VIDEOCONFERENCE MEETING

STATE OF CALIFORNIA

ENVIRONMENTAL PROTECTION AGENCY

OFFICE OF ENVIRONMENTAL HEALTH HAZARD ASSESSMENT

PROPOSITION 65

CARCINOGEN IDENTIFICATION COMMITTEE

ZOOM PLATFORM

MONDAY, DECEMBER 6, 2021

10:00 A.M.

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

Michele La Merrill, PhD

Joseph Landolph, PhD

Dana Loomis, PhD

Peggy Reynolds, PhD

Mariana Stern, PhD

Luoping Zhang, PhD

STAFF:

Lauren Zeise, PhD, Director

Vince Cogliano, PhD, Deputy Director, Division of Scientific Programs

Carol Monahan Cummings, Chief Counsel

Neela Guha, Phd, MPH, Research Scientist III, Cancer Toxicology and Epidemiology Section, Reproductive and Cancer Hazard Assessment Branch

Jennifer Hsieh, PhD, MS, DABT, Staff Toxicologist, Cancer Toxicology and Epidemiology Section, Reproductive and Cancer Hazard Assessment Branch

Julian Leichty, Proposition 65 Implementation Program

APPEARANCES CONTINUED

STAFF:

Kate Li, PhD, DABT, Staff Toxicologist, Cancer Toxicology and Epidemiology Section, Reproductive and Cancer Hazard Assessment Branch

Elizabeth Marder, PhD, Senior Environmental Scientist, Cancer Toxicology and Epidemiology Section, Reproductive and Cancer Hazard Assessment Branch

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Karin Ricker, PhD, Staff Toxicologist, Cancer Toxicology and Epidemiology Section, Reproductive and Cancer Hazard Assessment Branch

Martha Sandy, PhD, MPH, Chief, Reproductive and Cancer Hazard Assessment Branch

Meng Sun, PhD, MS, Chief, Cancer Toxicology and Epidemiology Section, Reproductive and Cancer Hazard Assessment Branch

Feng Tsai, PhD, MS, Staff Toxicologist, Cancer Toxicology and Epidemiology Section, Reproductive and Cancer Hazard Assessment Branch

ALSO PRESENT:

John Bottorff, CleanEarth4Kids.org

Suzanne Hume, CleanEarth4Kids.org

Jimena Diaz Leiva, PhD, Center for Environmental Health

Steve Risotto, American Chemistry Council

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PROCEEDINGS

WELCOME AND OPENING REMARKS

DIRECTOR ZEISE: Well, welcome, everyone to this December 2021 meeting of our Carcinogen Identification Committee. I'm Lauren Zeise. I'm Director of the Office of Environmental Health Hazard Assessment. Welcome, everyone. Good morning.

The Committee today is going to be considering for potential listing under Proposition 65 as a carcinogen: perfluorooctane sulfonic acid, PFOS, and its salts, and transformation and degradation precursors. We'll also have a consent item considered by the Committee as well as staff updates on various Proposition 65 actions since the last Committee meeting.

This meeting is being recorded and transcribed and the transcription will be posted on OEHHA's website.

And I'll now turn the meeting over to Dr. Elizabeth Marder who is handling the logistical aspects of this virtual Zoom webinar. And she's going to let everyone know how they can best participate in the meeting.

Elizabeth.

(Thereupon a slide presentation.)

DR. MARDER: Thank you, Lauren. Individuals who wish to make an oral comment at today's meeting are asked

to do two things. First, join the Zoom webinar, and second, fill out a speaker request card. Information on how to join the Zoom webinar is shown on the slide that is being presented now. Go to the link bit.ly/registercic2021 and register for today's Zoom webinar. You will receive a link to join the webinar at the end of the registration process. And if you provided a working email address, you will also receive an email with a link to join the webinar. Information on how to access the speaker request card is also shown on this slide. Go to bit.ly/oehhacic2021 and request to speak on a specific agenda item. It is requested that your Zoom display name match the name you used to fill out the speaker request form. Individuals who have not submitted a speaker request card may also indicate their wish to make an oral comment by using the raise hand function when requested by the Chair.

DIRECTOR ZEISE: Okay. Any other things to cover, Elizabeth, before I introduce the Committee?

DR. MARDER: No. Please proceed.

DIRECTOR ZEISE: Okay. Thank you so much. All right. So welcome to the Committee. And I'll introduce the Committee to everyone. And as I introduce you, if you could just hold up your hand, so that people might be able to spot the movement.

Okay. So first starting with Dr. Jason Bush, Professor of Cancer Biology and Chair of the Department of Biology, California State University, Fresno.

Dr. Catherine Crespi, Professor and Resident of Biostatistics at the University of California Los Angeles, Fielding School of Public Health.

Dr. David Eastmond, Emeritus Professor of Cell Biology from the University of California, Riverside, Department of Molecular Cell and Systems Biology.

Dr. Michele La Merrill, Associate Professor, from the University of California, Davis, Department of Environmental Toxicology.

Dr. Joseph Landolph, Associate Professor of Molecular Microbiology and Immunology at the University of Southern California, Keck School of Medicine.

Dr. Dana Loomis, Director Plumas County Public Health Agency and Research Professor at the Desert Research Institute.

Dr. Thomas Mack, Professor of Preventative Medicine at the University of Southern California, Keck School of Medicine.

Dr. Thomas McDonald, Research Fellow, Global Stewardship at the Clorox Company.

Dr. Peggy Reynolds, Adjunct Professor at the University of California, San Francisco, Helen Diller

Comprehensive Cancer Center in the Department of Epidemiology and Biostatistics.

Dr. Mariana Stern, Professor of Clinical Preventative Medicine and Urology, and 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, everyone. Thank you for taking time out of your busy schedules to support California as we move ahead in our Proposition 65 activities. We very much appreciate your participation in this meeting. I'm going to note now that Dr. Dana Loomis will be chairing the meeting today on behalf of Dr. Mack.

Now, I'm going to introduce the OEHHA staff. So staff if you could turn on your cameras as I introduce you. Dr. David Edwards, who's our new Chief Deputy Director at OEHHA, will be joining us at 10:30 and when he joins we can introduce him then; so Carol Monahan Cummings, our Chief Counsel; Dr. Vince Cogliano, our Deputy Director for Scientific Programs. And then from the Reproductive and Cancer Hazard Assessment Branch, Dr. Martha Sandy, the Branch Chief; Dr. Meng Sun, the Section Chief of the Cancer Toxicology and Epidemiology Section.

And now for introductions of the staff of the Cancer Toxicology and Epidemiology Section that the Committee will be hearing from later today: Dr. Feng Tsai, Dr. Neela Guha, Dr. Kate Li, Dr. Karin Ricker, Dr. Jennifer Hsieh, and Gwendolyn Osborne. Good morning, everyone.

And now from our Proposition 65 Implementation Program, Julian Leichty, Special Assistant for Program and Legislation. And then other staff in the program that will be participating in today's meeting, Esther Barajas-Ochoa, And Tyler Saechao.

Okay. And now I'm going to ask Carol Monahan Cummings, the OEHHA Chief Counsel, for some introductory remarks on Bagley-Keene and other legal issues related to today's meeting.

Carol.

CHIEF COUNSEL MONAHAN CUMMINGS: Thank you. Good morning, everybody. Good to see you all again. I just want to give you just a few reminders before you get started with the meeting. First, please remember that all your discussions and deliberations need to be conducted during the meeting, not on your breaks, or lunch, or with individual members on or offline, including via phone, email, chats, or text messages, or any other communication method.

Today, you will be considering the listing of chemicals that Dr. Zeise already mentioned. OEHHA takes no position regarding whether a chemical should be listed. Staff are available to answer questions or locate information for you, if needed. The Governor appointed you because of your scientific expertise to be the State's qualified experts on carcinogenicity of chemicals. And there's no need for you to feel compelled to go outside that charge.

We have provided you with the listing criteria adopted by the Committee. And you can base your decisions on the information and the criteria, but it is pretty broad and certainly allows you to apply your scientific expertise to the questions in front of the Committee.

Committee members should base your decisions on the scientific principles outlined in the guidance document as I mentioned, but you don't need to consider the potential future effect of a listing such as warnings on particular products.

You need to apply the criteria that the chemical has been clearly shown through scientifically valid testing, according to generally accepted principles, to cause cancer. That's the standard that you are applying. And it's a scientific judgment call. It's not a legal standard of proof.

The Committee can decide to list based on animal evidence. A chemical need not be shown to be a human carcinogen or whether or not the anticipated human exposures to the chemical are high enough to cause cancer at this time. If you need more information, need more time to think about the evidence or discuss it further before making a decision, there's no requirement that you make a decision today.

Feel free to ask clarifying questions of me or the other OEHHA staff during the meeting. If we don't know the answer to your question, we'll do our best to find it and report back to you.

Any questions?

Thank you.

DIRECTOR ZEISE: Thanks, Carol.

Okay. Now, I will turn the meeting over to today's meeting Chair, Dr. Dana Loomis.

COMMITTEE MEMBER LOOMIS: Thank you, Lauren.

I'd like to reiterate your greeting, welcome to everybody. Thanks for participating to members of the Committee and the public who are joining us today.

We'll now move on to the first substantive agenda item. So I'll call on Vince Cogliano to introduce the staff report.

CONSIDERATION OF PERFLUOROOCTANE SULFONIC ACID (PFOS)

AND IT SALTS AND TRANSFORMATION AND DEGRADATION PRECURSORS AS KNOWN TO THE STATE TO CAUSE CANCER

STAFF PRESENTATION

DR. COGLIANO: Thank you, Dana. Good morning, everyone.

I'd like to endorse Lauren's welcoming remarks, especially our appreciation for your service as experts on this Committee. You have an important role in bringing current science to bear on decisions to benefit the health of all the people of California. We know you're here today as a public service. And so to assist you, OEHHA has summarized the scientific evidence you will consider.

I'd like to turn the screen over to the Chief of our Reproductive and Cancer Hazard Assessment Branch, Dr. Martha Sandy, who will introduce the staff presentation.

Martha.

DR. SANDY: Thank you, Vince. Good morning, everyone. Let me provide some background information on the process by which perfluorooctane sulfonic acid, or PFOS, and its salts and transformation and degradation precursors was given a high priority and selected for listing consideration.

PFOS and its salts and transformation and degradation precursors was first brought to the CIC for consultation and prioritization back in 2010. With the

availability of new data, it was brought to the CIC for consultation and prioritization again last year in 2020, at which time the CIC recommended that PFOS and its salts and transformation and degradation precursors be placed in a high priority group for future listing consideration.

In 2021, OEHHA selected, "PFOS and its salts and transformation and degradation precursors", for consideration for listing, and in March of 2021, OEHHA solicited from the public information relevant to the assessment of the evidence on the carcinogenicity.

Information received at that time was reviewed, and considered by OEHHA in the course of preparing the September 2021 document. This document, as well as the references cited within it, the public comments received on the document, and an additional recent publication identified by a CIC member have been provided to you, the CIC, for your consideration.

I will now ask Dr. Meng Sun, Chief of the Cancer Toxicology and Epidemiology Section, which prepared this document, to make a few remarks.

DR. SUN: Thank you, Dr. Sandy. Good morning. The staff presentation that you'll be hearing and seeing today has been prerecorded and will consist Of two parts, with a brief Q&A break in between and another Q&A break after the presentation. I would like to request that the

Committee members please hold your questions until the breaks.

OEHHA staff scientists are present at the meeting and will be able to answer any clarifying questions from the Committee during the breaks.

Thank you.

(Thereupon a slide presentation.)

DR. SANDY: So is it possible to start the presentation?

DR. MARDER: Yes. My apologies. One moment.

DR. TSAI: Good morning. Today we are here to present the evidence on the carcinogenicity of perfluorooctane sulfonic acid, also known as PFOS and its salts and transformation and degradation precursors. This presentation is an abbreviated version of the data that were reviewed in the hazard identification document, or HID for short.

I'd like to acknowledge that this HID was a group effort from all staff in the Cancer Toxicology and Epidemiology Section, not just those who are presenting today.

NEXT SLIDE

DR. TSAI: Before I start, I'd like to clarify that the evidence reviewed in this HID includes studies of PFOS and PFOS salts, and a few studies of PFOS precursors

that provide relevant information to evaluate the effects of PFOS. Here is an overview of today's presentation. We will start with some background information, such as use and exposure, and the systematic literature review approach that we implemented.

Next, we will present carcinogenicity data from human epidemiological studies followed by animal cancer bioassay data and data from mechanistic studies. Discussion of mechanistic data will include a brief summary of pharmacokinetics, a summary of data related to 8 of the 10 key characteristics of carcinogens, and a comparison of PFOS and PFOA. We will end the presentation with a brief summary of the evidence.

NEXT SLIDE

DR. TSAI: PFOS is a man-made chemical belonging to the group known as PFASs. As shown in this figure, PFOS has a fully fluorinated 8-carbon chain with a sulfonic acid functional group. PFOS is in equilibrium with PFOS anion in the environment. PFOS and its salts and transformation and degradation precursors cover all chemicals that may form PFOS. Seventeen PFOS salts were identified, including PFOS potassium salt that was used as the test substance in the animal bioassays.

PFOS precursors are defined as substances containing this chemical moiety that can transform or

degrade to PFOS. Many PFOS precursors have been used in the manufacture of PFASs. We identified a non-exhaustive set of 169 PFOS precursors from literature review and verified them by computational model predictions or expert judgment.

NEXT SLIDE

DR. TSAI: PFOS and it salts and precursors are used widely in many applications for their stain-, grease-, heat-, or water-resistant properties. Two examples of consumer product uses are non-stick cookware and waterproof textiles. Human exposure to PFOS mainly comes from contaminated food and water. Given the strength of the carbon-fluorine bond, these chemicals are persistent and bioaccumulative. PFOS continues to be detected in the environment and in biomonitoring studies, such as Biomonitoring California and NHANES, or National Health and Nutritional Examination Survey. Even though the domestic production and use ended in the early 2000s.

A decreasing trend with time has generally been observed in biomonitoring studies, but PFOS levels in some populations, such as firefighters in California remain elevated.

NEXT SLIDE

DR. TSAI: This slide lists reviews of the carcinogenicity of PFOS conducted by California EPA and

other health agencies. In July 2021, OEHHA proposed a public health goal of 1 ppb for PFOS in drinking water, based on findings of liver and pancreatic tumors in laboratory animals. In terms of other reviews, U.S. EPA reviewed PFOS in 2016 and concluded that there was suggestive evidence of carcinogenic potential for PFOS. No other Proposition 65 authoritative bodies, such as IARC or NTP, have reviewed or classified PFOS as to its carcinogenicity.

In its 2021 review, ATSDR included U.S. EPA's conclusion and did not make its own. Health Canada acknowledged that chronic exposure to PFOS has been associated with both cancer and non-cancer effects in animals and humans. Both Health Canada and EFSA concluded that human evidence is equivocal or insufficient.

NEXT SLIDE

DR. TSAI: This slide provides an overview of the literature search and screening process used in developing this HID to ensure a comprehensive review of the studies that are most pertinent to the evidence of carcinogenicity.

First, primary searches in major biomedical databases, such as PubMed and Embase were conducted with defined literature search terms. Additional focused literature searches were conducted to identify more

subject-specific references. A web-based tool, Health Assessment Workspace Collaborative, or HAWC, was used for the systematic review of these references. These references were uploaded to HAWC for screening using specific inclusion and exclusion criteria.

In Level 1 screening, references were screened and tagged by the titles and abstracts. In Level 2 screening, the full papers were reviewed and tagged based on a predefined tagging tree in HAWC.

Table Builder, a web-based application, was used to systematically extract and analyze the epidemiological data.

Overall, more than 1,400 references were included in the HAWC project. And around 500 references were cited in this HID.

NEXT SLIDE

DR. TSAI: This slide presents the multiple data streams that provide evidence relevant to carcinogenicity, including human and animal cancer data and mechanistic data. The mechanistic data consists of studies on pharmacokinetics, data related to the 10 key characteristics of carcinogens, and a comparison of PFOS and PFOA, which focused on animal cancer data and mechanistic information on data-rich endpoints.

With regard to the key characteristics of

carcinogens, carcinogens often share one or more KCs as multiple mechanisms may be related to carcinogenesis. The KC approach provides a framework for broader consideration of the mechanistic evidence. We use these 10 KCs to systematically identify, organize, and summarize the available mechanistic information. For today's presentation, we will focus on the eight KCs with more informative data shown in this figure.

Next, Dr. Guha will present the evidence from human epidemiological studies.

NEXT SLIDE

DR. GUHA: I will now present the epidemiologic evidence.

NEXT SLIDE

DR. GUHA: For the epidemiologic studies, our literature search identified 23 relevant studies that investigated associations between exposure to PFOS and cancer, 18 of which met the eligibility criteria for inclusion. We included studies that were of cohort and case control designs. Cross-sectional studies were excluded, due to the potential for reverse causation. However, similar concerns about reverse causation may also apply to case control studies with cross-sectional designs.

Ecologic studies without exposure data on the

individual level were excluded due to the potential for ecologic fallacy and confounding. We excluded case reports because of the lack of a comparison group and conference abstracts because the results are considered preliminary as they have not been subject to peer review for journal publication.

Studies without original data, such as reviews or editorials, were also excluded, but reviewed to identify publications with primary data that may have been missed in the literature search. The were no exclusions based on study location, language, or statistical adjustments. The table shows that breast cancer was the endpoint with the largest number of studies. Therefore the review of this site will be presented in more detail later in the presentation.

For the cancers that arise in other sites, data may be too sparse to draw conclusions. More detail can be found in the hazard identification document.

NEXT SLIDE

DR. GUHA: The quality of each study identified for inclusion was evaluated using criteria similar to those described in the NTP Report on Carcinogens handbook and the IARC monograph's program Preamble. In assessing study quality, special attention was given to the assessment of biases, which in observational studies are

usually grouped into selection bias, information bias, and confounding. Hill guidelines were considered for causal inference, such as consistency, temporality of the association, magnitude of association, and dose response.

NEXT SLIDE

DR. GUHA: There were also several considerations specific to assessing the epidemiologic literature on PFOS and cancer. One concern is that epidemiologic studies generally measured PFOS levels in the blood at a single time point. This could miss long-term changes in exposure or relevant exposure periods despite a long half-life for PFOS, which has been reported to range from 1.7 to 8.7 years.

Another concern is the potential for reverse causation, particularly in the studies where serum PFOS levels were measured at or near the time of cancer diagnosis. Hormonal or other physiological changes, as well as behavioral changes, associated with the onset of disease and treatment may alter serum PFOS levels. Even though the half-life of PFOS in human blood can be long, it is unknown whether serum PFOS levels measured at or after the time of diagnosis reflect the PFOS levels in the time window relevant to cancer causation.

Co-exposures to other PFASs were not accounted for in most studies, and therefore could potentially

confound the results.

NEXT SLIDE

DR. GUHA: Here, we present the exposure characteristics of the studies of breast cancer stratified by timing of PFOS assessment before or after cancer diagnosis. The studies differed in PFOS exposure levels and the way they were reported, such as means or medians. The highest PFOS levels were observed in the only occupational study, which was conducted in a manufacturing facility in Decatur, Alabama.

This facility consisted of two plants, a chemical plant and a film plant. At the chemical plant, the major sulfonated fluorochemical manufactured was perfluorooctanesulfonyl fluoride, which can degrade or be metabolized to PFOS. Hence, these workers were considered to be exposed to PFOS.

Among chemical plant workers, the geometric mean serum level of PFOS was 900 nanograms per milliliter. Among film plant workers considered to be unexposed to PFOS, geometric mean serum levels were 100 nanograms per milliliter. This was high compared to the other populations as seen on this slide. This would bias risk estimates towards the null when comparing the exposed and unexposed.

Exposure to other fluorochemicals was likely,

including PFOA, due to the production of the chemicals themselves or as by-product of production. Biologic monitoring in this cohort showed that serum levels PFOA were slightly lower than PFOS, but correlated. The Inuit population of Greenland was highly exposed to PFOS and a number of other persistent organic pollutants, such as PCBs and organochlorine pesticides, making it difficult to disentangle the effect of individual compounds.

