COMMITTEE MEMBER LOOMIS: Dr. Eastmond?

COMMITTEE MEMBER EASTMOND: I'll probably go with medium to high, so put me at medium.

COMMITTEE MEMBER LOOMIS: Medium you say?

COMMITTEE MEMBER EASTMOND: (Nods head.)

COMMITTEE MEMBER LOOMIS: Dr. La Merrill?

COMMITTEE MEMBER LA MERRILL: High.

COMMITTEE MEMBER LOOMIS: Dr. Reynolds?

Can't hear you, Dr. Reynolds

COMMITTEE MEMBER REYNOLDS: Oh, high. I didn't hear you.

COMMITTEE MEMBER LOOMIS: Okay. Dr. Stern?

COMMITTEE MEMBER STERN: High.

COMMITTEE MEMBER LOOMIS: High.

Dr. Zhang?

COMMITTEE MEMBER ZHANG: High.

COMMITTEE MEMBER LOOMIS: High.

Dr. Crespi?

COMMITTEE MEMBER CRESPI: Voting for high.

COMMITTEE MEMBER LOOMIS: Dr. Landolph?

COMMITTEE MEMBER LANDOLPH: Medium. Medium.

COMMITTEE MEMBER LOOMIS: Dr. Mack?

Dr. Mack?

CHAIRPERSON MACK: High.

COMMITTEE MEMBER LOOMIS: High. Okay. I heard that.

And Dr. McDonald?

COMMITTEE MEMBER McDONALD: Medium.

COMMITTEE MEMBER LOOMIS: Medium.

Okay. And so I think we go to high.

Let's see, we've been going an hour on that compound and I'm still without power here, so I'm going to have to change back to my phone. So I'll suggest another five-minute break, so let's reconvene at about seven minutes after 3:00.

(Off record: 3:02 p.m.)

(Thereupon a recess was taken.)

(On record: 3:07 p.m.)

COMMITTEE MEMBER LOOMIS: Okay. So let's go ahead with the last substance then. That is trifluralin. And Dr. Bush is the first discussant.

COMMITTEE MEMBER BUSH: All right. Thank you. Good afternoon, colleagues. I'd say last, but not least, right? It's been a interesting afternoon.

I do want to thank OEHHA staff for providing the brief and other review materials. And thank you to the public commentary from the Gowan Company. I have read your 12-page comment document and have factored that into my wing of the evidence of trifluralin.

So I'll briefly discuss the major contributing factors to my deliberation of the toxicological and the mechanistic data and I'll leave the details of the epi data to be explained by Dr. Loomis. But, in summary, I found the collective epi data to be limited.

So some quick background. As the brief indicated, usage in California is about 347,000 pounds as reported in 2017 by DPR. Nationwide, the available data is around 14 million pounds, but that -- the data that I could see was last reported around 2001, so presumably it's more than that at this point. So that makes trifluralin one of the most widely used herbicides in the country.

And now trifluralin, like other members of the dinitroanilines is an antimitotic compound that affects presumably microtubule depolymerization, thus interfering with mitosis, particularly in the meristematic regions of

plant roots, since it's generally applied to the soil.

We know that, as a consequence, mitotic spindle doesn't form, that causes misalignment, chromosome segregation artifacts, and potential some non-disjunctions.

As a class, the dinitroanilines have different affinities to tubulin proteins. Of course, the basic component of cellular microtubule networks for those in the audience. Dinitroanilines, like trifluralin, generally have high affinity for plant tubulin. But I'm going to remind people that tubulins are one of the most conserved proteins across eukaryotic cells and that includes animal cells and human cells.

Considering the putative chemical degradation of trifluralin, you can see that it promotes dealkylation of the amino group. This herbicide tends to receive two oxygens -- excuse me electrons. So a suggestion of some electrophilicity. We know that that, of course, increases the toxicity. And this facilitates this compound to bind with the polar groups, particularly of cellular membranes.

So there's some alternative mechanisms suggested that trifluralin may interfere with the permeability - excuse me - of plasma and mitochondrial membranes. This can change the quantity of particularly calcium flow within the cytoplasm. And it's been noted in the

literature that trifluralin action can alter calcium-dependent biochemical and physiological processes.