NEXT SLIDE

DR. GUHA: The results were inconsistent in the eight published studies that reported on the main effect of PFOS exposure and breast cancer. This forest plot is a snapshot of the studies with one estimate displayed per study when available. The hazard identification document presents the data in more detail.

In three studies that measured PFOS levels at or after breast cancer diagnosis, the results were mixed and reverse causation bias cannot be fully ruled out. However, the results were also mixed in the five publications that collected data on PFOS exposure prior to breast cancer diagnosis. Category level data are reported for two of these studies, Cohn and Mancini. The Cohn study differed from the other studies in that it assessed the association between maternal pregnancy serum PFOS levels and breast cancer in daughters. This study did not

present the main effects of PFOS, but stratified results.

This concludes the summary of the epidemiologic evidence. Next, Dr. Li will present the animal evidence.

NEXT SLIDE

DR. LI: I am going to present carcinogenicity studies in animals.

NEXT SLIDE

DR. LI: Here is an overview of available animal bioassays. Two-year carcinogenicity studies of PFOS in male and female Sprague-Dawley rats were conducted and reported by the 3M Company, authored by Thomford and the data were later published in the peer-reviewed article by Butenhoff et al. In these studies, 41-day old male and female rats with 50 animals per group, per sex were administered PFOS potassium salt in the diet at doses of 0, 0.5, 2, 5, or 20 ppm for two years. Each study also included a 20 ppm recovery group with 40 animals per sex, in which the animals were administered 20 ppm PFOS potassium salt in the diet for one year, and then received basal diet for an additional year.

In addition, there is one tumor promotion study in rainbow trout. In this study, six-month dietary exposure to PFOS was examined as the tumor promoter after initiation with aflatoxin B1. We will present the tumor findings from these studies in the next few slides.

NEXT SLIDE

DR. LI: In the two-year study in male rats, liver hepatocellular adenomas were statistically significantly increased in the high dose group compared to controls, and the increase was significant by trend test. In the pancreas, an increase in islet cell carcinomas was statistically significant by trend test. One animal in the 5 ppm group developed islet cell carcinoma that metastasized to the liver. There was no increase in islet cell adenoma or combined islet cell adenoma and carcinoma.

NEXT SLIDE

DR. LI: In the male rat 20 ppm PFOS recovery group, the incidence of thyroid gland follicular cell adenoma was significantly increased by pairwise comparison with controls. As noted in the HID, one thyroid follicular cell carcinoma was also observed in this group.

NEXT SLIDE

DR. LI: In the two-year study in female rats, a statistically significant increase in mortality was observed in the 2 ppm dose group compared to controls from week 80 onwards. And in the 20 ppm dose group, a statistically significant decrease in body weight was observed compared to controls starting at week three. Feed consumption was initially lower in the 20 ppm dose group, but was no longer different from controls after

week 36.

As shown here, in the liver, the incidence of hepatocellular adenoma and adenoma or carcinoma combined were significantly increased in the high dose group by pairwise comparison with controls with significant dose-related trends. One rare hepatocellular carcinoma was also observed in this group.

In the thyroid gland, two rare follicular cell adenomas and one rare follicular cell carcinoma were observed in the 5 ppm group, and one rare follicular cell adenoma was observed in the 20 ppm group.

In the mammary gland, the incidence of mammary fibroadenoma was significantly increased in the low dose group by pairwise comparison with controls.

NEXT SLIDE

DR. LI: In the female rat, 20 ppm PFOS recovery group, one rare thyroid follicular cell adenoma was observed.

NEXT SLIDE

DR. LI: In this slide, I'll present the tumor promotion study conducted by Benninghoff et al. In rainbow trout treated with aflatoxin B1 as a tumor initiator, PFOS potassium salt in diet for six months as a promoter, and observed for two additional months. There was an increase of combined liver adenomas and carcinomas

indicating the tumor promotion activity of PFOS. In this study, tumor incidence was reported as the percentage of fish with tumors.

This concludes our summary of the animal tumor data.

NEXT SLIDE

COMMITTEE MEMBER LOOMIS: Okay. Let's see whether the Committee has any questions of clarification at this point. Perhaps the best way to do that is to use the raise-hand feature, because I can't see everybody on the screen at one time. Are there any questions from the Committee?

COMMITTEE MEMBER EASTMOND: I raised my hand.

COMMITTEE MEMBER LOOMIS: Okay. Dr. Eastmond has a question.

COMMITTEE MEMBER EASTMOND: I have a couple of questions. And some of these refer to the document itself. So I guess the first one is with regards to these rare tumors, how is rare kind of defined among OEHHA?

DR. SANDY: Meng, do you want to take that or do you want me to?

DR. SUN: I can say a few words, and, Martha, if I miss anything, you can add.

So, Dr. Eastmond, a rare tumor is defined as occurring at the rate of less than one percent in control

animals that are not treated. We have been referring to several different historical databases for the SD rats. And these are all documented in the hazard identification documents for each tumor site.

COMMITTEE MEMBER EASTMOND: Okay. Thank you. I have a couple other related questions. So I noticed in the document that the historical controls were provided simply as a mean value. You know, it's the total number of tumors seen over a number of animals. And while that's helpful, I find it much more helpful to find the historical control ranges, because the way it's presented, you're showing the average historical range and not the actual -- I mean, the average historical incidence for these tumors and not the range that's seen over a series of studies, which I think is more informative or that -- like the 95 percent confidence interval on that incidence of tumors. And I don't know if you have that information or not, but it was one thing that at least certainly in future reports, I hope you'll put the confidence intervals ranges down in addition to the sort of average.

And the one last -- I don't know if you have that information?

The last comment I have is -- has to do with just a couple of things. In Table 8, this is in the -- essentially the tumor incidence in the liver in the female

rats, there's a difference in the number of animals between the -- evaluated for adenomas and carcinomas. And I didn't know if that was just sort of typo error or there was some explanation for it.

DR. SUN: For the denominators we're trying to use the number of animals alive at first occurrence of tumor. So if the adenomas and carcinomas happened on different day, the first tumor happened on different day, then the denominators could be different.

COMMITTEE MEMBER EASTMOND: So that's the first day you saw that type of tumor or that's the first day you saw a tumor?

DR. SUN: It would be the first day we saw this hepatocellular carcinoma in any of the groups.

COMMITTEE MEMBER EASTMOND: So --

DR. SANDY: So, David, to clarify, when we do this effective number calculation, which is standard for many -- for EPA and OEHHA in many instances, we are looking for each particular tumor type. So if we're looking at hepatocellular carcinoma, we look at the first occurrence of hepatocellular carcinoma in any treatment or control group, and then we look at those animals that were alive at that day, the first occurrence of tumor onward and develop the denominator. And for hepatocellular adenomas, we do the same thing. And then for combined,

it's the day of first occurrence of either hepatocellular adenoma or carcinoma.

COMMITTEE MEMBER EASTMOND: Okay. So -- well, let's -- I see that, but I mean it's somewhat interesting when it's combined. So if we're looking at the liver data there, there were 32 animals alive when the first carcinoma was seen, but when the first adenoma was seen, there were only 31 animals alive. Is this correct? So when you combine them, there were 32?

DR. SUN: Yes.

COMMITTEE MEMBER EASTMOND: Okay.

DR. SUN: Yes, that's correct. The first adenoma happened on day 666, which is later than the first carcinoma, which happened on day 653.

COMMITTEE MEMBER EASTMOND: Okay. All right. Well, thank you. That's helpful.

COMMITTEE MEMBER LOOMIS: Anything else, Dr. Eastmond?

COMMITTEE MEMBER EASTMOND: Well, it just seemed to me -- well, maybe I'll look at this -- look at the numbers here again in light of something. So I just going to -- wanted to point out that maybe I'm wrong, but it seems like in Table 6 that for the -- if I have this correct, for the islet cell adenoma data, the control incidence in this particular case exceeds the historical

control values that you listed in the document and I'm assuming I'm interpreting that correct, does that seem correct to you?

DR. SUN: Dr. Eastmond, could you clarify, by Table 6, do you mean in the hazard identification document?

COMMITTEE MEMBER EASTMOND: Yes, in the hazard identification document.

DR. SUN: And which tumor type are you referring to, the pancreatic tumors?

COMMITTEE MEMBER EASTMOND: Pancreatic tumors, the islet cell adenomas, there were four seen out of 44 animals in the animals dosed at zero parts per million, the control. And that seems to exceed the reported historical controls on the previous page, is that correct?

DR. SUN: The reported historical control incidence is around 8 percent for combined.

COMMITTEE MEMBER EASTMOND: Yeah. And so this one is somewhat over 8 percent, right? It's about 9 percent. So, I mean, I just -- I guess this is bringing up this point again about -- it's why I think it's useful to see the range in the historical controls, the 95 percent confidence intervals, because as it's presented, we're seeing the average value across a whole bunch of studies. And some studies, half of them are going to have

higher values and half are going to have lower values.

Anyway, that was -- just those are my questions or points.

COMMITTEE MEMBER LOOMIS: Thanks. Maybe the staff can find that information for the Committee discussion later on.

Let's see whether there are any other questions of clarification from the Committee. Anyone else?

DR. MARDER: Dr. Bush has a question.

COMMITTEE MEMBER LOOMIS: Okay. Thank you, Dr. Bush.

COMMITTEE MEMBER BUSH: Thank you. Yes. So the pancreatic islet data, that was extracted from the original Thomford report, is that correct, from 2002, because it wasn't in the Butenhoff paper?

DR. SUN: Yes. And this from Thomford as well, yes.

COMMITTEE MEMBER BUSH: Okay. Thank you. I must confess I didn't read the Thomford paper report, because it was a 4,000-page beast, so we're taking your word for that. But it wasn't published in the Butenhoff paper. So just a point of clarification.

Thank you.

COMMITTEE MEMBER LOOMIS: Okay. Thanks. Anything else from the Committee at this point?

I think I'll need the facilitator to let me know if any hands are raised. I can't see that function on my screen.

DR. MARDER: There are no more hands raised.

COMMITTEE MEMBER LOOMIS: Okay. Let's go ahead then with the second part of the staff presentation. We'll move on to pharmacokinetics and the key characteristics of carcinogens.

NEXT SLIDE

DR. RICKER: We are now at the second part of our presentation, which covers mechanistic considerations and other relevant data. I will start with pharmacokinetics.

NEXT SLIDE

DR. RICKER: Here is a short summary of the pharmacokinetics of PFOS. PFOS is well absorbed following oral administration in animal studies. PFOS binds to proteins such as serum albumin and the liver fatty acid-binding protein. It is widely distributed in the body with preferential accumulation in liver, plasma, and kidney, but it has also been detected in lung, brain, gonads, bone and other tissues. As indicated here, PFOS cross the blood-brain barrier and placenta. It is also detected in breast milk.

Excretion is slow and includes urinary and fecal excretion, and incorporation into nails and hair. In

animals, excretion rates and amounts can vary amongst species. PFOS undergoes enterohepatic circulation in humans and animals.

In females, additional PFOS elimination routes include pregnancy related losses, elimination via breast milk, and menstrual blood loss.

PFOS is not known to be metabolized. The half-life in humans is long compared to other species, and ranges from 1.7 to 8.7 years. It is up to 200 days in monkeys and it is 83 days or less in rodents.

Several precursors, such as perfluorooctane sulfonamides, have been shown to form PFOS via biotransformation in in vivo or in vitro studies, as discussed in more detail in the HID.

NEXT SLIDE

DR. RICKER: We are now going to present mechanistic data for PFOS organized by the 10 key characteristics of carcinogens. These are the key characteristics exhibited by human carcinogens identified through a comprehensive review of mechanistic information available on IARC Group 1 carcinogens.

We will be presenting a brief summary of the cases that had more informative data shown here in bold on this slide. More detailed descriptions of individual findings for these eight KCs can be found in the HID. The

KCs will be presented in numeric order. I start with KCs 2 and 4 through 6. Dr. Hsieh will present KCs 7 through 10.

NEXT SLIDE

DR. RICKER: We begin with Key Characteristic 2 is genotoxic. For this KC, there is some evidence on mutagenicity and suggestive evidence of chromosomal effects and DNA damage induced by PFOS. PFOS is not mutagenic in bacterial assays, but induced mutations in transgenic mice and fish, and in rodent cells in vitro. Several studies found induction of micronuclei, although one study showed negative results in a human cell line.

In rats, increased micronuclei in bone marrow, peripheral blood cells, and hepatocytes were observed in several studies. No increase of micronuclei were reported in one study in male erythrocytes.

In mice, increased micronuclei were seen in hepatocytes of transgenic mice, but not in mouse bone marrow. Increased micronuclei were also seen in zebrafish and in mussels and onion. As to effects on chromosomal aberration, one study reported no effect in human peripheral blood cells, while another reported increase chromosomal aberration in onion cells.

NEXT SLIDE

DR. RICKER: We continue with KC 2. Positive

evidence for induction of DNA damage was observed in humans and various experimental systems.

Evidence for DNA strand breaks. There were increases in one of three studies conducted in human HepG2 cells, but no effects in sperm cells in vitro obtained from human volunteers; increases in bone marrow, peripheral blood cells, and hepatocytes of treated rats, but no effects in Syrian hamster embryo cells in vitro; increases in primary mouse Leydig cells and increases in peripheral blood cells of fish and in most, but not all other species tested.

There is additional evidence on DNA damage. One study reported increased gamma-H2AX, a biomarker of DNA damage in transgenic mouse cells in vitro; increases in the number of foci of the DNA damage checkpoint protein Hus-1 in germ cells of C. elegans. The serum levels of PFOS was associated with the level of 8-hydroxydeoxyguanosine in human urine samples in two out of three studies. PFOS did not increase unscheduled DNA synthesis in rat primary liver cell cultures.

This is the summary of the evidence for KC 2.

NEXT SLIDE

DR. RICKER: Moving on to the next key characteristic, KC 4, induces epigenetic alterations. A number of studies related to epigenetic alterations that

may be relevant to carcinogenesis were identified in humans and animals. Here are some of these effects and examples.

Prenatal PFOS exposure was associated with DNA methylation in cord blood of two CpG sites in two human genes. Both genes have been found to be altered in several human cancers.

Global Alu hypomethylation was also associated with PFOS in cord blood in the birth cohort study. A global pattern of hypomethylation is one of the characteristics of a cancer cell. One mouse and two rat studies found changes in microRNA profiles that have been linked to malformation. MicroRNAs play a crucial role in the regulation of cancer-associated processes, including proliferation, differentiation, and apoptosis.

Finally, DNA methyltransferases, DNMT for short, can lead to reduced expression of tumor suppressor genes. Expression of DNA methyltransferase 3a was increased in two Studies in rats. Altered DNA methyltransferase expression was also seen in humans cells in vitro.

This is the summary of evidence for KC 4.

NEXT SLIDE

DR. RICKER: Now, we come to KC 5, the induction of oxidative stress. Positive findings from human studies are presented in bold on this slide. As mentioned under

KC 2, two out of three human studies observed a positive association between urinary 8-hydroxydeoxyguanosine, a biomarker for oxidative DNA damage and PFOS levels in serum. Significant increases of reactive oxygen and nitrogen species, and lipid peroxidation were also reported in human studies and in multiple experimental test systems.

Changes were also reported in the total antioxidant capacity, the antioxidant enzyme activities or levels, and glutathione status.

Up- or down-regulation in the protein or gene expression of Nrf2 were observed in mice and zebrafish. Nrf2 is a key regulator of cellar resistance to oxidative stress. Reduced levels of Nrf2 protein were observed in mice, and increased levels of Nrf2 gene or protein in zebrafish during the uptake phase and decreased expression during the depuration phase.

There's also some evidence from omic studies. Microarray and bioinformatic analyses showed that several pathways or genes related to the oxidative stress response were significantly modified in the PFOS-treated group. That's the summary of evidence for KC 5.

NEXT SLIDE

DR. RICKER: The next KC is the KC 6, induces chronic inflammation.

The effects of PFOS on pro-inflammatory cytokine production, have been tested in multiple human cell types in vitro and in several animal studies in vivo and in vitro.

In humans, the following results were reported:

Increases of interleukin 1 in two studies in human -- in human bronchial epithelial cells and lymphocytes; decreases of interleukin 10 and interferon gamma in two studies using human peripheral blood leukocytes; decreases of tumor necrosis factor alpha secretion mRNA expression in human blood cells in two studies and decreases of the chemokine CXCL 10 in one study; findings for several other interleukins were unclear with decreases, increases, or no change reported; in animals, increases of interleukin 1 were observed in multiple species; decreases of interleukin 2 in mice and interleukin 8 in chicken embryo cells; increases of interleukin 15 and transforming growth factor beta, both in zebrafish, neither increase nor decrease was reported for interleukin 5 production in mouse cells; and findings for several other interleukins and cytokines were unclear with decreases, increases, or no change reported.

This is the summary for evidence for KC 6. I'm now handing over the presentation to Dr. Hsieh.

NEXT SLIDE

DR. HSIEH: Our next key characteristic of carcinogens is KC 7, is immunosuppressive.

IgM responses were suppressed in several studies in mouse both with and without antigen challenge. Two studies reported no change. One study in rats reported an increase in IgM following PFOS treatment. PFOS reduced the number and the proliferation of thymocytes and splenocytes in mice in multiple studies. Two studies, one in mice and one in rats, reported no change. In a study using dolphin peripheral blood leucocytes, PFOS-induced dose-dependent T cell proliferation.

Regarding natural killer cell, or NK cell, activity, one human study and four studies in mice reported decreases in NK cell activity following exposure to PFOS. Two studies reported increase in male mice.

That's the summary of evidence for KC 7.

NEXT SLIDE

DR. HSIEH: In the following four slides, I will cover the key characteristic 8 receptor-mediated effects starting with estrogenic effects.

Several studies shows that PFOS has effects on estrogen receptor, or ER for short, on estradiol levels. PFOS was negative associated with estradiol levels in women and girls in several studies, but several studies did not find an association. In human cells, in vitro,

PFOS increased ER alpha and beta reporter activity, increased cell proliferation in breast epithelial cells, and down-regulated expression of estrogen-responsive genes. PFOS also reduced estradiol levels in placental cells and increased estradiol levels in adrenal cells.

In rodent studies in vivo, PFOS increased expression of ER alpha and beta, altered the estrous cycle in rats, and induced gene expression profile similar to the profile of known ER alpha agonist. PFOS also increased estradiol levels in female rats, decreased estradiol levels in female mice, and had no effect in male mice. In fish, PFOS increased or decreased vitellogenin expression at different time points, altered gene related to ER production, and altered ER alpha and beta expression and, weakly bound to liver ER in trout. It also increased estradiol levels in female zebrafish.

NEXT SLIDE

DR. HSIEH: Continue on androgen receptor and testosterone effects. Several observational studies in humans found significant associations of PFOS with testosterone levels, many but not all were inverse. In human cells in vitro, PFOS antagonized dihydrotestosterone, or DHT for short, induced androgen receptor activity in humans cells in one study. PFOS increased testosterone in two studies and decreased in one

study.

In an in vivo study in rats, PFOS increased or decreased androgen receptor expression in different tissues. It also decreased testosterone in rodents in vivo and in vitro.

Lastly, PFOS antagonized DHT-induced human androgen receptor activities in a reporter gene study in Chinese hamster ovary cells.

NEXT SLIDE

DR. HSIEH: Next, regarding other receptors, PFOS also induced peroxisome proliferator-activated receptor, or PPAR-alpha activity in several test systems, including human cells in vitro, rodents in vivo, animal cells in vitro, and several species of fish. It seems that PFOS is a weaker agonist of human PPAR-alpha compared to rats or mouse PPAR-alpha. Yet, PFOS was able to activate PPAR-alpha-mediated gene expression in human hepatocytes in two studies. Additionally, two studies with PPAR-alpha-knockout mice demonstrate that PFOS can exert effect through PPAR-alpha independent mechanisms, although PPAR-alpha appears to be the primary nuclear receptor target of PFOS in rodents.

NEXT SLIDE

DR. HSIEH: Last, but not the least, PFOS also affected other receptors, such as PPAR-gamma, pregnane X

receptor, PXR for short, constitutive androstane receptor, CAR for short, and PPAR-beta/delta in human cells in vitro, rodents in vivo and animal cells in vitro, and fish studies.

Regarding effects on thyroid hormone, there were no consistent trend in effect on thyroid hormones across studies in the general human population. In animals, the overall body of evidence suggests PFOS decreases thyroid hormone levels. Mechanistic studies suggest it may interact with thyroid hormone transporters and receptors.

That conclude the summary of evidence for KC 8.

NEXT SLIDE

DR. HSIEH: Now, we move on to KC 9, cause immortalization. There are only a few studies available on PFOS on KC 9 listed as follows.

Inconsistent results has been reported for the association between serum PFOS level and telomere length from human blood samples, with positive associations in a U.S. population, a weakly positive association in a California birth cohort, and inverse associations in a Belgian population. One study reported that PFOS increased the transformation frequency of Syrian hamster embryo cell and another study reported that PFOS induced malignant transformation of a normal human breast epithelial cell line. That's the summary of evidence for

KC 9.

NEXT SLIDE

DR. HSIEH: The last KC I'm presenting is KC 10, alters cell proliferation, cell death, or nutrient supply.

Multiple in vitro studies shows an increase in proliferation in human cells. In two rat studies, PFOS increases cell proliferation or inhibits apoptosis in the liver.

A third rat study reported early transcriptional changes related to cell cycle control, apoptosis, and proliferation in the liver of rats exposed to PFOS in utero and through lactation. PFOS also altered the expression of proteins linked to cell proliferation, including increased level of cell cycle proteins and growth factors in a human liver cell line.

One study reported that PFOS inhibits gap junctional intercellular communications in the rat liver cell line. An in vitro study in primary salmon hepatocytes reported a slight decrease in apoptosis and a significant decrease in caspase 3B.

That's the summary of evidence for KC 10.

I'm now handing the presentation over to Dr. Osborne. She will start with the comparison of PFOS and PFOA.

NEXT SLIDE

DR. OSBORNE: I'm going to present a brief comparison of the data for PFOS and PFOA starting with tumors observed in rat cancer bioassays. We have PFOS in the middle column and PFOA on the right with tumor sites found in both chemicals in bold.

PFOS and PFOA both induce liver tumors in male and female rats. Pancreatic tumors were seen in male rats treated with PFOS and in male and female rats treated with PFOA, although they were different cell types. Mammary gland fibroadenomas were also observed in female rats treated with PFOS or PFOA.

NEXT SLIDE

DR. OSBORNE: We also looked at some data-rich endpoints for each chemical. Both have evidence for genotoxic effects, including chromosomal effects and DNA damage. They both induce effects related to oxidative stress, such as oxidative DNA damage, increased reactive oxygen and nitrogen species, and both alter total antioxidant capacity. Each can also suppress the immune system, as shown by reduction of IgM production and decrease in cellularity and proliferation of T and B cells.

Finally, both have quite a bit of data related to receptor-mediated effects. For example, both have shown they can alter expression of genes related to ER alpha,

PPAR-alpha, PPAR-gamma, PXR, and CAR.

That concludes our brief comparison of PFOS and PFOA.

NEXT SLIDE

DR. OSBORNE: Now, I will present a summary of the evidence from today's presentation.

NEXT SLIDE

DR. OSBORNE: To summarize data from carcinogenicity studies, the majority of human epidemiological studies looked at breast cancer. The results were mixed regardless of whether PFOS levels are measured before or after breast cancer diagnosis. There were not enough studies to draw conclusions for other cancer sites. For animals, long-term carcinogenicity studies were conducted in male and female rats.

Liver and thyroid tumors were observed in both males and females. Pancreatic tumors were observed in male rats and mammary gland tumors were observed in female rats. In a tumor promotion study in rainbow trout, in which PFOS was administered as the promoter after initiation with aflatoxin B1, liver tumors were observed.

NEXT SLIDE

DR. OSBORNE: Finally, there were data for many of the key characteristics of carcinogens. For KC 2, there is some evidence of mutagenicity and suggestive

evidence of chromosomal effects and DNA damage.

For KC 4, studies have reported altered methylation of regions associated with specific genes, global methylation, and microRNA changes, and alterations in expression of DNA methyltransferases.

For KC 5, there are data showing PFOS induced oxidative DNA damage, generation of reactive oxygen or nitrogen species, and lipid peroxidation from studies in humans, rodents, zebrafish, and plants.

For KC 7, the available data on IgM, T cells, B cells, and NK cells suggest that PFOS can suppress the immune system in ways that allow neoplastic cells to evade immune surveillance.

For KC 8, animal studies reported that PFOS alters the expression of genes regulated by multiple different receptors. PFOS also altered androgen receptor expression in rats. Animal studies reported increases in estradiol levels and decreases in thyroid hormone levels. Additionally, evidence for an estrogenic effect of PFOS in humans comes from increased estrogen receptor reporter activity, and cell proliferation in several human cell lines.

For KC 10, studies reported increased cell proliferation, inhibited apoptosis, and inhibited gap junctional intercellular communication in rats and/or in

human and rat cells

For two KCs, the data are unclear or mixed. For KC 6, the effects on pro-inflammatory cytokines are unclear. For KC 9, inconsistent results have been reported for the association between serum PFOS levels and telomere length from human blood samples. And that concludes our presentation of the data regarding the carcinogenicity of PFOS, its salts, and transformation and degradation precursors.

Thank you for your attention and we're happy to take any questions.

COMMITTEE DISCUSSION

COMMITTEE MEMBER LOOMIS: Thank you.

Let's do the same thing again. We'll invite the Committee to ask any questions of clarification. Best to raise your hand and then the facilitator will let me know if there are any questions.

DR. MARDER: Dr. La Merrill has her hand raised.

COMMITTEE MEMBER LOOMIS: Okay. Go ahead please.

COMMITTEE MEMBER LA MERRILL: Yes. Good morning. I'm just curious if we could elaborate a little bit on the evidence for lowered thyroid hormone, which was presented as part of KC 8. It seemed in the materials that were provided to us that it was kind of a summary of a summary. And I was wondering if, in particular, you could elaborate

on which species that was evaluated in, and perhaps, you know, how many studies contributed to that summary?

COMMITTEE MEMBER LA MERRILL: Did my audio work? Do you hear me okay?

COMMITTEE MEMBER LOOMIS: No, we do now.

DR. MARDER: We did hear your question.

COMMITTEE MEMBER LOOMIS: So is anyone on staff able to respond to that question?

DR. MARDER: I'm hearing that Dr. Sun's audio has frozen on Zoom, of course.

Dr. Sandy.

DR. SANDY: Yeah. So let's -- when Dr. Sun has her audio back, we'll let her respond. I can say that we -- if we can't respond right now, we'll get back to you in a few minutes.

COMMITTEE MEMBER LOOMIS: Well, while we're waiting, let's see if there are any other questions for the Committee -- from the Committee rather?

DR. SUN: Hello. Can you hear me?

DR. MARDER: It looks like we have Dr. Sun back.

COMMITTEE MEMBER LOOMIS: Okay. Let's go ahead with the response then. Thank you.

DR. SUN: Thank you. Sorry for the technical glitch. My Zoom was frozen.

Yeah. Regarding thyroid hormone effects, our

summary is basically taken from the OEHHA draft document for the proposed PHG, the Public Health Goal, which reviewed the U.S. EPA documents on thyroid effects. And what we have in the hazard identified document is based on animal studies over a body of evidence. There is suggestion that PFOS decreased thyroid hormone levels. And we also summarized several studies in the human population. So you can refer to page, let me see, 121 for a brief summary.

COMMITTEE MEMBER LA MERRILL: Yes I have that page in front of me. I was just hoping that you could elaborate on the summary of the summary. But I suppose you're saying that you're unable to specify which animal species that contribute to or how many studies were incorporated into that statement?

Thanks.

DR. SUN: We can check on that and get back to you later.

COMMITTEE MEMBER LA MERRILL: Thank you.

COMMITTEE MEMBER LOOMIS: Okay. Let's move on then and see if the Committee has any further questions.

DR. MARDER: Both Dr. Landolph and Dr. McDonald have their hands raised.

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

DR. MARDER: Dr. Landolph.

COMMITTEE MEMBER LOOMIS: Dr. Landolph, I did call on you.

COMMITTEE MEMBER LANDOLPH: Can you hear me now?

COMMITTEE MEMBER LOOMIS: Yes.

COMMITTEE MEMBER LANDOLPH: Yeah. Thank you.

In the -- in the reactive oxygen species induction and the formation of 8-hydroxydeoxyguanosine, were those results dose dependent upon these compounds and was the apoptosis decrease was that dose dependent, and were the cell transformation studies in the SHE cells and the normal human breast epithelial cells, were those inductions of transformed cells dose dependent?

DR. SUN: I can start by answering the question on the oxidative DNA damage measurement. If you take a look at the document Table G1, there is dose dependence in several of the studies.

COMMITTEE MEMBER LANDOLPH: Thank you.

DR. SUN: And your other question is on the cell transformation studies?

COMMITTEE MEMBER LANDOLPH: Um-hmm.

DR. SUN: Let me check on that right now.

COMMITTEE MEMBER LANDOLPH: Thank you.

COMMITTEE MEMBER LOOMIS: If you need a few minutes to check that, we can go on to Dr. McDonald's

question. How shall we proceed?

DR. SUN: I can just quickly say that in the cell transformation study in rats SHE cells, there were effects at 0.37 and 3.7 micromolar, but not at higher concentrations. And both these doses are considered non-cytotoxic.

COMMITTEE MEMBER LANDOLPH: Thank you again.

COMMITTEE MEMBER LOOMIS: Okay. Anything else for you, Dr. Landolph?

COMMITTEE MEMBER LANDOLPH: And the inhibition of the gap junctional communication, was that dose dependent with these compounds at non-cytotoxic concentrations, do you know?

DR. HSIEH: Yeah, I can answer that question, yes. A particular study shows dose dependent on the gap junction inhibition.

COMMITTEE MEMBER LANDOLPH: Thank you very much.

DR. HSIEH: Um-hmm.

COMMITTEE MEMBER LOOMIS: Anything else?

All right. Let's go on to Dr. McDonald then.

COMMITTEE MEMBER McDONALD: Yeah, I just had a question around chronic inflammation. I did notice in the two-year bioassay, which is the only chronic study, that there was no evidence of inflammation based on histopathology. I also saw that you included a lot of

acute and subacute two-week studies. I just wondered how much you think we should focus on the validity of those short-term studies for chronic inflammation?

DR. SUN: Yes. We did gather the data that we have in regard to the release of inflammatory cytokines and chemokines, but how to interpret it is up to the committee for chronic inflammation.

COMMITTEE MEMBER MACDONALD: Okay. We can discuss it during the Committee time.

COMMITTEE MEMBER LOOMIS: All right. It looks like Dr. Eastmond has a hand up.

Go ahead, please.

Can't hear you.

DR. MARDER: You are muted, Dr. Eastmond.

COMMITTEE MEMBER LOOMIS: You're muted.

(Laughter.)

COMMITTEE MEMBER EASTMOND: All right. Thanks.

I've just been thinking a little bit about sort of the doses on these studies. And so for a compound which is really poorly excreted, such as PFOS, and when you start looking at, you know, even intermediate term exposures, you're really getting accumulation of chemical over time. It would seem to me that -- so the effective dose -- internal dose is actually quite a bit higher than one would think based upon the administered dose. Did

that go into any of your thinking or discussion on some of these endpoints?

DR. SUN: For the two-year animal cancer bioassays, we did report serum concentrations, a myriad of -- measured at variable time points, and calculated achieved lifetime average daily dose daily concentration, and it's in the hazard identification document.

COMMITTEE MEMBER EASTMOND: Okay. I was thinking of that from -- it's more of sort of interpreting some of these things that are intermediate doses, where you think it's happening at fairly low doses, but in reality, there's -- the body burden in these animals is probably much higher than we're thinking, because it's so poorly excreted.

The stability of this compound is one of the challenges, both in the environment, but also in a living organism. So I thought I'd ask.

Thanks.

COMMITTEE MEMBER LOOMIS: Thank you. Are there any other clarifying questions for the staff?

Very good.

Hearing none. We'll move on to the next part of the agenda, the Committee discussion. And so the way we'll go through this is that we'll begin with the human studies, and then work through the animal cancer studies

and discussion of mechanistic studies.

So for each one of those areas, the pro -- the initial discussant will go first. So for human studies that will be Mariana Stern and then I'll add to her comments. For the animal cancer studies, Dr. Landolph followed by Dr. Bush. And for the mechanistic studies, Dr. La Merrill, then Dr. Eastmond, and Dr. Zhang.

So what I'd like to do is ask the initial discussions -- initial discussants not to read their reports verbatim, if they have a written report, but to provide a summary for the Committee. And then the second discussant, and third discussants if there is one, can simply add to those any additional comments or other assessments of the data, if that's okay. So we'll begin with the epidemiologic studies and, Dr. Stern, I hope you will agree to lead that off.

COMMITTEE MEMBER STERN: Yes. Thank you, Dr. Loomis. So I'll try -- given that we got a very nice presentation from the staff, I'll try to not repeat too much, but I'll try to summarize the evidence that was provided to us and that we studied.

So as it was mentioned, there were 19 total studies that were identified that met the requirements, that include at least 10 different cancers with the main cancer being breast cancer. The studies include both

studies that ascertain PFOS before diagnosis of the cancer, which is the ideal scenario is to determine causality, as well as studies that assert the PFOS exposure at the time of diagnosis.

There were four different prospective cohorts that reported studies, which included the -- an occupational cohort in Alabama from the 3M Company, a Danish birth cohort, the Child Health and Development Study cohort here in California, and a French cohort.

So I won't provide details of the cohorts, but if there are any questions, I'm happy to respond to those. So as mentioned, the main cancer site that was studied was breast with a total of 10 studies, five that examined PFOS before diagnosis, and five that examined PFOS after -- at the time of diagnosis.

I'll focus mostly on the -- on the four cohort studies that reported on PFOS, because those are the data that we think are most valuable. And the Decatur cohort, which is the Alabama cohort, which is the only occupational cohort that reported on PFOS, and as described compare individuals who work in the chemical plant to individuals who work in the film plant, which are supposed to be non-exposed.

That said, as shown by the staff, the level of exposure of individuals in this cohort is considerably

higher than what has been reported for the general population. This raises concern, because we are basically comparing people that already have a very high level of exposure to people who have even higher level of exposure, so there is a chance that we may not detect that difference in incidence or mortality.

In spite of that, they did report a positive association with mortality, when comparing the two groups. However, it was based on very small numbers, because they didn't have enough people to count enough deaths. So that information is important, but it's based on very small numbers.

The Danish cohort did not report positive associations for PFOS. They did see some associations here and there, but nothing consistent. Now, the French cohort did report positive associations for PFOS and breast cancer. And what I found interesting is that they found that the association was stronger when considering subtypes of breast cancer tumors, in particular tumors that are estrogen and progesterone positive tumors.

This is one of the few studies that took into account breast cancer subtypes. And I think this is important because it might be that PFOS association with that particular type of breast cancer and there's a synergy between PFOS and estrogen. And that might not be

present in tumors that are estrogen receptor negative or progesterone receptor negative.

Unfortunately, there were not many other studies that took that into account. The California pregnancy cohort reported a positive association between breast cancer and EtFOSSA but not with PFOS. And as reported before, EtFOSSA is a precursor of PFOS.

So overall for prospective studies, the data seems very limited and inadequate, because there were few studies. And the one that I found most informative is the one that actually considers subtypes of breast cancer and that study did find a positive association with PFOS, and as well as the occupational cohort, although that is based on small numbers.

Now, among the studies that ascertain PFOS at the time of diagnosis, there were five studies. Four were done among Inuit women in Greenland and one was nested within the California Teachers Study. For the studies done in Greenland, and as reported by the staff, this is a population that has a high level of exposure not only to PFOS, but other chemicals. They did report a positive association with PFOS, which was confirmed in a follow-up study within these women.

However, one concern in this cohort is that there could be correlation with other chemicals and they were

not able or they did not adjust for these potential confounders. The California Teachers Study did not show evidence of association with PFOS across the participants.

So altogether, the evidence for PFOS and breast cancer seems inadequate. Most studies showed, if we look at the data altogether as shown in that forest plot, there is a trend towards a positive association. However, that it's only significant in a few of the studies. However, I want to highlight that it seems that estrogen at that dose may matter. And that one study from the French cohort supports the evidence that it could be. They show a dose response trend and a significant trend of association with estrogen receptor positive and progesterone receptor positive.

For the other cancers that we investigated, the data was very sparse. Altogether, the occupational cohort from Alabama showed positive association with bladder cancer, but it's based on small numbers, and no association with prostate cancer or any of the other cancers.

The Denmark cohort show association with bladder, pancreas, and liver -- did not show association with bladder, pancreas, and liver. And it showed a non-significant positive association with prostate. So -- and when we look at all the other studies that assess

exposure at the time of diagnosis, there was overall -- the only remarkable thing that I observed was the significant positive association with prostate cancer among many in Sweden, which was restricted to men who had family history of cancer and a significant positive association with renal cancer among participants of the PLCO trial. However, when they adjusted for other PFAS, this association was attenuated.

So my final conclusion is that the evidence for prospective studies seems limited in breast cancer with some evidence for an association with estrogen-receptor and progesterone-receptor positive cancers. And there's inadequate evidence for the other cancers with the potentially strongest one being prostate cancer and renal cancer.

The main concerns across all studies is potential correlation with other PFAS, which was considered in a few of the studies, but not consistently considered across all the studies. And the other concern is that -- two additional concerns. One is that the association could potentially be limited to one particular subtype or subtypes of breast cancer, and this was not considered in all the studies. And the other concern is that there is the thought -- and this is mentioned across many of the studies, that there could be an important window of

exposure for PFOS, perhaps when women -- for breast cancer for women when they are in their puberty. And some of these studies, because of the timing, they did not capture that or the women have not been exposed to PFOS because of the timing of when PFOS was available in the environment.

Yes, so I think that I'll stop here and let Dr. Loomis add anything that I may have missed.

COMMITTEE MEMBER LOOMIS: Thank you. That was an excellent summary. I don't have very much to add. I will say that I find all of these studies to be quite challenging. There are not many studies available on human cancer and PFOS. Even 11 for breast cancer really shakes out to just a small number of cohorts.

That Alabama occupational cohort study is kind of an outlier among all of these. It's the only study that assessed exposure with a method other than blood or serum measurement of PFOS. So it's interesting to look at those results. However, that study, as Dr. Stern already pointed out, is challenging, because the comparison occupational population had fairly high exposures already. And there's also selective reporting in that study, so going through the results for all of the sites other than breast cancer, the Alabama study comes up several times with positive results, but that's because they only reported the cancer sites that did have positive

associations. So it's a bit of a -- you know, it's a bit difficult to assess the results of that study.

So for me, I would agree that the evidence for all of the cancer sites except breast is essentially inadequate. I noted some positive findings for prostate cancer, but there are only three studies. And one of those three, the one from Sweden, as Dr. Stern already said, was based on sampling at time of diagnosis, so there are questions about the interpretation of the exposure data in that one and then other urinary cancers, the California -- or the PLCO study also had positive results, interesting, but just one study. So -- and that one is also inadequate for me.

So that leaves us with the breast cancer studies. I largely concur with Dr. Stern's assessment with those. Again, they were quite challenging because of the exposure assessment issues. The five studies that assessed exposure at or after diagnosis result from only two different study populations. And all of those are really difficult to interpret, because of the potential for what we're now calling reverse causation.