Furthermore, biodegradation derivatives like anilines and halogens from this group are known to induce meta-hemoglobin formation and thus also be toxic to kidneys and liver, either in vitro or in vivo. And this is -- you know, that possibly contributes to the fact that trifluralin is known to be acutely toxic in fish.

So moving on into the animal carcinogenicity bioassays, basically, the brief provided us with a total of seven studies, four in rat and three in mice. Two of the initial long-term studies from the late '70s I'm not going to use in my calculus, because of potential contamination of the trifluralin with carcinogenic NDPA, which is presumably an off-reaction that occurs in this class of chemicals during synthesis. So that effectively gives us five animal studies.

I'll briefly go through them. The -- there was a 1966 study evaluated by the U.S. EPA in 1986 on Sprague-Dawley rats. There was effectively no treatment-related tumor findings, but the highest concentration in that feed study was around 2,000 ppm. That was followed up in 1980 by studies on 344 rats, so that's a two-year study. That showed some statistically significant high dose response at 6,500 ppm within the

feed. That led to some increases in urinary tract and combined thyroid tumors in males and urinary bladder tumors in females.

Now, some of this information is disputed by the public comments and it was speculated in the U.S. EPA report that those tumors that we're seeing are a result of non-target organ effect, but I didn't see any data to directly support that -- that conclusion.

Moving on. In '87, there was then a 28-month study in Wistar rats that identified that identified some benign brain and liver tumors. But this was suggested to be related to age and not due to treatment.

And then there are two mice studies. Another one in 1980 that showed effectively no treatment-related findings in either sex and then a different strain of mice in '87 with NMRI mice. There was no treatment-related findings in female mice, but some liver and lung tumors by pairwise comparisons with the control, but no statistically significant trend in dose response in the males.

So taking that information, I would say that the data is limited for the animal studies and suggests to me, you know, a low to medium priority.

But delving into the key characteristics of carcinogens, it gets interesting. The data is mixed

again. But unlike the public comments from Gowan, I largely see a positive association with genotoxic, genomic instability. That includes some chromosomal abnormalities, potential DNA damage in human and other mammalian cells. That would fit with the mechanism of interfering with the mitotic spindle.

In general, mutagenicity is negative, and it -- particularly in bacteria. You wouldn't expect that since we don't really have -- don't really have conventional tubulin, thus this wouldn't be a target for them.

There's some recent published studies demonstrating positive correlations with altered DNA repair and induction of reactive oxygen species, again in both human and rodent cell models. And that suggests then mechanistically that there is something going on, at least in my reading of the data.

So mechanistically, we know that there's some modulation of various hormone receptors, both in vivo, and in over 10 percent of the 883 ToxCast assays. That included responses from estrogen receptor, pregnane X receptor, thyroid hormone. And that's particularly disconcerting towards the dysfunction in key pro-growth signaling cascades. And that may validate some of the carcinogenic effects we're seeing in some of the animal studies.

OEHHA staff identified trifluralin positive in 4 out of the 10 key characteristics of carcinogens from table 2 in the brief that they gave us. I'd argue that the degradation pathways kind of bring in a potential fifth characteristic of electrophilic nature.

So when I take this information and consider that, along with the structural similarities to other dinitroanilines that have been listed as carcinogenic under Prop 65, in particular, oryzalin. If you look at the structure of oryzalin and trifluralin basically overlap them, taking those into consideration, the evidence becomes a lot more compelling, even without considering the limited epi data.

So considering the available data in the context of the key characteristics of carcinogens. And I'm going to get on a soap box just a little bit. Those key characteristics carcinogens as unified in Smith et al. in 2016 and adopted by IARC. There's two concepts that come to mind and I'll quote from the paper directly.

First, the description by Hanahan and Weinberg of hallmarks of cancer is predicated not on morphology or the impact of carcinogens, but on changes in gene expression and cell signaling.

Secondly, in 2012, participants at the two workshops -- and some of the committee may have been

there. Participants at the two workshops convened by IARC in France extensively debated the mechanism by which agents, identified as human carcinogens, produce cancer, that is the Group 1 carcinogens. They concluded that these carcinogens frequently exhibit greater than one of the 10 key characteristics. To me, trifluralin is exhibiting at least five of these characteristics.

Now, integrating the streams of evidence using the IARC model, I see trifluralin as probably carcinogenic to humans, and thus, I would rank it as a high priority.

Thank you.

COMMITTEE MEMBER LOOMIS: Okay. Thank you for that summary. That's very helpful.

I won't -- I don't have very much to add. I'm the second discussant. I don't have very much to add to my colleague's summary of the key characteristics, except to say I was at those meetings and I think, you know, that concept of the key characteristics of carcinogens has been really useful for IARC and now I'm happy to see it applied elsewhere.

And I also noted those characteristics in my review, but I'm going to focus on the epidemiologic data, which is spotty. Essentially, we have information on a lot of different cancers from the Agricultural Health Study, as I count them, five different case control

studies of different adult cancers in the U.S., midwest. A case control study by Dr. Reynolds of childhood cancer in California and another study of ovarian cancer in Italy.

So we have data on about a dozen different cancers, but there are only a few for which data has been reported in more than one study, so I'll highlight those.

Non-Hodgkin lymphoma was increased in men who ever use trifluralin in two case control studies in the U.S. midwest but not associated with increasing the lifetime exposure to trifluralin in the Agricultural Health Study. All types of leukemia combined, which we've already discussed not really the way we like to do things any more, but that's the way it was reported in many studies, not associated with any measure of exposure to trifluralin. But in the childhood cancer study in California, acute lymphocytic leukemia was elevated, but not statistically significant in high-use areas.

Brain cancer was associated with every use of trifluralin in a study of adult male farmers in the U.S. midwest, but the authors noted that that association was primarily in subjects who are -- who's information was obtained in interviews with proxies rather than with the subject himself. Brain cancer wasn't associated with trifluralin in the childhood cancer study.

So there's data for a number of other cancers, cancer of the stomach, esophagus, and colon, rectum and so on, but those findings were reported in one study each, most of those in the cohort analysis of the Agricultural Health Study and those findings are basically unremarkable.

So we have, in essence, rather sparse data that doesn't demonstrate, as I see it, any consistent association with cancer at any site in exposure to trifluralin. So exposure response data are available only from the Agricultural Health Study and the Childhood Cancer Study. And the only significant trend was observed for colon cancer in the Agricultural Health Study, but that wasn't -- that cancer wasn't studied in any other case control study or cohort study.

So the data are, I would say, on the border between inadequate and limited in consideration of the animal and mechanistic data. I also was on the point somewhere between medium and low priority. After hearing Dr. Bush's summary, I think I would move up to medium.

Now, let's see whether there are any comments from other members of the Committee, if someone could again help me and identify anyone who wants to speak.

DIRECTOR ZEISE: Okay. Dr. La Merrill.

COMMITTEE MEMBER LA MERRILL: Yeah, I have a

question.

COMMITTEE MEMBER LOOMIS: Go ahead, please.

COMMITTEE MEMBER LA MERRILL: Thank you. I have a question for Dr. Zhang. Since you do work with hematopoietic origin cancers, I was wondering if you could comment. You know, I don't love the way that they were aggregated, but we just heard from Dr. Loomis that it sounded like there might be something going on there. Do you think the mechanisms that Dr. Bush told us about would support that?

COMMITTEE MEMBER ZHANG: See, I think hematopoietic cancers little bit complicated, because that's all, you know, many come from a stem -- stem cells -- you know, hematopoietic stem cells. But it also depends on the health in -- you know, mechanistically health in where? It's in early stem cell or a little bit of later or in the progenitor stem cells.

So that's -- that's a little bit difficult to say, because I think using the ICT -- ICD code, they still could classify different type of cancer. But I think mechanistically for me I would really think, you know, if we had had it in an early primitive stem cells, I would say that could -- you know, it could go from top of stem you can go either lymphoma, you know, headed in lymphoid stem cell or myeloid stem cell. So that still could be,

you know, generate either lymphomas or leukemia.