So going back to the other five studies on breast cancer, they're also rather difficult to interpret. The reverse causation problem is not there. But still despite the long half-life of PFOS, you know, we're typically

looking at exposure measurements that were made at one point in time in trying to relay those to cancer occurring later, so all of these studies are rather limited in terms of exposure assessment.

The most informative one for me was the French Teachers Cohort Study, which is very interesting, because it's the only one that looked at breast cancer subtypes and did find those positive results with receptor-positive cancer. So I concur with the assessment of the breast cancer studies. I find the evidence to be limited at best. Happy to discuss that with the Committee when we get to that point in the Committee report.

But now let's move on to the animal cancer studies, and Dr. Landolph's assessment first.

You're on mute.

COMMITTEE MEMBER LANDOLPH: Okay. Gotcha. Can you hear me now?

COMMITTEE MEMBER LOOMIS: Yes.

COMMITTEE MEMBER LANDOLPH: Thank you. Thank you, Dr. Loomis. And I really appreciated reading through this document. It's prepared very well by Dr. Lauren Zeise and her staff and the scientists.

The studies in the Sprague-Dawley rats on the page 47, the liver studies, hepatocellular adenomas, increased in a dose-dependent fashion and the trend test

was positive at the 0.006 level. The islet cell adenomas of the pancrease were just flat. It's flat all the way across, so that's no induction. For the pancreas, the islet cell carcinomas went up in a crudely dose-dependent fashion and the trend test was positive at 0.048. And so I accepted those studies. Of course, you rarely see repeats of them, which is something I always like to see, but you almost never see.

For page 48, the thyroid follicular cell adenoma was up by a factor of 3 at the 20 parts per million dose, which was the only one tested in addition to 0. And then in addition, for the two-year studies in the Sprague-Dawley rats, again you go to liver, and that was dose dependent, but it really comes up at the highest dose, but the trend test was positive at P is less than 0.01. And the carcinomas was zeros across the board until the high dose. But when you add the two together, adenomas and carcinomas of the liver, you got a dose-dependent effect and statistically significant at the high point and the trend test was positive at P less than 0.01.

Then for the thyroid -- the follicular cell adenomas didn't show but a few tumors. And the trend was not significant. The follicular cell carcinomas there was one and that was not significant for trend and when you

combined them it was not significant for the trend. And for the thyroid adenomas, the background was too high to make any conclusions for that for me.

And then they did also tumor incidence in female animals, rats. And they did a very weak -- got a very weak induction at 20 parts per million for follicular cell adenomas from zero to one, so that's kind of a weak effect.

And then the -- they did a study in rainbow trout using aflatoxin B1 as an initiator and PFOS as a -- potassium PFOS as a promoter. And that went from one percent up to 13 percent and it was statistically significant at P is less than 0.01.

So my conclusions there are that data was positive in a number of tumors in different experiments and there was statistical significance in the trend test, so I accepted that. It doesn't blow the doors off. It's not, you know, so positive that it's as strong as something like aflatoxin, but I would call it kind of a moderate response.

And then I was impressed by the reactive oxygen species going up, some of the antioxidant enzymes going down, and it was dose dependent as the staff reported. There were immunosuppressive effects in the key characteristics. And then the senescent cells went down,

apoptosis went down, and the immortality went up, so that leads to the disturbing idea that in this -- these ancillary characteristics, you're seeing the properties of carcinogenesis coming up. The gap junctional inhibition of communication -- gap junctional communication went down and that was reported to me to be statistically -- I'm sorry to be dose dependent by the staff.

And let's see what else. And the cell transformation provoked my interest, because it was a dose-dependent induction of transformed cells and SHE cells.

So all this together leads me to integrate this together and indicate that I think the carcinogenicity studies in animals are positive and the ancillary data, which is the gap junctional communication inhibition and the oxygen radical species leading to oxidative damage going up, and some of the gene toxicity database leading up, as I integrate that data, it looks to me like these are positive. I'm a little bit bothered that the major -- some of the major authoritative bodies haven't either not taken this on or didn't come to any significant conclusions yet. So that puts us a little bit out in front, if we were to call this positive.

But I would say that the animal carcinogenicity data and the ancillary cell transformation data gap

junctional communication inhibition look positive to me.

Thank you.

COMMITTEE MEMBER LOOMIS: Okay. Thank you very much. Let's move on to Dr. Bush for any additional comments on the animal cancer studies.

COMMITTEE MEMBER BUSH: Yeah. Thank you, Dr. Loomis. I appreciate that. And great summary from Dr. Landolph. I do want to as well commend Dr. Sandy and the OEHHA team for compiling the hazard ID documents. No small task for this class of chemicals. And I have read the public comments from the seven submissions that were given to us.

I'm going to take a slightly different approach than Dr. Landolph. I was less enthusiastic about the animal data. And regrettably, there aren't more animal studies to make a more compelling argument. The tone of the hazard document for me in the executive summary kind of paint a clear picture. But then when I dig into the animal data, it's a little less clear.

Just a couple of -- well a few notes to piggyback off of Dr. Landolph's observations. You know, the authors themselves indicate that when it come to the mortality from PFOS surprisingly and paradoxically the authors note in the Butenhoff paper that survival was unaffected in females at the two highest doses and then actually

increased for males in the two highest dose groups, which is a little weird and maybe explained by some of the liver pathology that we're seeing.

In terms of the Sprague-Dawley study, the -- for me, the hepatic adenomas were really -- well, statistically significant still seemed marginal to me. I didn't see as much of a dose response there. For the other hyperplasias in the thyroid and the mammary, they seemed rather unremarkable to me. And, in fact, the authors refer to them as spurious. So we've got this kind of inconsistency between dose response and some of the temporal patterns, that when we compare the between male and female.

The thyroid follicular cell adenomas were increased in males exposed to the highest dose, but not males that were exposed to the same dose at the full two years of the study. So again this inconsistency that we're seeing.

The combined follicular cell adenomas and the carcinomas were increased only in the females in the second highest exposure, but not in the high-dose females.

For the pancreatic islet carcinomas, again while statistically significant, it is still really marginal for me in the Sprague-Dawley males. And then the other study, the rainbow trout, while the data was a little more

convincing there, the study was really meant to be a model of independence as -- or independence from peroxisome proliferation. So this two-step approach of using an initiator and then like aflatoxin, and then the promoter, initiation with aflatoxin seemed to show a significance in liver cancers, but only with that initiation. PFOS alone did not generate any liver tumors, and that's in Table 10 in the document.

And surprisingly, and not reported in the -- in the HID that this same paper also used a second initiator, MNNG, to induce liver carcinogenesis, they used PFOA instead. But there is -- and saw tumors, but there was no statistical change in tumor profile when you compare with just the initiator alone.

That then kind of builds into the third potential paper, or animal study, excuse me, the Filgo paper from 2015 that used the PPAR-alpha knockout model. While they found increased hepatocellular adenomas, there was really no malignancy. There was only the hypertrophy hyperplasia. The other tumor types weren't statistically significant, and many that were didn't have a clear dose response.

So for me, taken together, the animal data, while close and suggestive, you know, does not appear to be definitive enough. And so I would -- I would defer to my

colleagues in hearing some of the -- their perspectives on the mechanistic side. And I think for the same reasons that other authoritative bodies, like Health Canada, U.S. EPA, and the European Food Safety haven't ruled on this, I need a little more convincing. Some of the studies were just too problematic for me. So with that, I will yield my time.

COMMITTEE MEMBER LOOMIS: Okay. Thank you very much. Well, it sounds like we need to hear about the mechanistic evidence. And so that's what we'll do next starting with Dr. La Merrill's summary.

COMMITTEE MEMBER LA MERRILL: Okay. Just scrolling up on my notes. Just a moment.

So we heard the really nice summary from OEHHA staff. And thank you all for all the incredibly hard work you put in to make this service easier for all of us on the Committee.

I didn't, in particular, find any PK aspects that I thought were particularly relevant to my interpretation of the mechanistic data. I will though acknowledge that the half-life is significantly longer in humans compared to rodents and monkeys, which may be at play for some of you.

It looked like the ToxCast data that was provided had issues, because the purity levels weren't stated and I

ignored the assays as a result of the concern that was raised in our report.

KC 1, electrophilic was -- had inadequate -- it wasn't really even covered in the report. For genotoxic, I would say that we did see evidence of mutagenic effects of PFOS in transgenic mice and fish, as well as rodent in vitro models, but not bacteria.

DNA strand breaks was probably where we had the most evidence. There was dose-dependent effects in rats. There was also evidence of DNA strand breaks in primary mouse Leydig cells, as well as a number of non-mammalian species, zebrafish, carp, earthworms, flatworms, daphnia, onion. And then there was three studies of HepG2, which is a human hepatic cancer cell line, and in one of those three, we saw DNA strand breaks there.

Some of the null data with respect to DNA strand breaks also included a study of human sperm, human lymphocytes, and Syrian hamster embryo that was hybridized with human chromosome 11, where they did an actual assay on strand breaks in chromosome 11 from the human.

And then as we heard, there was some evaluation of gamma-H2AX, which is a protein and it tags DNA strand breaks. And that was increased in a transgenic mouse cell line. There were 8-oxodG changes, which I'd rather discuss with oxidative stress, since it's really a marker

of oxidative DNA damage. But I thought that was quite compelling and that it had two -- two human studies where there was a dose-dependent relationship between PFOS and circulation and 8-oxodG DNA damage, with a third study being null.

And then there's a couple of micronuclei studies, where we had in vivo -- in vivo effects, and a couple of rat studies, mussel and onion, in vitro in rodents, but it was negative in human and hamster cells and mouse. So, you know, depending on where the Committee wants to think about 8-oxodG, which I think is quite strong, I would say that evidence for genotoxicity is limited in the sense that while we're seeing it across multiple species, and that is frankly compelling and makes me look more carefully at the data, the fact that when people looked in the human systems, it wasn't as supported and made me question whether or not this was actually relevant to the human condition.

For KC 3 DNA damage and repair with instability, I thought that the evidence was inadequate. There really wasn't any evidence.

KC 4 is the key characteristic on epigenetics. So I have broke my assessment of that into different classes of DNA methylation first and then there was also some evidence for non-coding RNA, specifically microRNA.

So with respect to global DNA methylation, which has been attributed to genome stabilizing functions, and those are usually hypomethylated with cancer, we've got -- we have a handful of different studies across people and rodents indicating that there's hyper global methylation, hypomethylation, and null. I think it's in general pretty much all over the place and I couldn't apply in that sense.

There's a number of different ways that we look at global methylation were sensitive, literally global methylation, including these things called Alu and LINE and Sat-alpha units. And again, I thought that the data was pretty equivocal in those, with LINE being more often hypomethylated compared to just one -- or two studies rather, that were null. Yeah, actually that's a wash. Sorry I misread my notes there.

Moving on to DNA methylation specifically in gene sites. What I was really looking for apparent consistencies in more than one study, and particularly if it was going to appear in humans. There were only one, two, three DNA methylation marks near genes that were repeated and independently in more than one human study, and the same direction in both of those studies. There was an additional three DNA methylation marks that were significant in more than one study, but the direction of

the change in methylation relative to PFOS wasn't the same in both studies, so I consider that a bit weaker.

I did -- these three that had the same direction are CYP2E1, SMAD3, and SLC17A9, whereas the ones that were in two studies, but not the same direction, are KLHL35, HOOK2, and ZBTB7A.

I did just a quick search to identify whether or not there was any meta-analyses or systematic reviews in the literature relating any of these genes to cancer just to look for additional evidence to support whether or not the -- this is plausible from a causality perspective. And I did find one meta-analysis from BMC Cancer that basically identified that SMAD3 is a transcription factor that is basically negatively regulated by a different gene called WWOX. And this can repress gene expression activities through typical transcription factor activity to basically modulate lung cancer metastases related to breast cancer. So I thought that sounded relevant to the fact that we have this limited evidence for breast cancer. That was the only one that I found anything worth mentioning.

With respect to specific DNA methylation genes, there were a couple of pathway analyses done on DNA methylation. So the Faroe Island population, they found cord blood was enriched with changes in DNA methylation

and the cancer pathway. And another study looked at human mesenchymal stem cells, which are pluripotent stem cell line, which had enrichment for molecular mechanisms of cancer and G1/S checkpoint. They used different softwares for the pathway analysis, so the fact that the exact name of the pathways doesn't match is to be expected in that context. You know, so I would consider that supporting evidence at best.

With respect to non-coding RNA, there was only studies for microRNA, no long non-coding RNA, for example. So I want to say there was perhaps half a dozen or so microarray studies, a number of them were using human cancer cell lines and then a couple of them were in rodents. There was two rat studies and one in mouse. And so I only identified microRNA that appeared in at least one study.

So for microRNA 22, it appeared in two human neuroblastoma cell lines and was increased in those cell lines, but decreased in rat liver, so three studies total. I will point out that one of the things that people who do epigenetic research all stand by is the fact that these are basically signals that allow for tissue and cell specificity. So looking between tissues I think is -- and expecting the same direction of change is not necessarily anchored in biological reality. I did not find any

meta-analysis or systemic reviews indicating that 22 is associated with cancer.

For microRNA 192, we had it decreased in two different rat liver studies. And it was increased in the blood from a mouse study. And this increased level of 192 in blood, so in the same direction as blood was mentioned measured in the -- in the mice is increase -- is associated with increased cancer survival in five studies with meta-analysis. So perhaps not the correct association direction, if you will.

Now, microRNA 122 was decreased also in the livers of rats and it was increased in the blood from mice. This one I thought had the strongest evidence and relevance to the outcomes here. We saw -- oh, excuse me, I looked for microRNA 122 systemic reviews and there was a number of meta-analyses looking at it with respect to cancer, so I just -- in the last two years, there was three. They were all focused on hepatocellular carcinoma, one by a group Zhang et al. in 2019 associated low microRNA 122 with poor HCC-related survival. And that was based on 11 different human studies, and was validated using data from the Cancer Genome Atlas. So that's again the same direction that was seen in the change with the rats.

And then a study last year Wei et al., 2020,

indicated that 122 could be diagnostic for HCC. That was based on six studies. And then in the same year, a different group suggest it could be diagnostic based on the criteria that led to 13 studies included in their systemic graph. So, of course, there's strengths and limitations -- or, excuse me, that was a meta-analysis -- to each type of meta-analysis, but overall I could see just by skimming the earlier meta-analyses that you were getting more of the same.

Let's see, the last microRNA that was changed in more than one study was microRNA-200C. And this was increased in mouse blood and in the rat liver from one of the earlier rat liver studies. So increased microRNA in two different rodent studies of 200C. And then again when I did the meta-analysis search, high microRNA-200C is associated with worst cancer survival in 58 studies actually by a group named Wang et al., '19. And then upregulation of microRNA C has been associated with it looks like ovarian cancer more frequently, but I didn't get a chance to look into meta-analyses specific to each cancer, but there's a -- there's a lot of meta-analyses on the microRNA-200s.

There's only one study of histones. I thought it was pretty unremarkable. With respect to what is often referred to as readers, writers, and erasers of epigenetic

processes, there's these DNA methyltransferases that can be involved in the maintenance and de novo application of DN -- of methylation to DNA. There was one that came up a number of times in particular and that was DNMT3a. It was increased in two rat studies and it was increased in one of the human neuroblastoma studies, but it was decreased in human trophoblast study. So two out of three studies in one direction. Overall, I would say that I think that this epigenetic data is limited to perhaps strong. And with strong I think in particular the consistency of DNA methylation and microRNA. With the DNA methylation being from several human studies in particular that were independent, I thought was strong, and then being supported by the consistencies in microRNA that are associated with human cancer conditions.

Lots in the epigenetic section. Moving on to KC 5, oxidative stress, I thought this also actually was strong on the basis of the two human observational studies that had the dose response with 8-oxodG that I mentioned when we were talking about genotoxicity.

So just to share in that, we had two observation studies. One was a study of 126 people who were over 60 in years. The other was almost 600 people and that was 22 to 63 years old. The third study that was null was larger. And I did a little bit of looking at kind of what

was the potential differences. They were all based on the Asian continent, but the third null study that had 848, I noticed that that group was quite a bit younger. They were only 12 to 30 years old. And so I don't know if that could be related perhaps to aging.

But I think the fact that we're seeing a dose-dependent change in 8-oxodG and association of that with PFOS in humans in two independent populations to me is already strong enough that I don't need to look really at the other data for oxidative stress. However, there is certainly other support. 8-oxodG was also increased in lettuce seedlings. There was no other data on 8-oxodG with respect to other species to support it. But overall, I think the data for that is strong.

There's a number of studies indicating that PFOS is associated with oxidative stress with oxygen, reactive oxygen species as well as nitric oxide. Let's see here. Multiple experimental test systems, including HepG2, which is the human liver cancer cell line. There's also evidence for these in human umbilical cord vein, epithelial cells -- excuse me, endothelial cells, also endothelial cells of the microvasculature system in humans and human lymphocytes. And then there was some qualitative support of it in one of the neuroblastoma cell lines from humans. So quite a number of human species

there, as well as being increased in Chinese newborn child cord plasma in study of about 581.

And then I think I'll stop there. There's a few more pieces of evidence that were mentioned previously on oxid stress, but I think that point is made.

For KC 6, chronic inflammation, the data is really inadequate. As we heard earlier, there's no evidence of inflammation in a two-year chronic rodent study and the remaining evidence that has been ascertained for us is really just some cytokine levels in vitro that have nothing to do with the chronic situation.

In KC 7, we have immunosuppressive. I believe this is also strong actually. There is quite a lot of evidence. And I think what I'll do is defer to my next colleagues, particularly I know Dr. Zhang is an expert in immune suppression and I think she'll more elegantly summarize that work on our behalf.

KC 8, receptor-mediated is also going to be quite long. So for estrogen receptor, there was, let's see here, one, two, three, four -- four in silico models of the human estrogen receptor alpha that indicate that PFOS would bind ER. It was also modeled for rat and rainbow trout and ER alpha and beta expressions were also increased in a number of studies, Let's see, Sprague-Dawley rat uterus, the human umbilical vein

endothelial cell model, and zebrafish embryos. It was null in a breast epithelial cell line from humans the MCF10A and mouse liver and actually decreased in a few other studies. So I think probably the receptor expression itself is pretty equivocal. There's a similar distribution of data for ER beta, and I'd be happy to summarize that if anyone wants to hear it.

With respect to the activation of a receptor that might be predicted by those in silico models of binding that I mentioned, there seems to be quite a bit. The reporter assays of ER alpha suggested that PFOS can activated in several kind of standard systems, so a human transfected -- a human -- an ER alpha transfected into human kidney cells the HEK293T model would act -- PFOS activated it from one to a thousand nanomolars throughout the range, and in a nice dose-response manner. Also, a different human model where you've got the human breast cancer cell line MCF-7 transfected with luciferase where you're seeing that ER alpha reporter activation.

There were a few studies that reported that PFOS was actually null on ER alpha, but showed that it strongly enhanced the effects of estradiol. So it shifted the potency of estradiol at the receptor that occurred in a different study of the HEK293, which was the cell line I mentioned previously but a different group, as well as a

different human breast cancer cell model called T50 -- excuse me T47D, and also some cells that are uncommonly used call CV-1 African green monkey kidney cells.

The ER beta reporter studies were basically not as often conducted, but in the same study that saw that ER alpha was not activated in the presence of PFOS alone, but enhanced the estradiol effects, they also reported the same for ER beta.

There's a number of different studies looking at proliferation where we see increased proliferation in response to PFAS, and ER positive breast cancer human cells in vitro. And in particular, I was pleased to see that that effect on these cells by PFOS was inhibited by ICI182780, which is an inhibitor specifically of ER, because, of course, proliferation can occur for many reasons and is not always ER dependent. So to be able to block that with a potent antagonist of ER strengthens your confidence that this is a specific proliferative response.

There was a few studies that did show proliferation was null. However, they didn't have that same type of control built in for the ER antagonist, so I didn't think that those were as informative. They were also notably already cancer cells. Whereas, the one with the ER antagonist that I mentioned first was the MCF -- the MCF-10A cell line, which is a breast epithelial cell,

which you can think of in terms of are we talking about causing cancer or modulating cancer behavior once cancer occurs? You might think that -- about that in a different way.

We heard already that the estrous cycle was altered, so I just wanted to point out it was specifically altered, and by having increased diestrus. And this was a dose-dependent effect in Sprague-Dawley rats and was also reported in ICR mice. So I thought that was quite impressive, because it's quite hard to measure cycling. And the fact that somebody got it with dose response in one rodent and then supported it with a total -- a different rodent species, I think is pretty strong evidence for that. And a different group also measured cycle length and found it increased, whereas a third group did not find a change in cycle length.

With respect to target gene expression, there was a number of groups that reported in fairly controlled ways. I thought this was really, you know, kind of secondary supporting information of some of the other material I presented. That target gene includes vitellogenin, which is like a target gene in fish basically in a number of fish species.

There seems to be some influence of PFOS potentially on the production and/or secretion of

estradiol or estrogen. There's a couple of different studies where they found this increased and in the different models. So when those human kidney cells that are transfected with human ER alpha, they saw increased secretion into the media of the estrogens. They also showed that in the same cell line in two other studies -- wait, three, four -- wait, sorry, let me count real quick. Yeah, in five studies. So basically whenever anyone uses this kind of standardized approach in five different labs, they're all getting the same answer, which is quite consistent. And it was actually the secretion was decreased in trophoblasts, which are placenta cells for those of you that are not familiar with that, and decreased also in some mice.

Let's see here, estrogen levels in humans was really inconsistent, but I would note that human studies are never collecting blood while knowing which part of the estrous cycle that people are on and given that estrogen levels vary on a -- on a cycle, I really don't put any weight into those. So that's the summary for ER.

AR, I would say, I -- you know, I could be perhaps persuaded otherwise, but I thought the data for AR was a bit inadequate. There was -- there was some increased AR expression itself in one human study. They found among infertile Italians, an association between

PFOS levels and AR, and -- but I thought, you know, that was kind of a weird way of doing it and I was worried about subgroup analysis issues that could arise from that. And it was supported by AR expression being increased in male Sprague-Dawley rats. There has been some work on reporter expression of AR. And one study said it was repressed -- or repressive and then another study said it was null and a basal condition, but increased with DHT, which is a testosterone.

That was the same study that also found that ERs were -- had null activation by PFOS under basal conditions and then it was enhanced by E2. I thought it was unusual that this particular lab kept having that result which is kind of a weird result. So, you know, it may be something a little strange with their hands in the lab.

Let's see here. There was a couple of studies that found that testosterone was decreased and a couple that found it was increased in humans again. Let's see here, there was with a decrease a dose-dependent effect in a human cell line, and also that occurred in Danish men. And then the C8 Health Project, boys and girls both, as well as in Taiwan, teen girls. Whereas, the increase came from an Avon study, NHANES, and Danish amniotic fluid. So a little bit more in favor of the decrease, but, you know, the null also came from Danish men and women, so this is

why I was saying I feel like it's a bit inadequate, but perhaps limited would be better.

I actually didn't pay too much attention to the PPARs, because I don't find that they're that relevant to cancer. They're just -- so, yeah, if someone wants to talk about them, we can.

For thyroid hormone, I asked about that earlier. And one of the reasons I was interested is because TSH, there's a review that came out from a group named Boesen et al. in 2020 and I wasn't sure if it was included, where they were looking at TSH levels in neonatal infants as well as women. And they -- in the infants, TSH was; increased in three studies, decreased in one, and null in another. And then in the mothers, there were five studies that found significantly increased levels to PFOS of TSH and two that found significantly decreased TSH levels in association with PFOS, and only three that found it null. And so there might be something going on there. I think it's really difficult to measure hormones in circulation in people well, because of the fact that they're so contextual.

KC 9, I -- let's see, wait, did I skip something? No, that's right.

Okay. So that's the end of receptors. I guess the -- just to summarize again, since it took a long time

to go through, overall, I think that the estrogen evidence looks strong. There's a number of species represented, nice dose response work, good work with antagonist to modulate specificity that I think supports that conclusion. And so, you know, some of the other aspects, like how strong I rank AR or thyroid, I think is -- you know, those are just really supporting secondary comments.

So moving on to KC 9 immortalization, that really wasn't covered. That was considered inadequate. There really wasn't a lot of evidence in the literature on that at all.

So the final key characteristics is KC 10, cell fate, I like to think of it as, which includes proliferation, death, and nutrient supply. I thought the -- you know, I've already talked to you all about proliferation. I did think that there was one element of proliferation that hasn't gotten mentioned, which I thought was quite strong. Three human cell lines, when they looked at cell cycle phasing found increased presence of the cells in S phase, or synthesis phase, of the cell cycle in the context of PFOS exposure. And so that included the MCF-10A, human breast epithelial cell line, as well as the human breast cancer cell line, and MCF-7, and -- let's see here. I apologize. I didn't write down the last cell line name, which was qualitative. I thought

it was a bit odd they didn't -- oh, I see what happened. Excuse me. So one was the HL-7702, which is a human fetal hepatocyte cell line.

The other information is really that, you know, RNA related to cell cycle and proliferation, protein related to cell cycle and growth factors. You know, the protein was shown extensively in the human fetal hepatocyte cell line. It was also shown in the human mammary epithelial cell line. And then, as you heard, the gap junction, I agree that that was important because of the contact inhibition of proliferation.

There was also some evidence for cell death being modulated, but not as strong as for proliferation. I think that having the gap junction data, and dose response, and the strong S phase enhancement across three different human cell lines, particularly with all three of the cell lines being in tissues that were discussed as part of the animal pathology, I think that that is strong as well.

So let's see about the death, we've got inhibited apoptosis and two different rat studies, both were Sprague-Dawley, and it was an assessment of their livers. And then there was a slight level of apoptosis and hepatocytes from salmon in culture. Some RNA consistent with that. Some protein consistent with that. Those

evidences came from livers of salmon and rats. And then decreased P53, which of course is a tumor suppressor. The decreased P53 was found in the human mammary epithelial cell line MCF-10A and the human fetal hepatocyte cell line I mentioned earlier.

With respect to kind of fate above and beyond just dying and growing, I did want to point out also a study that was cited in the report, but these outcomes weren't mentioned, that the MCF-10A, the cells that are the human epithelial for mammary glands, had increased migration in an invasion from the exposure to PFOS. So it became more cancer like and more in an aggressive manner.

There's a giant literature on modulation of the PFOS chemical class, including PFOS relating to changes in lipid molecules, like fatty acids and cholesterol. And their -- those lipid molecules are known to be involved in numerous cancers. I decided for the -- and I said that wasn't scoped in the summary, that was out of the range of my attention.

So thank you for listening and I know that was quite long. There's a lot of KCs and material to get through.

COMMITTEE MEMBER LOOMIS: Well, thank you for taking that on. That's certainly a lot of material to summarize. I just have one question for you. I don't

think I heard, maybe I missed it, but your summary of KC 10.

COMMITTEE MEMBER LA MERRILL: Yeah. Okay. I would say that is strong on the basis of the proliferation evidence.

COMMITTEE MEMBER LOOMIS: Okay. Thank you. Let's go on and see what Dr. Eastmond has to add.

COMMITTEE MEMBER EASTMOND: Sure. Thank you.

I want to make a few comments. First of all, I'd like to thank the staff at OEHHA for putting together a pretty impressive document. And they had to summarize a large amount of literature. It was, I'm sure, a fairly heroic effort within the agency. So I appreciate the work that they did.

I'd like to make a couple of comments sort of on the approach. So the key characteristics of carcinogens, in my mind, puts together sort of a structured and systematic framework, by which you can evaluate effects that might contribute to carcinogenesis. They don't describe a mode of action, an adverse outcome pathway, or mechanisms of carcinogenesis.

So, in essence, we're looking at the components that can be put together to form a mechanism or mode of action, but we don't have a mechanism or mode of action, which is compelling on any of these, in my opinion. But

let me comment on a couple of them. The first one, which was kind of skipped over is that as far as electrophilic DNA reactive, this structure is not similar to other carcinogens that I'm aware of. In fact, it's quite different than most other carcinogens.

The one suggestion that may be -- that was kind of buried within the genotoxicity is there's some suggestion that it could be an intercalator into DNA. And so that may explain some of its effects. But if I look through on the various key components of -- certainly of carcinogens and Michele went through them in quite a bit of detail. I certainly won't do that. The two that stand out for me as being probably the most compelling -- and there's evidence for most of them to some degree, but we don't know how that evidence fits together into a mechanism of carcinogenesis, is certainly the oxidative stress. It looks like there's some pretty strong evidence that PFOS does cause oxidative stress in model systems and in humans. And to some degree, the genotoxicity -- the positive results in genotoxicity, which was really a mixed bag, and I'll come back to that in a second, appear to be due to oxidative stress as well. So the one mutation that was seen in a transgenic mouse assay, they came back and said that what was -- the title said it was due to hydrogen peroxide, that it was really due to reactive

oxygen species.

And the other one which -- so I think there's quite a bit of evidence for oxidative stress, but oxidative stress is not sufficient to cause cancer in my mind or at least in most cases. There are well known agents, such as diquat, which are acts of mechanisms, which generates reactive oxygen species, yet it's not been shown to be carcinogenic in animal bioassays.

So, you know, these are components that fit in and there's multiple components that go together to create the mechanism of carcinogenesis. And so at this point, we don't what it is for PFOS, if it indeed is carcinogenic. As far as genotoxicity, there is some evidence for mutagenicity and suggestive evidence for chromosomal effects and DNA damage. And that was the conclusion on it by OEHHA. I would agree with them on that.

I might point out that PFOS is generally negative in sort of the standard validated genotoxicity test. But when you get into sort of non-standard in other types of species or in assays which are oftentimes prone to sort of -- are very finicky and prone to false positives, the DNA strand breaks can frequently occur and get positive results for people that don't really understand how to conduct the assay very well. In fact, in -- I had graduate students that were working on it in my lab and we

abandoned the assay, because it was -- we considered it unreliable in our hands. But I know in some labs where they have a lot of experience doing it, it can be reliable. But oftentimes, when this assay is taken into other sort of non-validated systems, the people who are doing it, don't have a lot of experience, and so I tend to put less weight in those outcomes.

So my bottom line on genotoxicity, there's some evidence, but it's compelling. As I mentioned, there's some evidence for epigenetic alterations. It's not clear how those fit into carcinogenesis in this case. There's certainly evidence for oxidative stress, which I think is consistent, but it's not sufficient, in my mind, to explain how PFOS could cause cancer. We have some evidence for chronic inflammation, some evidence for immunosuppression again, but these are not sufficient to under -- explain the mechanism of tumorigenicity.

Receptor-mediated effects there does appear to be a fair number of positive ones. As Michele indicated, the estrogen pathways appear to be -- there's some evidence for the involvement of estrogenic pathways. And that ties into some of the human epi studies as well.

There's also evidence for the peroxisome proliferator-activated receptor, alpha and gamma, the PXR, and the CAR. And those are particularly relevant in this

case, because they're associated with rodent carcinogens -- rodent carcinogenesis. And a number of agencies are using those mechanisms to reduce sort of the concern about carcinogenesis induced by rodent carcinogens, if they're acting through those definite mechanisms. But again, we don't have enough evidence here to make any -- draw any conclusions, but there's suggestive evidence for many of these different pathways. And the same goes on for the other key characteristics, I should say.

So I guess the bottom line for me is we don't have a defined mechanism. We have components that could be put together into defined mechanisms, but we don't have a clear mechanism at this point for carcinogenesis, and as indicated, the human data is pretty muddled and the animal data can be interpreted in different ways depending on how you look at it. So anyway, I think I'll end there, unless people have questions.

COMMITTEE MEMBER LOOMIS: Okay. Let's move on to Dr. Zhang, any additional comments that you might have.

I think you're muted.

COMMITTEE MEMBER ZHANG: Sorry.

COMMITTEE MEMBER LOOMIS: Can't hear you.

There you are.

COMMITTEE MEMBER ZHANG: Sorry. Can you hear me

now?

COMMITTEE MEMBER LOOMIS: Yes.

COMMITTEE MEMBER ZHANG: Okay. I really want to thank Dr. La Merrill and Dr. Eastmond. They both did a really thorough summary. And also I think I totally agree with David, I think OEHHA staff did a really, really good job in this mechanistic section and it's a lot of work and, you know, they really made it a very comprehensive documents together.

So I don't have much to add, but I just want to give my overall my opinion on that mechanistic data, specifically on the key characteristics. And it looks like very clear for oxidative stress, KC 5, and immunosuppression, KC 7, and that -- I would come give a little bit more -- and receptor -- the modulate the receptor-mediated effects, so KC 8. It looks like for these three KCs are pretty strong and pretty consistent.

And since Dr. La Merrill asked me to focus on the KC 7, actually number one, I'm not the expert on the immunosuppression, but I did some more work on this part for other chemicals, so I would say overall the data is pretty consistent. And especially, you know, after the NTP 2016, they are review on both PFOA and PFOS. And, you know, based on that, I think OEHHA staff now actually really did a lot of updating on that immunosuppression

section, you know, including new studies.

And so the data from immunoglobulin, and especially IgM or IgG, you know, the reduced response on Immunoglobulin is pretty strong to me and also a few other outcomes, you know, like interferon gamma or interferon alpha changes. So all the data I think to me is -- it's pretty strong. So I would say these three KCs, 5, 7, 8 is pretty consistent.

And a couple others. Like I say, KC 4, the epigenetic effects, I think although study number is limited, but very consistent. And also -- so that's when I was trying to looking at more, I found this new study just very recently published by Goodrich, so to me actually KC 4, the genotoxic mechanism could be -- play another very important role. So even though limited studies, but consistent and strong. So I was also thinking KC 4 could be updated.

So -- and now I'm just trying to shift to the -- you see epigenetic mechanism is strong, so I sort of agree with Dr. Eastmond on the genotoxicity, the KC 2 data. KC 2 data is a little, you know, messy, I would say. You know, some data support it, as you know, genotoxic, some not. And I would say if PFOS considered as genotoxic, in my opinion, could be a weak genotoxic compound. So I would say it may -- I think PFOS may play more important

roles through epigenetic pathways or immunotoxicological pathways to -- to -- you know, if cause cancer. So that would be a more relevant mechanism or pathway, we should consider. So that's actually -- basically, it's my very general summary about the, you know, KC approach.

So I heard -- okay, David, you can correct me. I heard you are saying, if that's what you are saying, is you are thinking about oh, your, I want to say, doubt about if that's necessary or if it's correct using the key characteristics pathways to analyze the mechanistic data. So I don't know if I hear you really correctly.

But I think -- yeah, I think I agree with, you know, if you only look at the, let's say, oxidative stress by itself, it may not be, you know, sufficient enough. I guess maybe that's what you were saying. But, you know, if you look at the other different key characteristics together, this is, I think, the way I think both IARC and EPA now wants to practice. Can we use the KC approach to evaluate the chemicals for the -- for the mechanistic, you know, evidence?

So that's all I want to say. I hope I didn't forget anything. I don't want to go one by one. I'm sure the other three KCs OEHHA doesn't think that's important because we do not have enough studies or evidence. So that's the KC 1 -- that's 1, 3, and 9.

So, in general, that's what I have -- I can put together here. But generally, I think the mechanistic data is still pretty strong, especially the KC 8, which is Dr. La Merrill's expertise on that, especially that is related to really strongly supported the human data, whether they found the strong association with breast cancer. So I think that's -- I think that that's a strong point for the PFOS.

Okay. I think I'm just going to stop right now.

COMMITTEE MEMBER LOOMIS: Very good. Thank you so much. Thanks to everybody who's already presented. It's now 12 almost 12:40. We need to break for lunch at some point, so I'm going to ask the Committee and the staff whether this would be a good time or whether we should go ahead with the Committee discussion and then break for lunch. So let's see if there are any votes to continue or advice from the staff that's -- that that is what we should do in the interests of protocol.

DIRECTOR ZEISE: I don't believe there's a protocol limitation. You can break now, if you would like the time, and resume the discussion when you come back from lunch.

COMMITTEE MEMBER LOOMIS: So looking at this gallery view, I see heads nodding for breaking now. Is there any strong preference to discuss now and then have

lunch?

Okay. Hearing none, we will break now. But before anyone leaves, I would ask Committee counsel, I think Carol Monahan Cummings had to step out, but her substitute, to give the Bagley-Keene warning before we break.

DIRECTOR ZEISE: We're waiting for Kristi Morioka.

DR. MARDER: Kristi, I'm asking you to unmute, please.

CHIEF COUNSEL MONAHAN CUMMINGS: Hi, everybody. This is Carol. I haven't quite left yet, so let me just say that if you could make sure that you don't discuss the -- any of the items that you've been discussing today outside of this meeting, that includes phone calls, texts, emails, just go ahead and have a nice lunch, but don't talk about what you've been talking about all morning.

Thank you. We'll see you in the afternoon.

COMMITTEE MEMBER LOOMIS: Okay. Very good. So I believe the break is to be an hour long, is that correct?

DIRECTOR ZEISE: It's up to the Committee, but you might wish an hour.

COMMITTEE MEMBER LOOMIS: Yeah. Let's go ahead and take an hour, so we'll come back at 1:40.

Okay. See you all then.

(Thereupon a lunch break was taken.)

AFTERNOON SESSION

COMMITTEE MEMBER LOOMIS: I am here, so let's go ahead and resume. I'm assuming that everyone else is here as well. So we left off at the end of the discussants reports and the three evidence streams, so now it's time for Committee discussion, which could include comments from members of the Committee who haven't spoken yet, questions for the discussants and so on.

So I'm going to go ahead and start with one comment, which pertains to the human studies of cancer.

COMMITTEE MEMBER EASTMOND: Dana, do we have public comments in here some time?

COMMITTEE MEMBER LOOMIS: Yes, they come after the --

DIRECTOR ZEISE: Yes, it will be -- Dr. Loomis, I wonder if also you want -- you'd asked for some follow-up and staff indicated they were going to follow up, and any time you would like staff to clarify on those two points that they were going to bring back to you, they can do that.

COMMITTEE MEMBER LOOMIS: Right. Okay. If they're ready to do that now, we could take that up before we go to Committee discussion then.

DR. SUN: Okay. Thank you, Dr. Loomis. I can

report back to Dr. La Merrill, and Dr. Eastmond, and the Committee regarding the two questions. The first question from Dr. La Merrill is on the thyroid hormone effects in animals. So to answer your question based on summaries from OEHHA's proposed public health goal draft document for PFOS, the data available include those summarized by U.S. EPA 2016 and more recent data. So U.S. EPA 2016 identified several studies reporting thyroid effects. In general, there was a reduction in three thyroxine, or T4, and total T4 levels without significant change in TSH or thyroid stimulating hormone. The effects were consistently observed in rats. So these were rat studies.

Specifically, in pregnant rats, PFOS reduced T4 and triiodothyronine, or T3, levels in the dams and T4 in the pups. In monkeys, there was a significant decrease in total T3 and T4 levels in females only, with no change in TSH. So the newer data seems U.S. EPA 2016 include NTP 2019 and the monkey study.

NTP 2019 reported decreases in T3, three T4, and total T4 in both sexes of SD rats. And the monkey study showed a slight reduction in serum total T4 in both sexes. No significant changes in TSH or free T4. So these are the thyroid hormone effects in animals.

Regarding Dr. Eastmond's question on the range for the historical control values. So I'll start by

saying concurrent laboratory controls are always the most appropriate direct comparison with an experimental group. The historical control data were included in the hazard identification document were not from the same laboratory as the Thomford study, but from other control SD rats from oral studies used by Charles River Laboratories.

So the Thomford 2002 study started in 1998 and lasted two years. Therefore, we reported historical data from 1995 to 2002, which means these studies were conducted within two to three years of the Thomford study. Specifically, for the pancreatic islet cell adenoma, the range was 0 to 25.7 percent in male rats and pancreatic islet cell carcinoma range was 0 to 14 percent in male rats.