So that's why I think previously NCI would have, you know, kind of together to say what's across -- the lympho -- lympho myelo -- you know, so put them all together, right.

So it really depends. I would say if we have limited studies or limited cases, I think it's okay to put them all together or if we understand the mechanisms, the head is at the earlier progenitor, or the later progenitor, or stem, then you can separate them. I don't know, Michele, did I -- did I answer your question.

COMMITTEE MEMBER LA MERRILL: Yeah. Thank you.

COMMITTEE MEMBER ZHANG: Yeah. That's the point. Okay.

COMMITTEE MEMBER LOOMIS: Are there any other comments from the Committee? Again, somebody please help me.

COMMITTEE MEMBER EASTMOND: This is David.

DIRECTOR ZEISE: Dr. Eastmond. Go ahead, Dr. Eastmond.

COMMITTEE MEMBER EASTMOND: I've got one.

I just want to mention trifluralin, these compounds do induce aneuploidy (inaudible) spindle apparatus. That doesn't necessarily mean they're carcinogenic. A couple of evidence -- certainly

colchicine and albendazole are well known inhibitors of mitotic apparatus that aren't associated with rodent cancer or human cancers to our knowledge.

We did a -- I recently did a fairly major review of this with a group -- with the International Working Group on Genotoxicity Testing, and -- anyway, it appears that some types of aneuploidy-inducing agents. If that's the sole change they make, it doesn't appear to be associated with cancer. They're frequently associated with other types of effects, so there's multiple type of modes action, and then aneuploidy does play a role, and can play a role in carcinogenic, but it's usually combined with something else. I thought I'd mention that.

COMMITTEE MEMBER LOOMIS: Thank you.

Further comments?

DIRECTOR ZEISE: Not seeing any hands.

COMMITTEE MEMBER LOOMIS: All right. Seeing no hands, let's see whether there are comments from the public. I'm not aware that anyone has asked to speak, but Clara, can you verify that.

MS. ROBINSON: Yes I can verify that we do not have any hands raised at this time. Again, just a reminder, if you do want to make a public comment, go ahead and click on the hand raise feature please and thank you.

COMMITTEE MEMBER LOOMIS: Okay. We'll wait a moment to see if anyone raises their hand.

MS. ROBINSON: And no one has.

COMMITTEE MEMBER LOOMIS: No one has, so let's then take another moment and see whether there's any final discussion from the Committee before we proceed to a vote.

Okay. Not hearing anything, let's go down the roll again.

Dr. Bush?

COMMITTEE MEMBER BUSH: I appreciate Dr. Eastmond's comments. I'm still going to stick with high, given the broad use of this chemical and it's very similar structural similarity to oryzalin.

COMMITTEE MEMBER LOOMIS: Okay. Dr. Crespi?

COMMITTEE MEMBER CRESPI: Medium.

COMMITTEE MEMBER LOOMIS: Dr. Eastmond?

COMMITTEE MEMBER EASTMOND: I'm going to go with medium.

COMMITTEE MEMBER LOOMIS: Dr. La Merrill?

COMMITTEE MEMBER LA MERRILL: It's tricky. I think I'll go with -- how about medium.

COMMITTEE MEMBER LOOMIS: Medium. Okay. Seems to be the middle ground.

Dr. Landolph.

COMMITTEE MEMBER LANDOLPH: Medium.

COMMITTEE MEMBER LOOMIS: All right. And I put it at medium.

Dr. Mack?

CHAIRPERSON MACK: I started out with low, but I think I've come up to medium, so medium it is.

COMMITTEE MEMBER LOOMIS: Medium.

Dr. McDonald?

COMMITTEE MEMBER McDONALD: Medium also.

COMMITTEE MEMBER LOOMIS: Okay. Dr. Reynolds?

COMMITTEE MEMBER REYNOLDS: I'm with Tom, I've moved up to medium.

COMMITTEE MEMBER LOOMIS: All right. Dr. Stern?

COMMITTEE MEMBER STERN: Medium.