So as you've observed, the value in the control was higher than the average, but it is still within the historical control range.

For the thyroid follicular cell tumors in female rats, these are rare tumors, so the range for adenoma is 0 to 1.16 percent and the range for the thyroid follicular cell carcinoma is 0 to 0.6 percent.

So these are my answers. Thank you.

COMMITTEE MEMBER EASTMOND: Thanks. I'm wondering if you could do that for the hepato -- the liver tumors as well.

DR. SUN: Liver tumors, the liver hepatocellular adenoma in male rats range is 0 to 8 percent. The liver hepatocellular carcinoma range is 0 to 6 percent. And in female rats, the range for liver hepatocellular adenoma is 0 to 0.29 percent, and the hepatocellular carcinoma in female rats range is 0 to 0.71 percent.

COMMITTEE MEMBER LOOMIS: Good. Thank you for that.

Now, let's move on to Committee discussion. And I did have one additional comment that I wanted to offer about the human cancer studies. This is with respect to the studies of breast cancer in which serum PFOS was measured before diagnosis. So I mentioned a concern about those studies in that despite the long half-life, there is some loss of that material. And typically, the exposure is only measured at one point in time. And so what this means is that there's some unpredictable measurement error in that information. So not knowing anymore about it, my first suspicion would be that since it's essentially random measurement error, it's likely to result in bias toward the null and that entire group of studies. So that's something to keep in mind in thinking about, you know, the mix of positive and negative results that we see in some studies, so that when we see positive results, it's likely to mean that those are studies that may have

had better exposure information than the ones that have more equivocal results, weaker associations and so on. So that was my comment about that.

So now let's go ahead with discussion with other members of the Committee who have questions or comments to offer, and we can try to do what we did before and use the raise hand function. If Dr. Marder is still watching, maybe she can help me in --

DR. MARDER: Absolutely, Dr. Loomis.

COMMITTEE MEMBER LOOMIS: Thanks. I'm -- just let me know if I miss anybody. I'll try to watch, but I can't see all the speakers at once on my screen.

DR. MARDER: Dr. Crespi has her hand raised.

COMMITTEE MEMBER LOOMIS: Go ahead, Dr. Crespi. We can't hear you.

COMMITTEE MEMBER CRESPI: Here we go. I'm trying to get off of mute there.

Yeah, I just want to first thank OEHHA staff for putting together a very comprehensive report, so I really appreciate their work. And I had a question that was directed to the members of our Committee and maybe also OEHHA staff regarding the animal studies, and some of the comments by 3M. In particular, their comment was arguing that the liver tumors in rats are basically observation, you know, are due to a mechanism of action that's not

relevant in humans. So I wondered whether there was anybody who could -- who could speak to that evidence one way or the other, and to that particular comment. Should we discount that finding of liver tumors in rats because that biological mechanism is not something that operates in humans?

COMMITTEE MEMBER LOOMIS: Thanks. Would anybody like to answer that question?

Dr. Eastmond.

COMMITTEE MEMBER EASTMOND: I appreciate that. What they're referring to is mechanisms in which tumors are induced -- liver tumors are induced in rodents through these nuclear receptor-mediated mechanisms. And they tend to be the PPAR-alpha and gamma, or the CAR or PXR. And the challenge is that may be true, but they really haven't provided enough evidence to substantiate that. That's the problem I have with it. I think that may be the case, but usually there's follow-up mechanistic studies to demonstrate that's what's happening and they don't seem to have done that, or at least I couldn't see that. So that's the way I interpret that.

COMMITTEE MEMBER LOOMIS: Okay. Anybody else want to contribute to that question?

All right. I think Dr. Reynolds had her hand up for a question as well.

COMMITTEE MEMBER REYNOLDS: Actually, I was actually going to make a comment. Comment a little bit further on the epi evidence. I can do that later, if you want to stick with questions right now or --

COMMITTEE MEMBER LOOMIS: Well, just go ahead. I think we'll take it all.

COMMITTEE MEMBER REYNOLDS: I wanted to definitely add my thanks to the OEHHA staff for their always impressive work in putting together these hazard identification documents and providing us with the original articles. I also did want to acknowledge some informative comments from the public which I thought were quite helpful. There is no question that although population levels are declining, there's been a wide spread and continuing exposure to this group of compounds.

And this is -- we've come to a chemical where actually finally we do have some epidemiologic research. Often we do not, when we do these reviews. I appreciated that Dr. Stern and Loomis gave a nice review of the epi data. And although limited, the cancer studies really have focused on breast cancer outcomes. It's been a topic of some interest to me. Probably this research is focused on breast cancer because of the endocrine disrupting properties attributed to PFOS and that it's one of the most common cancers in women.

So as articulately discussed by my colleagues, as well as from public comments, the evidence from these studies is most certainly mixed for a number of reasons intrinsic to the challenges of conducting such human health studies. Much of the evidence does come from case control studies in which exposures based on a single blood sample taken at or subsequent to diagnosis of the cases. Since we know little or nothing about the metabolic effects of disease progression or treatment on measured levels, this leads to the associated potential as discussed for reverse causation or difficulties in interpretation in general.

Similarly, biospecimens were obtained at various points in time, reflecting some fairly strong secular differences in exposure. And as I'm glad Dr. Stern pointed out, few studies, including my own study, focused on important windows of susceptibility during the life course. And I think there has, nonetheless, been some provocative evidence from the epi literature for risk associations by breast cancer subtype. Both pre-menopausal versus post-menopausal, and also for ER positive versus negative tumors, suggesting that the risk may not be entirely null.

And just to share, I do want to mention that our own rather null study in California actually saw a

non-significant positive association with PFOS for hormone receptor positive breast cancers in contrast to an also known significant inverse association for ER- and PR-negative tumors, suggesting that there might be some very differential effects.

Also, there are a couple studies that were published this year that weren't included in the document that we might want to just consider. One was a fairly large hospital-based case control study from Japan that was 400 cases with blood collected at diagnosis in the early 2000s and 400 controls. And that's the only study, as far as I know, to examine risk associations for linear and branched isomers separately.

So while that study found an inverse association for PFOS with most models, they also intriguingly noted the opposite effects for linear versus branched isomers for another PFOS, for perfluorotridecanoic acid, if I pronounced it correctly.

Also, not included in the HID is a small case control study published in July of this year from Manila with a suggested elevation in breast cancer risk for PFOS. Although, it was no longer statistically significant when adjusting for a variety of covariates. So as blood was collected in the mid to late 1990s in the French study, which is the study that both reviewers found most

informative, probably both because of prospective blood collection and also for the assessment by hormone receptor subtypes, the levels of PFOS were quite a bit higher than in some of the more recently conducted studies.

It's interesting to note also that positive results were reported in that study and in the two albeit small studies of populations that reflected high levels of environmental exposure, the Greenland Inuit and women in the heavily industrialized area of Manila.

Nonetheless, as Dr. Eastmond says, the human data are muddled. And I would appreciate a little more discussion from my colleagues in terms of the key characteristics. They were somewhat generously summarized by Dr. Zhang for perhaps four of the eight as being supportive in terms of mechanisms of risk. And I'm still not entirely clear about the con -- the lack of consensus from the animal literature, which is also a bit mixed. Nice to know it's not only the epi literature that gets the mixed results. So I just wanted to add those few comments.

COMMITTEE MEMBER LOOMIS: Thank you for those comments.

Let's see whether the colleagues who reviewed the key characteristics would want to respond to any of those questions. And I have a question for them as well. So

maybe they could take both of these at the same time. So in my mind, strong mechanistic evidence usually means that we have evidence from studies of exposed humans. And my impression is that there are not very many of those studies, but I didn't go through and count. So I'd like -- I'd like to hear your thoughts about what makes the evidence strong, if it's true, that there aren't very many studies in exposed humans.

COMMITTEE MEMBER LA MERRILL: I can jump in and kind of go back and just highlight some of those that are focused solely on humans, if you'd like.

Okay. So let me just scroll to the top here. Okay. So I think we all agreed that there wasn't much going on in genotoxic, so I'm going to skip that.

For epigenetics, I suggested it was limited to perhaps strong, and that was based on the fact that there were on a number of studies of DNA methylation in humans with PFAS -- PFOS exposure assessment. One that got brought up was the recent Firefighters Study that Dr. Zhang shared with us. And that one I noticed in particular -- I lost my place momentarily -- that they did some specific work on DNA methylation of certain gene called RAD1. This is an important checkpoint gene. I thought that was relevant, because we had those consistent changes in the position of the cells and the cell cycles.

So consistent with this idea that you could have estrogen receptor-mediated proliferation that was driving more cell cycle synthesis is kind of like a synonym, if you will, for that. That what you have is these molecular signals in the cell where we go through the cell cycle. If there's a damage or problem that arises, these checkpoint genes basically slow down the cycle, so that that damage can be addressed either by repair, or cell death, or other processes.

And so RAD1 having differential methylation status with respect to PFOS in this human cohort is interesting. It's also perhaps relevant to the group, because there's immunohistochemistry evidence that there -- it's able to be a significant prognostic indicator for both liver and breast cancer in humans, looking at like the Protein Atlas, which is a like repository of data of this nature.

The other DNA methylation data that I brought up was two studies in cord blood, one based in Japan and one based in Taiwan that both found DNA methylation increased in association with PFOS for the gene CYP2E1, the gene SMAD3 and a gene called SLC17A9. And SMAD3 is basically a gene that regulates other genes involved in a process that's been shown to relate to metastasis of breast cancer to the lung, so again something relevant to the breast in

that instance.

The other epigenetic data that I mentioned that came from a human study was the microRNA, but it was not as human direct in the sense that the only microRNA that was altered by PFOS in a human context was in two human neuroblastoma cell lines, but I didn't find evidence that that microRNA 22 was associated with cancer in my cursory analysis of the general literature.

So moving on to oxidative stress, where I believe all three of us indicated that we thought there was strong evidence for oxidative stress. That data comes from the evidence for 8-oxodG. So when you have oxidative stress to a cell, one of the consequences can be that these reactive oxygen species are able to bind macromolecules, including DNA. And so 8-oxodG is basically an adduct that forms on DNA that's a marker for oxidative stress. And there was three human observational studies that looked at that in association with PFOS exposure.

And two out of those three studies found a dose-dependent relationship between the PFOS exposure and the 8-oxodG adduct in those people. One of the studies was in 60-year old plus people, 126 of them. The other study that was significant with that dose response relationship was in 597 people of the ages 22 to 63 years old. And the third study that was null was in Taiwanese

people from 12 to 30 years of age, at a number 848.

And then that was an adduct that was also -- the only other study that looked for that type of adduct looked at lettuce seedlings of all things, but they also found it was increased there.

There was some evidence of reactive oxygen species also in a study of Chinese newborns, where they looked at plasma from cord blood in 581 and they saw increased evidence of oxidative stress as well. So quite a number of humans with the PFOS exposure associated with markers of oxidative stress there.

And then the receptor-mediated was the other one that got brought as a strong. And I think that there was agreement that that was mostly on ER. So as you recall, there's quite a lot of it, so let me just skim it real quick to make sure I don't overlook some of the key parts. I think there was, you know, for what it's worth, various -- four different studies that have modeled human ER in silico using what we know about the crystal structure to predict PFOS binding to the human estrogen receptor alpha. And that appears to be possible that it activates through a number of different human cell lines So not an observation study, but they've shown that the ER alpha can be activated, as it can cause promoter activity in human transfected kidney cells, as well as human breast

cancer cells. And -- yeah, I think that's right.

And then we also saw proliferation of human breast epithelial cells that was dependent on the ER as evidenced by using a selective antagonist of ER called ICI 182,780. I think probably if you want to just stay tight and focused, those would be some of the key human-related outcomes and the -- in the receptor-related section.

And then I had mentioned KC 10 as strong really as an extension of the ER. The other two reviewers didn't mention that. But this idea of increased proliferation seen across rodents and human cells, so they did the human fetal hepatocyte, human ovarian granulosa, tumor cell lines, several of them, and then the increased occurrence of human cells being in S phase or the proliferation synthesis phase. And that again was the human fetal hepatocyte model, and the human mammary epithelial cell model, and then the human epithelial cancer cell model.

So I think that probably captures it pretty well.

COMMITTEE MEMBER LOOMIS: Thanks. That helps a lot with my question. Let's see whether anybody else from the group that reviewed those studies in detail wants to jump in on these questions.

COMMITTEE MEMBER EASTMOND: Peggy, did that address your questions?

COMMITTEE MEMBER LOOMIS: That was what I was

going to ask as well.

COMMITTEE MEMBER EASTMOND: I mean.

COMMITTEE MEMBER REYNOLDS: I think so -- I mean, I'm hearing -- I'm hearing slightly different takes on the whole thing. I think that these key characteristics are very critical in terms of thinking about the sort of mechanistic likelihood of risk associations that we can't necessarily delineate from the human health studies. So it is -- it certainly is a complex area and there were sort of lots of issues that were out on the table. So I'm having trouble getting sort of the sense from each of you about how enthusiastic you feel about key characteristics.

COMMITTEE MEMBER EASTMOND: So if I can weigh in, I think of those as sort -- it's a framework by which we evaluate sort of the overall evidence picture, but these are all possibilities. So there's evidence for all these possibilities. But at this point, we don't have a compelling case for any of them. You know, we can tell you there's a little more evidence for this possibility or on that possibility. What you'd like to be able to say mechanistically is PFOS does this initially, and that leads to this second, and then this, and this, and this. And then you can put together this is a plausible mechanism for carcinogenesis, but I don't see that.

We have lots of possibilities there's evidence

for lots of these possibilities, but it hasn't been pulled together in my mind into a really coherent argument.

COMMITTEE MEMBER REYNOLDS: I hear you. Thank you.

COMMITTEE MEMBER LA MERRILL: I just want to acknowledge, I forgot to highlight the strong immunosuppressive aspects of things when I went through the summary. Luoping, I don't know if you want to highlight a couple of the key human studies that were involved in that. I didn't get into as deep of a dive on that since there was so much material.

COMMITTEE MEMBER ZHANG: Yes. I think it's just following what -- okay. Michele get back to the KC7 just in a minute. So let me following what David just said.

I think -- I think David was saying, well, how would other information here, there, or there come -- we put them together. I think that's a very good question in order to explain the potential, you know, carcinogenic pathways. So if we all agree, number one, oxidative stress, it looks like PFOS can induce that pretty strongly. And also see, but we maybe not form oxidative stress -- you generate reactive oxidation radicals. That also can link to the inflammation, right? So I'm just trying to see if -- how we could have, you know, one KC link to another one.

And back -- so for the chronic inflammation, the KC 6, didn't -- I think -- I think, Michele, you did -- you did really, you know, summarize that, but I also want to say OEHHA staff did a really, really good job to put up all the different type of the study on the chronic inflammation in that -- I forgot which appendix, H or something, I think that's a very informative summary. But even though if you look -- look at the study chronic inflammation is very difficult. I think this is a pretty difficult marker to -- trying to -- trying to define acute or chronical inflammation, when you look at the marker.

But I think the data we have so far, at least we -- I'm still thinking the case -- chronic inflammation, although we're still thinking it's limited, but what we do see the positive supporting evidence from all human animal an in vitro studies. So this is back to from oxidative how can link to the next to the inflammation. And also, we know the inflammation linked to the immunosuppression or immunoresponse. So from that pathway, I think there's a few KCs there. They actually link to see if we're -- you know, you can think about using the AOP or using current KC idea to form the potential path -- you know, pathways.

One thing also I just want to address what Dana was just asking. If you want to make one of the KC

anything strong has to be human, but I think from the IARC preamble, so it's human -- it doesn't have to be human in vivo exposure. So if there's evidence as a human in vitro or ex vivo data evidence, that still could count as the strong.

So at least I think what we have included oxidative stress, immunosuppression, and receptor-mediation effects. So this is -- I think this also we had evidence from the human studies. I think plus the epigenetics, four of them as well.

So back to the immunosuppressive, that's what Michele wanted me to address on -- and actually, somehow I don't -- I don't find it. I wanted to give a good example, but I think what I have seen here is included in one study captured the human blood cells, you know, to look at the NK cell activity, so -- and other studies that's in mice.

But I'm -- if I anybody can back me up, I actually thought we should have some -- do we have any in human -- I'm just really trying to look for in human in vivo studies, but it looks like there is one with -- in the documents about the CD4 and CD8 T cells exposure is only in vitro, but I thought I did see some studies in human cells as well, but it's not coming to me.

I can look at it a bit more or maybe OEHHA staff

can help me -- help me here and see if we have human -- more human in vitro data for the immunosuppressive -- immunosuppression. So I'll just end here for now.

COMMITTEE MEMBER LOOMIS: Great. Thank you for all those clarifications.

I see Dr. Stern has a hand up. Let's go to her question.

COMMITTEE MEMBER STERN: Yeah, just a quick comment, so -- to follow up on Dr. Zhang's discussions. So I saw a paper that I don't know -- I haven't heard if you included it, because it's pretty recent. I think it came out in October of this year is by Imir out of University of Illinois. And I don't know if you considered that one, because that was a study where they look at prostate cancer cell lines at xenograft models and they exposed them to PFOS and also high fat diets. And they actually saw that PFOS exposure increased proliferation of the cell lines.

And they did propose a mechanism through PPAR-gamma that was linked to -- I think to immunosuppression or something like that. So it kind of reminded me what you were discussing right now, so I wanted to make sure that that -- that you guys had considered that study, because it links PFOS to PPAR-gamma and to the immune system, particularly for prostate

cancer, which is the second cancer. So breast cancer was the main one, as you know, that was the focus of study for the human studies, but the other cancer for which there are three studies that reported on PFOS exposure was prostate. And one did report an intriguing association that was positive with a positive trend. So I was curious about that study and how -- whether you considered that one.

COMMITTEE MEMBER ZHANG: Could I ask what's the first author's name?

COMMITTEE MEMBER STERN: Imir. It's I-m-i-r.

COMMITTEE MEMBER LOOMIS: It looks like maybe Dr. Sun has a comment or an answer to that.

DR. SUN: Thank you, Dr. Loomis. I want to say two issues. One is a correction to what I said earlier about the historical control range for female rats, Dr. Eastmond. Yeah, for female rats, the liver adenoma range should be 1.1 to 3.07 percent. So it's above 1, instead of the 0 to 0.29 that I said earlier. So I want to correct that. Thank you.

COMMITTEE MEMBER EASTMOND: Thank you. I figured there was something wrong.

(Laughter.)

DR. SUN: The other thing is I want to answer Dr. Zhang's question on the KC 7, the human studies, I think

the only one we've found is the one on natural killer cell activity in cultured human peripheral blood mononuclear cells, there is a decrease in the natural killer cell activity.

COMMITTEE MEMBER ZHANG: Thank you.

DR. SUN: That's all for now. Thank you.

COMMITTEE MEMBER LA MERRILL: To answer Dr. Stern, I don't have in my notes about the Imir. I was just trying to log in to the portal with the primary publications to see if that was in there. But, you know, as far as -- the reason I called it strong was because of my experience with IARC, in terms of the fact that we do have three different human cell lines that have increased proliferation and three human cell lines that have increased occurrence in S phase. And so, you know, the fact that, you know, we're trying to say, okay, well, in this period of time, we're supposed to take this body of evidence that's organized by the KCs, which makes it very easy to efficiently not overlook any of the evidence, but it's still more comforting to us to make a decision if we can, you know, tie these things together.

From my perspective, when I think of estrogen receptor and being involved in proliferation, and then I see estrogen receptor-dependent proliferation upon exposure to PFOS, and I also see the cell cycle phase

being synched into that manner, and DNA methylation that's involved in cell cycle processes like the checkpoint RAD1 DNA methylation mark that I mentioned, to me that, you know, tells a story. And it's not weaving in yet the oxidative stress, which can be, I think, sometimes a non-specific reaction. It need not be. I mean, clearly 8-oxodG is a very specific type of DNA adduct. And the fact it came up consistently in two human studies with dose response, I think, is quite strong also. But I'm going to look for this Imir while other people talk.

COMMITTEE MEMBER LOOMIS: Okay. Let's see. Let's see, Dr. Sandy has a hand up.

DR. SANDY: Yes. Thank you. I'm pretty sure, and I'll ask Meng to confirm this, that we did not include that paper in our document. And it's probably not loaded on the FTP site, but if Meng can confirm that.

COMMITTEE MEMBER ZHANG: No.

DR. SUN: I think that's correct, Dr. Sandy. We're talking about the Imir paper, right?

DR. SANDY: Um-hmm, correct.

COMMITTEE MEMBER LOOMIS: All right. Let's go on and see if there are any other questions or comments from the Committee then.

I'm not seeing any hands. Does that mean that you are all satisfied with what we've heard do far and

ready to move on to public comments?

DR. MARDER: Dr. La Merrill has her hand raised.

COMMITTEE MEMBER LOOMIS: Okay. Thanks. I'm sorry I missed you. Go ahead, please.

COMMITTEE MEMBER LA MERRILL: No. problem.

Yeah. This is a question for you, Dr. Bush. I was wondering -- I know that you had said when you were giving your overview of the animal tumor work that you recognized that there was some statistical significance, but it sounded like you were on the fence about whether or not it was biologically significant and you wanted to hear more about the mechanisms, so I was wondering if maybe you could revisit some -- you know, that comment and really kind of reflect on some of the things that we've discussed. I'm just curious where you stand now.

COMMITTEE MEMBER BUSH: Sure. Yeah. Thanks for that, Dr. La Merrill. So the Covance study from 2002 was an independent study. And then 10 years later, Butenhoff and that published the data. The first three authors, including Butenhoff are all 3M employees. So when looking at this data, kind of looking at it -- you know, taking it with a grain of salt, they don't mention the pancreatic cancer or tumors profile. So, you know, thank you, OEHHA staff for generating that.

In reading the public comments though, I'm seeing

this discrepancy and Dr. Eastmond kind of alluded to it with respect to -- if PFOS is -- has a major route through the liver, and if -- if it is peroxisome proliferator, maybe that is responsible for these liver effects that we're seeing. I think it is controversial. But if we don't include those -- if we don't include that because of the controversy, the numbers don't look that exciting to me when looking at the Sprague-Dawley male and female mice.

I was trying to quickly scribble down some of the historical comment -- historical tumor profiles that Dr. Sun was mentioning. And I believe you said hepatocellular adenomas were about 0 to 8 percent in Sprague-Dawley males?

DR. SUN: Yes, 0 to 8 percent is the range.

COMMITTEE MEMBER BUSH: Okay. So looking at Table 6 in the -- in our document, you know, the point 0.5 ppm is at 7 percent of adenocarcinomas, the 20 ppm is at 16 percent. So, you know, roughly double what we'd expect spontaneously anyway. Is that relevant, you know, maybe? I think I indicated in my comments that it's suggestive, but it's borderline for me in that regard.

With the female liver cancers, you know, it's -- we're not seeing this -- for me, I'm not seeing a compelling dose response. Yes, they can probably

statistically say that there's an increase with the 20 ppm treatment. But if this is a controversial area, we forget about liver effects altogether, then that really just leaves us with the pancreatic cancer -- pancreatic tumors, excuse me, and the thyroid tumors.

The thyroid tumors, as was indicated in the public comment from the American Chemical Society, right, U.S. EPA, has itself warned against the assessment of thyroid follicular cell tumors. And it may be considered less relevant to humans. So there's just not a lot of solid animal data that I can rely on.

So coming back to Dr. Eastmond's comments about the key characteristics, I do see bits and pieces there. And if that could be corroborated by the animal data, then a more compelling argument can be made, but I need more convincing. And some additional animal studies would certainly help. You know, it would be good to have, you know, teasing out whether there's a difference between the linear and branch versions of PFOS and derivatives.

And so at this point, hearing the mixed information about the human, the epidemiologic data, the bits and pieces with respect to the key characteristics and I would say mixed or marginal animal data, for me, I'm still not convinced when I weigh the evidence.

COMMITTEE MEMBER LOOMIS: Thanks. Dr. Landolph,

I'd like to hear from you now that you've had a chance to hear all this discussion, because at least initially, you were a bit more positive about the animal data, I think. Would you like to revisit your comments?

You're muted.

Can't hear you.

You're still on mute.

COMMITTEE MEMBER LANDOLPH: Can you hear me now?

COMMITTEE MEMBER LOOMIS: Yes.

COMMITTEE MEMBER LANDOLPH: Yeah. Yeah. You know, I'm looking at Table 6 and I'm going to assume just for ease of the discussion that the denominator is the same. It varies a little bit. But for liver, hepatocellular adenoma, they go 0, 3, 3, 1. So it goes 0, 3, 3, 1, and then 7. So it's crudely dose dependent. The 7 out of 43 at the 20 parts per million, that's the highest dose is -- let's see, they list that as statistically significant at P is less than 0.01. And the trend test P value is 0.006. I don't -- I don't feel compelled to throw that data way. To me, that data supports, you know, the hypothesis that it is a carcinogen.

The islet cell adenoma for pancreas, I indicated I would throw that away, because it's basically the same number that's a spontaneous result. The islet cell

carcinoma for pancreas goes -- there's one tumor at 0. There's two at 0.5. There's two at 2 parts per million. Then it jumps up -- so it goes 1, 2, 2, 5, and 5, so it's kind of crudely dose dependent. It's not perfectly, but -- and the trend test P value 0.048, so that looks like pretty good data to me.

And then the thyroid data on page 48, Table 7, it jumps up by a factor of three and they only did a 0 dose and a 20 parts per million dose. And that went from roughly 3 out of 31 to 9 out of 29, so that's like a threefold increase, but it's positive. I could not throw that data away.

And then the data on page 50, Table 8 for the female rats, the adenomas in the liver go 0 at 0 dose, then they go 1, 1, 1, and 5. So that's kind of a slight increase. And then it's flat and then it takes off at the 20s, so there could be, you know, some toxicity or something at the end there. I'm not sure. But that data is statistically significant at the 20 parts per million dose. And the trend test is P is less than 0.01. So that's pretty good data.

The combined adenoma and carcinoma for the liver in the females goes 0, 1, 1, 1, and 6. And that's statistically significant at 6. And the trend test is P is less than 0.01. The follicular cell adenoma for the

thyroid goes 0, 0, 0, 2, and 1. So that's kind of a marginal increase there. The follicular cell carcinoma goes 0, 0, 0, 1, and 0. And if you add them together, it doesn't get you much more and it's not statistically significantly. And the fibroadenoma is statistically significant at the 0.5 dose, but not at the others, and the background is very high.

So -- and then the follicular cell adenoma in the female rats exposed to potassium PFOS goes 0 at 0 doses at 0 parts per million, and jumps up barely to 1 at 20, so that's kind of marginal data.

And then we had that data from the aflatoxin. And then the summary, if you look at that, on page 126, the PFOS is positive in males and females for thyroid follicular cell adenoma and/or carcinoma. You didn't get anything for PFOA. For liver hepatocellular adenoma and/or carcinoma, it goes positive in the males and females for PFOS and PFOA. For pancreatic tumors, it's positive in the male -- and positive in the male and female. And for the testicular Leydig cell adenomas, it's positive in the male. And the mammary gland fibroadenoma, I think that data is marginal. They say it's positive in both females.

So to me, there is data there that's positive and I could not throw that out. I think the data more

supports the hypothesis that it is a carcinogen than it does the data that it's not a carcinogen, because there's dose dependence and there's statistical significance. So I haven't changed my mind on that.

I certainly would like, as Dr. Bush would and others would, to see more animal data, but we don't have it. We've got to deal with what we've got, and -- but I can't throw that data away, other than what I said I felt was marginal.

COMMITTEE MEMBER LOOMIS: Okay. Thanks.

Dr. Eastmond has another comment or question.

COMMITTEE MEMBER EASTMOND: Thank you. This is a question more for OEHHA, but I notice for everyone of these test doses there's approximately five statistical tests being done on each dose. You know, there's always this concern about multiple comparisons and error -- type 1 error that accumulates. Has OEHHA looked at trying to control for multiple comparison when they do these analyses?

DR. SANDY: I'll take a stab at that. So typically when evaluating cancer bioassay data, as is done usually by the National Toxicology Program as well as by OEHHA, we're looking at running pairwise comparison tests and trend tests for individual tumor types in certain organs. And we do not usually do any correction for

multiple comparisons, because the assumption is you're testing something to see if it is causing an increase in tumors and you're -- oftentimes, the test chemical is going to target one, two, or three different target organs and that's -- and we're not running this -- these tests on every single organ in the animal's body, just --

COMMITTEE MEMBER EASTMOND: But they have been. The tests have been run on every single tissue. You only see the ones that were positive.

DR. SANDY: Well, we -- I'm not sure that's the case. We looked at the original study data, the Thomford et al. report, and looked at tumor incidence without running any tests, and looked at which sites we thought there might be something going on, and then we applied the test. I wonder if Dr. Cogliano has anything to add.

DR. COGLIANO: Well, I think you pretty much covered it. I think that, yeah, there's a lot of tumor sites where there's no increase and it's -- they're generally not reported in the published paper, and we don't -- we're not running it on 40 different sites. We're running on what we -- on what we see as positive. I think that's where the whole question of biological plausibility comes into play. And, you know, we look at the mechanistic data and key characteristics as indicators of biological plausibility of the tumor sites that we find

to have apparent increase.

COMMITTEE MEMBER EASTMOND: But essentially don't you mean then this is a post-hoc analysis, because you've already looked at the data and then you've chosen the ones to analyze based upon the results.

DR. COGLIANO: I think when there's only a couple of bioassays, that's pretty much the only thing you can do. It's not like this is something that's so well studies and then we go out and design another study with a priori hypothesis that would affect the thyroid and pancreas or some other organ.

COMMITTEE MEMBER EASTMOND: No, I mean, the reason I brought this up is, you know, it comes down to me the liver tumors are what's driving this story and they appear to be increased, both by a trend test at the high dose by pairwise comparison and they exceed historical control, so it makes some sense.

But the P values on some of these tumor incidences are really pretty modest, when you go into the pairwise comparisons. They're between 0.05 and 0.01. So they're not huge increases, but the consistency is there. I guess that's my thought.

DR. COGLIANO: No, I think those are good observations. This is -- this is something that's -- you know, it does require some discussion and we try to put

together the different types of evidence and see where you come out. The statistics is one part of it, the -- and plausibility is another part of it.

COMMITTEE MEMBER EASTMOND: It makes sense.

DR. COGLIANO: Thank you.

COMMITTEE MEMBER LOOMIS: If you're really concerned about those P values, you can divide by the number of tests and get a sort of rough approximation of what you would have otherwise.

So Dr. La Merrill has a hand up again.

COMMITTEE MEMBER LA MERRILL: Yeah. Just addressing that there was numerous rodent studies that observed pancreatic tumors and -- well, they're all rats. And in male and in females, it seems that the carcinogenicity of PFOS hasn't been studied (inaudible) in terms of multiple species.

But, you know, there -- I didn't see any mechanistic data in the body of literature that we were provided related to the pancreas, but I did just type in PFOS and insulin into the Internet and there's about four or five different studies that have just come out in the last couple years consistently showing in rodent models that PFOS can modulate insulin secretion from pancreatic beta cells. I don't -- I don't see anything addressing the pancreatic cancer aspect specifically, but it does

appear that it's a -- that the tissue, the pancreas, is a target of PFOS.

COMMITTEE MEMBER LOOMIS: Thank you.

Are there any other questions or comments from the Committee before we close this part of the discussion?

COMMITTEE MEMBER LA MERRILL: Can I just ask. I recall on the -- OEHHA's slides this morning that there was indication that somebody had done some studies related to genetic manipulation of the PPARs to try and address some of the doubts that are created about the relevance of PPARs in the context of PFOS associated liver tumors, but I didn't see what the outcomes were or the details of that. Do you all happen to have that handy, OEHHA?

DR. SUN: Yeah, I can briefly describe the PPAR-alpha related knockout mice study. I think PPAR-alpha knockout mice, this one study reported PFOS-induced hepatomegaly and one study reported upregulated genes in the liver of these mice. And also -- yeah, and the Imir study that we discussed earlier, PFOS activated human PPAR-alpha in vitro and in this xenograft mouse model.

COMMITTEE MEMBER LOOMIS: Thanks.

Now, Dr. Crespi has a hand up.

COMMITTEE MEMBER CRESPI: Yeah. So I wanted to just a little bit relevant to the multiple testing issue.

I think that -- you know, I think it's fine not to correct for multiple testing here. I think that we should think of the P values as giving us some kind of rough evidence and we should not draw a bright line at 0.05. That we need to think of everything in the totality and in the context, but -- so like, for example, for this finding for -- in the male rats, the pancreas islet cell carcinoma 0.048. You know, I wouldn't give that too much credence, given the number of tests that have been done here.

But thinking about the liver tumors where there are -- the trend tests do have relatively low P values, and also there's consistency across the two sexes. So to me that -- you know, there -- that gives it that association more weight because of the consistency perhaps across the two sexes. And that's why I'm a little bit stuck on this -- why I'm trying to think about how relevant that might be, if that's translatable to humans. That's kind of where I feel a little bit stuck.

COMMITTEE MEMBER LOOMIS: Would anyone like to comment on the question of human relevance?

COMMITTEE MEMBER LA MERRILL: Isn't that the finding at IARC that they consider tumors and rodents and tumors in people, that even if they're not at the same site, they still consider it kind of carcinogenic one spot at a time in that sense?

COMMITTEE MEMBER LOOMIS: It is. You know, the concordance between humans and animals isn't expected, according to the IARC criteria.

COMMITTEE MEMBER LA MERRILL: Does that help Kate -- Dr. Crespi?

COMMITTEE MEMBER CRESPI: Yeah. Definitely. I mean, we don't -- that part I understand. We don't expect if there's liver cancer in one species, then, you know, that means liver cancer in the other species. Necessarily, it could just indicate carcinogenic potential. Yeah, I guess -- yeah, I guess I just wonder more about like is there anything, you know, special about this in this species of rats, that would make us discount that or not?

COMMITTEE MEMBER LOOMIS: Dr. Eastmond, do you have a comment on this point?

COMMITTEE MEMBER EASTMOND: Yeah, just quickly. Even the guidance within this Committee is essentially -- it's positive in rodents. You know, we go forward, unless we have evidence to conclude it's not relevant in humans. So that's the issue in so much -- you know, I think these may be caused -- these liver tumors may be caused through these mechanisms that are of questionable relevance to humans, but I don't think we have the evidence to conclude that. So that's the way I approach this.

COMMITTEE MEMBER LOOMIS: Thank you.

Okay. Let's see if we can close this portion out. One more time, is there a question or a comment that we haven't heard yet?

I don't see any raised hands.

DR. MARDER: No raised hands.

PUBLIC COMMENTS

COMMITTEE MEMBER LOOMIS: Okay. Very good. Then that concludes the Committee discussion and brings us to the public comment opportunity. So the way this will work is that we'll take comments from members of the public who've asked to speak. Those comments will be limited to five minutes each speaker. And to kick this off, I'll ask Dr. Marder to show the public comment slide.

So this is the housekeeping slide. So if anyone would like to make a comment, they can go to the URL shown on this slide and fill out a speaker request card. Some people may have done this already. Alternatively, you can click the raise hand icon on the zoom screen, if you would like to speak.

So first we'll go to those requests to speak that have already come in by speaker request cards. And I'll ask Julian whether we have any speaker request cards, and if so, how many?

MR. LEICHTY: Yes. So we have seven at the

moment. And the first, if we're ready for that, is Andrea Ventura of Clean Water Action.

COMMITTEE MEMBER LOOMIS: Okay. We'll go forward with that in just a moment, but I want to remind the other speakers that you have five minutes. And we'll take these speaker requests in the order in which they were received. So when one speaker finishes, Julian can announce the next one and we'll just go ahead in that order. So the first speaker you're welcome to go ahead.

DR. MARDER: Just a reminder to those speakers, they should have their name match that of the speaker card. So this speaker does not appear currently in our attendee list.

MR. LEICHTY: Okay. So the next is Jimena Diaz Leyva of the Center for Environmental Health.

DR. MARDER: I am allowing Jimena Diaz to speak. You must unmute yourself first.

DR. DIAZ LEIVA: Hello. Thank you for the opportunity to present comments. The Center for Environmental Health strongly supports the proposal to list perfluorooctane sulfonic acid and it salts and transformation and degradation precursors as known to the State to cause cancer under Proposition 65. We believe the weight of scientific evidence, including evidence of carcinogenicity in animals and mechanistic evidence of

carcinogenicity supports listing PFAS, its salts, and precursors. And we believe the listing is very crucial to protecting public health, because of widespread occurrence, persistence, mobility, and potential to cause health harms of PFOS.

Thank you.

COMMITTEE MEMBER LOOMIS: Thank you.

MR. LEICHTY: The next card is Amber Lee Woodby. Not someone I'm seeing on the attendee list. So that takes us to Steve Risotto of the American Chemistry Council.

DR. MARDER: Who is Present and I am allowing you to talk.

MR. RISOTTO: Thank you. Can you hear me okay?

DR. MARDER: We can.

MR. RISOTTO: All right. Awesome. Thank you for the opportunity to comment on the Committee's consideration of carcinogenic evidence for PF -- for PFOS. I'm Steve Risotto representing the American Chemistry Council.

ACC provided written comments in November. I would like to highlight a few points from those comments. As the Committee has discussed, the data from epidemiology studies and cancer bioassays are mixed and sometimes contradictory. The findings in human -- the finding in

human -- that appears in humans that appears to generate the most concern comes from the study of breast cancer among french women by Mancini et al. It is important to note that the association with estrogen receptor positive tumors was observed in only one of the three adjusted models applied by the researchers. The results from this model exhibit wide confidence intervals however that limit their interpretation.

In the one available animal study, the strongest evidence is for liver tumors. As has been noted, evidence exists that these tumors result from a rodent-specific mechanism or -- mechanism or mechanisms that may be of limited relevance to humans. This suggestion is strengthened by that fact liver tumors have not been reported in the available epidemiology.

In light of these equivocal data, OEHHA's focus is directed at the evidence for the 10 key characteristics of carcinogens as a basis for the proposed listing. The 2017 publication by Becker et al. that applied the key characteristics to the data from high throughput studies for over 200 chemicals evaluated by U.S. EPA's pesticide office however, found that the ability to predict cancer hazard was quote no better than chance, unquote.

OEHHA staff have themselves acknowledged that the key characteristics of -- are of limited evidence --

limited value for cancer hazard identification. While the key characteristics are useful for identifying and organizing data, the use of these characteristics does not meet the criteria for listing under Proposition 65.

Given this information, the available data do not support a cancer hazard listing for PFOS. This is the conclusion reached by the European Food Safety Authority, Health Canada, and the U.S. EPA.

Thank you.

COMMITTEE MEMBER LOOMIS: Thank you.

Is there a next speaker?

MR. LEICHTY: Yes. The next speaker is Suzanne Hume of CleanEarth4Kids.org.

DR. MARDER: Suzanne, if you unmute, you have been given permission to speak.

MS. HUME: Hello and thank you. Thank you so much to everyone here today. I just would like to say thank you to the fantastic OEHHA staff. My name is Suzanne Hume. I'm the Educational Director and founder of CleanEarth4Kids.org. We're a nonprofit dedicated to children's health, public health, environmental, and social justice, clean air and water.

We ask you to please list PFOS as Prop 65. Studies have concern -- have confirmed the human health risks of PFOS, especially for exposure through food and

drinking water. The job of OEHHA and the role of Prop 65 is to protect us. The American people are relying on you. And the American people do not need these studies in a neat package with a bow. Things are not always straightforward, but if they're causing cancer, if they're causing toxicity in animals and humans, we need you to take action. We rely on you to protect us.