COMMITTEE MEMBER LOOMIS: And Dr. Zhang?

COMMITTEE MEMBER ZHANG: Medium.

COMMITTEE MEMBER LOOMIS: Medium. Okay. I think we've settled on medium.

So that concludes discussion of the seven substances that we had on the agenda for today. The next agenda item on the preliminary agenda that you may have seen was a consent item, but that item has been removed, as there isn't anything for us to approve at this time.

So with that, we can move on to the last item -- next to last item, which is updates -- a set of updates from the staff. So I'll ask Julian Leichty and Carol

Monahan Cummings, if she's still here, to give those.

MR. LEICHTY: Thanks. Mario is going to be stepping in for Carol I think, but I'll start with this update on chemicals we have administratively added since the Committee's last meeting. You can see on the first slide bevacizumab was added for developmental toxicity and female reproductive toxicity.

P-chloro-a,a,a-trifluorotoluene, 2-amino-4-chlorophenol, 2-chloronitrobenzene, 1,4-dichloro-2-nitrobenzene, 2,4-dichloro-1-nitrobenzene, n,n-dimethylacetamide, para-nitroanisole were added for cancer.

Next slide, please.

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MR. LEICHTY: Chemicals currently under consideration for administrative listing are molybdenum trioxide, indium tin oxide for cancer under the Labor Code mechanism.

Next slide.

--o0o--

MR. LEICHTY: And as you can see here, since the Committee's last meeting, we've adopted four safe harbor levels into regulation, a no significant risk level of 0.7 micrograms per day for bromochloroacetic acid, a no significant risk level for 0.95 micrograms per day of

bromodichloroacetic acid, and a maximum allowable dose level of 28,000 micrograms per day for the oral route of exposure an 20,000 micrograms per day for inhalation for n-hexane, and a maximum allowable dose level of 0.58 micrograms per day for the oral and inhalation routes of exposure, and 7.2 micrograms per for the dermal route of exposure for chlorpyrifos.

And on the next slide --

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MR. LEICHTY: -- you can see that we've also proposed safe harbor levels for four chemicals. We're still in the regulatory process for a safe -- for safe harbor levels for p-Chloro-a,a,a-trifluorotoluene, trichloroacetic acid, dichloroacetic acid, and dibromoacetic acid.

And with that, I'll turn things over to Mario.

--o0o--

SENIOR STAFF COUNSEL FERNANDEZ: Okay. Thank you. Good afternoon. And these are some of the recent completed and open rulemakings. The coffee regulation became operative last October. And under that regulation, exposure to listed chemicals in coffee from the roasting of coffee beans or brewing a coffee are not considered to post a significant risk of cancer.

We also modified the Article 6 Clear and

Reasonable Warnings, in particular the responsibility to provide warnings for consumer products. And in that regulation, we clarified the responsibility of the intermediate parties in the supply chain to provide Prop 65 warnings. That became effective this past April.

We also have an open rulemaking for another amendment to Article 6. And the main change is to conform the alcoholic beverage tailored warnings to a consent judgment related to the delivery of alcoholic beverages. And we're close to finalizing that rulemaking.

And we are currently reviewing public comments for a proposed rulemaking related to chemicals created during cooking or heat processing. And in that regulation if a chemical is formed from cooking or heat processing, and the chemical is reduced to the lowest level currently feasible, there's no exposure. And we also have included a list of concentration levels for acrylamide. And those are primarily based on settlement levels.

Next slide, please.

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SENIOR STAFF COUNSEL FERNANDEZ: Okay. Next, I'll talk about the Prop 65 related litigation.

Wheat growers v Zeise is a case related to glyphosate. It's a federal case. The district court found that warnings to glyphosate were in violation of the

First Amendment limitations on compelled commercial speech. OEHHA is no longer a party to that suit and the Attorney General has appealed that to the Ninth Circuit.

The next case is American Chemistry Council v OEHHA. And that is the BPA case. And this was a challenge to the listing to BPA -- listing of BPA as a developmental toxicant via the authoritative bodies listing. The listing was upheld by the trial court and the court of appeal.

And then the next one is the ACC v OEHHA. That is a DINP case. And the main issue was whether the Committee followed written guidance when it made its decision during the meeting. The trial court and the court of appeal both upheld the listing and the California Supreme Court has declined review.

And the next is the Council for Education and Research on Toxics v OEHHA. And that's related to warnings for coffee and associated Public Records Act requests. CERT, the Council for Education and Research Toxics, dismissed all but the PRA claims. And the court entered judgment against CERT on the PRA requests.

Another challenge is the -- from CERT is CERT v Starbucks. And that was related to the coffee regulation as part of an enforcement action. And the trial court upheld the regulation and entered judgment for the coffee

companies.

And finally, we have Physicians Committee for Responsible Medicine v Newsom. And this was a challenge based on OEHHA's decision to not list processed meats. And a hearing is scheduled for February 21st of 2021.

And that concludes the regulatory and litigation updates.

COMMITTEE MEMBER LOOMIS: Okay. Thanks, Mario and Julian. Thanks.

And we move on to the final agenda item and that is a summary of committee actions. And for that, I'll turn back to Director Zeise.

DIRECTOR ZEISE: Okay. Thank you. We do have a slide that summarizes the Committee decisions.

Thank you.

So the Committee considered seven chemicals for recommending -- and recommended priorities for consideration for future review by the Committee for possible listing.

And those selected will be -- we would develop hazard identification materials on. So two of the chemicals the Committee ranked as high bisphenol A and Perfluorooctane sulfonate and its salts and transformation and degradation precursors.

Five chemicals -- four chemicals were ranked

medium, chlorpyrifos, decaBDE, methyl bromide and trifluralin.

And one chemical, coal dust, was given the rank of no priority.

So that summarizes the Committee's decisions today -- or recommendations today.

And I guess I would just like to add, at this point, my thank yous on behalf of OEHHA to the Committee for all the hard work that you did today at the meeting, as well as all the preparation prior to the meeting. It was a lot of work and really appreciate all the thoughtful review that you provided to us and the consultation. So thank you so much.

I'd also like to thank the Reproductive and Cancer Hazard Assessment Branch and our new Deputy Director for Science for all the work in preparing for the meeting, pulling the materials together. That, too, was a lot of work. So thank you for all of that.

And then to Implementation team, Julian, Esther Tyler, Monet for all their work in pulling this meeting together, as well as our IT staff to -- it sounds -- it's beginning to sound a little like the Academy Awards, but it does take a lot of individual effort to pull off a meeting like this. And I'd also like to thank Clara Robinson for her excellent facilitation of the virtual

meeting and also to our Legal staff, Carol and Mario.

And with that, I'll turn it -- and also just wish you all good health and a good Thanksgiving next week, and be well and safe. Safe journey if you are going to be traveling.

And I'll turn it back over to Dana.

COMMITTEE MEMBER LOOMIS: Thanks, Lauren.

DIRECTOR ZEISE: Dr. Loomis.

COMMITTEE MEMBER LOOMIS: Well, I'm Dana.

(Laughter.)

COMMITTEE MEMBER LOOMIS: Well, I'd just like to echo those thanks to the colleagues on the Committee for your efforts pulling together this review, and thoughtful comments on the chemicals we considered today, and for working through these circumstances, which are not optimal certainly.

And thanks too to the staff for all of the work they did in the background to make this meeting possible, and to the members of the public for their interventions.

And so, with that, I think we can adjourn the meeting. And I will give my apologies for my rather awkward participation by phone here and go look for some candles, because it's already getting dark.

So we are officially adjourned.

DIRECTOR ZEISE: Great. And I should have added

a special thanks to Dana for filing in. So thank you. Yes.

COMMITTEE MEMBER LOOMIS: You're most welcome.

(Thereupon the Carcinogen Identification Committee adjourned at 3:46 p.m.)

CERTIFICATE OF REPORTER

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

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

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

IN WITNESS WHEREOF, I have hereunto set my hand this 15th day of December, 2020.

JAMES F. PETERS, CSR
Certified Shorthand Reporter
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