When we talk about oxidative stress and cord blood in Chinese babies, it matters. When we talk about breast cancer, prostate cancer, pancreatic cancer, thyroid tumors, and liver cancer, it matters. We have deep concerns about PFOS causing oxidative stress and radicals that queue inflammation. Strong associations, epigenetics, and the number of methylation studies also demonstrated by a firefighter study that Dr. Zhang shared.

I'm deep concerned about DNA methylization -- methylation changes of cells in the cell cycle. Relevant epigenetic data regarding the breast and alteration of microRNA and risk associations and ER positives. We have concerns about receptor mediation -- so sorry -- mediation -- or mediated on ER-alpha promoter activity kidney and human breast cells, and increased proliferation of cells seen across human and animal studies, human cells being in S phase. We have concerns.

Studies have shown increased mutageneity[SIC],

chromosomal effects, DNA damage, oxidate -- oxidation, DNA damage, increased ROS -- RNS, and more.

I'm a little nervous, I'm must say, presenting to this panel of experts and scientists. You've read the research and it's clear and we've read this research as well. So sorry that I'm one the presenting this data and not saying it as clearly as you would.

We're very concerned about oxidative stress. We're very concerned about studies showing exposure to PFOS, you know, problems with neurotoxicity, reproductive toxicity, immunotoxicity, thyroid disruption, cardiovascular toxicity, pulmonary toxicity, renal toxicity in laboratory animals and many in vitro human systems. You know, and so, of course, we're very concerned and we're asking you to take action.

We're very concerned about the human health risks and chronic toxicity, molecular mechanisms of PFOS. So, as you know, PFOS really must be treated as a class. DTSC has already determined the regulation of individual PFAS is ineffective, and California treats them as a class shown by SB 343, AB 1200, and AB 1201, which were signed by Governor Newsom on October 5th. PFAS is a class and share many characteristics and toxicity. PFOA was listed under Prop 65 in September 2019, because it cause birth defects and other reproductive harm.

According to the EPA, both PFOS and PFOA are toxic to laboratory animals, producing reproductive, developmental, and systemic effects in laboratory tests and was suggestive evidence of PFOS and PFOA causing cancer.

PFOS are known as -- I'm sorry PFAS, PFAS are known as forever chemicals, as they're extremely strong and don't breakdown in the environment in our bodies, are linked to liver damage, thyroid disease, developmental reproductive problems, high cholesterol, obesity, Immunity issues, hormone suppression, and several types of cancer.

So today, and not very eloquently, I apologize, we are asking you to please take action to protect public health and add PFOS as carcinogenic and consider them -- consider adding all PFAS, PFAS as a class to Prop 65.

Additionally, just a quick note, of course, we're very concerned about the history and represent day of 3M and also the American Chemical -- Chemistry Council and manufacturers as well of PFOS being so intimately involved with the regulation of these chemicals. So we're asking you to please take action. The American public relies on you. Thank you so much for your dedicated work.

Thank you.

COMMITTEE MEMBER LOOMIS: Thanks for your comment.

Who's the next speaker, please.

MR. LEICHTY: John Bottorff also of CleanEarth4Kids.org.

DR. MARDER: You have been allowed to talk. You must unmute yourself. Thank you.

MR. BOTTORFF: Thank you so much. My name is John Bottorff with CleanEarth4Kids.org. I ask that you please list PFOS as carcinogenic under Prop 65. I also ask that PFAs be treated as a class and added to the Prop 65 as well.

According to the EPA, both PFOS and PFOA quote "Are toxic to Laboratory animals producing reproductive, development, and systemic effects in laboratory tests", unquote, with quote, "suggestive evidence that PFOS and PFOA may cause cancer", unquote.

PFOS and PFOA have a long history of harm. DuPont was sued in 1999 over PFOS and PFOA contamination. Court documents showed DuPont and PFOA inventor 3M had secretly been doing medical studies on PFOA and PFOS for decades. 3M researchers stated in 1978 that PFOA and PFOS quote, "Should be regarded as toxic", unquote. In 1981, 3M found that PFOA caused birth defects in rats. DuPont knew PFOA causes cancerous tumors in lab animals by the 1990s. In 2005, DuPont reached a settlement with the EPA for concealing their knowledge of PFOA toxicity.

And a lot of these -- this is all important, because a lot of these manufacturers block studies. They make sure that these studies are not funded. So just because we don't have studies has nothing to do with the fact that these may cause cancer. There is evidence that PFOS are a health risk, just like PFOA, and all the PFAS across the class.

Please take action to protect public health and add PFOS as carcinogenic and also consider adding all PFAS as a class to Prop 65. Thank you so much for your time.

COMMITTEE MEMBER LOOMIS: Thank you. Who's the next speaker, please?

MR. LEICHTY: The last speaker card is from Evelyn of CleanEarth4Kids, but I not seeing that speaker in the list.

DR. MARDER: And as a reminder, you may rename yourself in Zoom, if any of you have been called who have presented a speaker card, but don't have a matching name. I am not seeing any changes in names in the list.

Dr. Loomis.

COMMITTEE MEMBER LOOMIS: Very good. Thank you. So now, let's see if there are any raised hands.

DR. MARDER: There are no raised hands at this time.

COMMITTEE MEMBER LOOMIS: And have we received

anymore speaker cards in the last minute or two?

MR. LEICHTY: We have not.

COMMITTEE MEMBER LOOMIS: Okay. Thank you very much. Thank you to all the speakers. That concludes the public comment opportunity.

DR. MARDER: We do have a raised hand from one of -- from Dr. Sandy.

COMMITTEE MEMBER LOOMIS: Okay. Please go ahead.

DR. SANDY: Thank you. I just wanted to take a moment to correct a misstatement by the commenter for the American Chemistry Council. OEHHA has not made any comments questioning the usefulness of the key characteristics of carcinogens. The commenter seems to be confusing two very different things. The key characteristics of carcinogens with a set of high throughput screening assays, the ToxCast and Tox21 assays.

So as you know, the key characteristics of carcinogens were identified based on a comprehensive review of more than a hundred agents classified by IARC as known to cause cancer in humans. And there's many sources of data -- mechanistic data that can inform those key characteristics, including data from humans, human cells, animals, animal cells, and cell-free systems, and other high throughput screening assays.

And so in looking at the ToxCast and Tox21 high

screening -- high throughput screening assays, it's been noted by many people, including OEHHA, that those assays, which were not designed to cover the key characteristics of carcinogens, don't fully cover them. And recommendations have been made that those ToxCast assays should be improved and -- to be a better set of information that might inform the key characteristics. That's all. Thank you.

COMMITTEE DISCUSSION AND DECISION

COMMITTEE MEMBER LOOMIS: Thanks for that clarification. Let's move on, if there are no more raised hands, to Committee discussion and vote on the question before us.

So first before we proceed to a vote, I wanted to see whether committee members had any other comments that they would like to make?

Dr. Landolph.

COMMITTEE MEMBER LANDOLPH: Yes, sir. Thank you. Yeah, I wanted to go over just briefly again -- I had discussed slightly, which is that the PFOS and the PFOA cause oxidative damage the 8-hydroxydeoxyguanosine, there's data on immunosuppression, there's data that apoptosis is inhibited, senescence is inhibited, and the gap junctional intercellular communication is inhibited.

So all these characteristics are consistent in

the fact that they cause transformation in Syrian hamster embryo cells and normal human breast epithelial cells. So I come out of a cell transformation background and all these characteristics are ancillary data compared to the heart data like animal carcinogenesis, but they're all consistent with cell transformation, and therefore carcinogenesis.

So in my mind, I add this to the animal carcinogenesis data that's positive and that moves me towards not a perfect answer, but an answer that's consistent with support for the hypothesis that these are carcinogens.

COMMITTEE MEMBER LOOMIS: Thanks, Dr. Landolph. Any other comments from the Committee?

Go ahead, please, Dr. Stern.

COMMITTEE MEMBER STERN: I just want to add that there is one additional study that OEHHA excluded from review for good reasons, because, you know, a priori they made a decision that they would include only studies that met certain criteria. One of them was measuring PFOS at the time of diagnosis or before diagnosis. This particular study measured -- is a case control study in Taiwan that measured PFOS at various times between time of diagnosis and after. Yet, they measure to me -- measure it before treatment, so the concern is reverse causation.

That said, if there were indeed reverse causation, the more likely scenario is that it would bias the result towards the null, right? So that's kind of how we interpret that. In this particular study, they also found a positive association with breast cancer among ER positive women. So even though we did not include that in our review, I keep coming back to that in light of all the discussions that we've been having and I wanted to share that with the -- with the Committee.

COMMITTEE MEMBER LOOMIS: Thank you.

Are there any other comments from the Committee?

DR. MARDER: Dr. La Merrill has her hand raised as well, Dr. Loomis.

COMMITTEE MEMBER LOOMIS: Thanks. Go ahead, please.

COMMITTEE MEMBER LA MERRILL: And I just wanted to bring up the thyroid again. I was hoping that some of the public comments would help clarify some of my confusion about why we were supposed to discount the thyroid tumors in the rodents, but I do know that the thyroid in a systematic review of epidemiology studies, they found evidence of a positive association between PFOS exposure and TSH. And so, you know, I had summarized something I had found earlier on that level, but that does mean, you know, we've looked at numerous human studies

that are seeing changes in thyroid hormone. I'm a little concerned about that -- you know, that that might be getting glossed over a little bit, since we're seeing lesions in the animals that are -- I believe I remember reading that they were suggested to be rare. And it seemed like they were in both sexes. And then there's some evidence that this is operating in humans. So I just wanted to make sure that was known about the human study.

COMMITTEE MEMBER LOOMIS: Thank you.

Dr. McDonald has a hand up.

COMMITTEE MEMBER McDONALD: Yes. Thank you.

I really appreciate OEHHA compiling all this primary source information. You've done a Herculean job as well. I did want to speak to the thyroid tumors. Seeing we're on that topic, I wanted to make one point. With respect to male rats and thyroid tumors, there was an increase in adenoma benign tumor at the 52-week recovery group, but there was no tumors seen in the 104-week group, which as you would expect those to progress.

I also wanted to point out that if you look at the follicular cell carcinomas, they actually decreased. There's a dose-related decrease over all doses relative to control. And so for me, I just don't see much evidence for male rat thyroid. Female rats, granted they are rare, but there were no statistical significance.

So I'm kind of in the camp that, you know, these are suggestive, but limited evidence.

Thanks.

COMMITTEE MEMBER LOOMIS: Is there anything else?

So Dr. Crespi has a hand up.

COMMITTEE MEMBER CRESPI: Yeah. So I found what Dr. Stern said very interesting and relevant. And it makes me concerned that the HID may not have provided information on studies where the exposure assessment was undertaken after diagnosis. And I just wonder whether it might have made sense to include such studies, considering that this is a chemical with a very long half-life. My understanding is it's not really metabolized in the body or well excreted. So like the -- a reverse causation seems -- the hypothesis seems very unlikely. So I wonder if excluding such studies might have been, you know, not -- might have led to us missing some relevant information.

COMMITTEE MEMBER LOOMIS: Just to be clear, those studies that measured exposure at the time of diagnosis or afterward were included. They're reviewed in the section of breast cancer, but not in very much detail. However, the papers are available for the Committee to review. So they are there.

DR. SUN: Yes. Sorry to interrupt. I'll just

clarify that the study Dr. Stern mentioned, Tsai et al., the title says is a case control study, but it is of a cross-sectional design. So we have a list of studies that we initially identify, but we excluded, listed in the HID in the Appendix B, and we list the reason for exclusion.

COMMITTEE MEMBER LOOMIS: Thanks. Thanks for that.

Okay, Dr. Crespi?

COMMITTEE MEMBER CRESPI: (Nods head.)

COMMITTEE MEMBER LOOMIS: Does that address your question?

It looks like Dr. Landolph has another comment.

COMMITTEE MEMBER LANDOLPH: Yes. Thank you, Dr. Loomis. Dr. Stern, my friend and colleague from USC, you straddle both worlds as an epidemiologist and molecular carcinogenesis researcher, so my impression is that the epidemiology studies are somewhat insensitive. Is it possible that they're not sensitive enough yet to catch these materials, but the simpler things like the animal carcinogenesis, the gap junctional inhibition of intercellular communication, and assays like this could be sensitive to cancer and the epidemiology just is not big enough and has -- doesn't have the sensitivity to catch them yet, is that possible?

COMMITTEE MEMBER STERN: Yeah, I can provide an

answer and then I would like for my colleagues -- my epidemiology colleagues, Drs. Loomis and Reynolds, to also comment on this. But, yes, it is challenging with the epidemiological studies, because they're -- all of them did a one-time measurement, except for the Alabama cohort, which used a job matrix. The other ones did a one-time serum measurement.

So you are assuming that that one measurement captures the typical exposure of those individuals that may have contributed to the development of cancer. So that's always a challenge in epidemiology. In spite of that, we do see some studies that show positive associations, others don't show anything, and others show positive associations that are not significant, so we tend to get concerned when we see that, because we worry about confounding, we worry about particularly confounding by other PFAS such as PFOA. So, yes, it is tricky and is not as clean as the experimental studies.

COMMITTEE MEMBER LANDOLPH: Thank you.

COMMITTEE MEMBER STERN: I don't know if that answers your questions, but --

COMMITTEE MEMBER LANDOLPH: Yeah, It does. It does. Thank you.

COMMITTEE MEMBER LOOMIS: And I would just add that the limitations of exposure in a specimen are

probably the greatest limitation on the sensitivity of the studies that we have now. And that primarily relates to interindividual variability and the excretion of these compounds. You know, if it's true that half-life is relatively long, then perhaps within an individual, it doesn't matter that much when they're sampled, even though there's only one measurement in time, unless there are critical windows like we've missed that are somehow by a single sample, but there may be quite a bit of variation between individuals and how they process the chemicals and we really don't have any information at all about that.

Anything else?

Let's see, Dr. Reynolds.

COMMITTEE MEMBER REYNOLDS: I just wanted to piggyback on that comment that the one-time sample problem, I mean, some people have taken a look at that and it seems to be fairly high correlations in studies which have had multiple samples in multiple periods of time. But the one-time sampling, one issue is the persistent of the chem -- persistence of the chemical in the body, the other is the persistence of exposure, which in many of these cases is ongoing. So just to add that element.

COMMITTEE MEMBER LOOMIS: Thanks. Very good point.

Let's see, Dr. McDonald, did you have your hand

up again or was that from before?

COMMITTEE MEMBER McDONALD: No. I did -- I did want to ask my epidemiology colleagues on the panel. One thing that I noticed in a number of the studies was the quartiles -- you know, the difference between exposure amongst one group to the next was really tiny, like 20 percent difference -- 15, 20 percent difference. And I just wondered if those are meaningful?

I mean, you know, they just seem like such a narrow range within the population, that it's hard to break up into meaningful groups. Just wondered if that plays a role at all.

COMMITTEE MEMBER LOOMIS: Anybody want to field that one?

COMMITTEE MEMBER STERN: So, Dr. McDonald, are you referring to the change from one quartile to the next?

COMMITTEE MEMBER McDONALD: Yes.

COMMITTEE MEMBER STERN: Yeah. Often when we see a -- so ideally if there's a causal relationship between an exposure and disease, we like to see that -- as quartiles increase, we see nice increases. And a test of trend will give us a significant finding. Now, when we don't see that, they could be a dif -- there could be multiple reasons. One of them is that there is procedural confounding by something that we're not capturing or that

there's not a linear -- we're assuming a linear relationship when we do those tests. The relationship does not have to be linear. We know that from other examples, right, in epidemiology often exposures do not follow a linear relationship. There might be a plateau point, and above that point there's no further increase or there might be all kinds of complicated relationships that we still have not figured out.

So we do -- I personally think that it accounts in assessing causality, but we have to keep an open mind that there could be explanations for that. But the first thing that comes to my mind when I look at that, is that it could be residual confounding. I don't know what others feel like, Dr. Reynolds, or Loomis, or Dr. Mack.

COMMITTEE MEMBER REYNOLDS: I do think your point about linearity is a good one, because we do see for all kinds of exposures they're often not linear. And in epi studies sometimes there's some variability in measurement, so that it's useful, rather than trying to take a continuous variable to break it up into quartiles or quintiles to see whether or not there's some evidence of differences in extremes. So there are a variety of reasons I think for doing that and that does help interpret the evidence.

COMMITTEE MEMBER LOOMIS: So just to add onto

that, you know, one of the other challenges we had with sensitivity is that exposures in the general population tend to be quite low. And so that means whether you created quartiles or use a continuous exposure variable, well, you know, the changes are indeed likely to be small. So what we would really like to have would be some occupational studies, you know, of workers with higher exposures that would help to corroborate the evidence from the general population, but perhaps with greater sensitivity. Unfortunately, we just don't have those in this instance.

Dr. Zhang, comment, question.

COMMITTEE MEMBER ZHANG: Yes. Just to follow Dr. Reynolds comment on that one-time sample. I know Dr. Loomis is the first one to mention that. I thought I'd just add on that. For a lot of epidemiological studies, you know, lots of times we may not even have any biological samples. So one thing I think listed study has some, you know, biological samples and the date of exposure assessment. So that's -- I would still put it as a positive point for that study.

And the second I think also for the chemicals is whether it's stable, so it's not like some chemical like, you know, it could be, you know, half-life is really short, then that would be a problem. So I sort of -- on

that sense, so I still think give it credit to the study.

Another point I want to make is maybe just trying to make sure I express the -- previously one was comment on the KC 2, the genotoxicity of the PFOS, I think I want to do another, number one, is a self correction. I would say if even though it could be a weak genotoxic compound, but I think -- I think -- you know, I just look over the data one more time and I think the -- even though some data is contradictory, but overall I think the in vivo data exposing humans and exposed animal generally see as pretty strong. So what I'm saying is I was trying to say if PFOS can cause cancer, it may not just going through epigenetic pathway, or genotoxic pathway, or could be epigenetic, or could also play the role in non-genotoxic pathway.

So I don't think at this point, we -- I could to identify, if the PFOS is really a strong or weak genotoxic compound. So I want to take that back. Just try to get on the record.

COMMITTEE MEMBER LOOMIS: Thank you. I don't see any other hands raised at this moment. So unless there are any burning last-minute comments or questions from the Committee, I would propose we move on to a vote and decision.

Is everyone ready?

CHIEF COUNSEL MONAHAN CUMMINGS: Dr. Loomis, this is Carol Cummings. I just wanted to interject and remind the Committee, if you're not comfortable making a decision today -- it sounds like there's a lot of discussion back and forth, and you probably understand it better than I do, but I just want to make sure that you know that you don't have to make a decision today. If you aren't comfortable with that, you can ask for, you know, more data, you can table the question, or you can go ahead and vote. It's entirely up to you.

Thanks.

COMMITTEE MEMBER LOOMIS: So would it be appropriate then to ask if there is any proposals to table the decision?

CHIEF COUNSEL MONAHAN CUMMINGS: Sure.

COMMITTEE MEMBER LOOMIS: Is there a proposal to table the decision?

DR. MARDER: You have Dr. Bush --

COMMITTEE MEMBER ZHANG: Yes.

DR. MARDER: -- with his hand raised.

COMMITTEE MEMBER BUSH: Thank you. I'm not proposing that. I wanted to know is abstention an option for us?

CHIEF COUNSEL MONAHAN CUMMINGS: Yeah, you can -- this is Carol again. You can always abstain, if you're --

if you're not comfortable saying yes or no. It has the -- essentially the effect of a no answer however.

COMMITTEE MEMBER BUSH: Thank you.

CHIEF COUNSEL MONAHAN CUMMINGS: Um-hmm.

COMMITTEE MEMBER LOOMIS: All right. I don't hear any other proposal to table.

So let us proceed to the vote. The question for decision is this -- has perfluorooctane sulfonic acid, PFOS, and its salts and transformation and degradation precursors been clearly shown through scientifically valid testing, according to generally accepted principles, to cause cancer?

So on that question you can vote yes, no, or abstain. And I'll go through and call for your votes in alphabetical order.

Dr. Bush?

COMMITTEE MEMBER BUSH: Abstain.

COMMITTEE MEMBER LOOMIS: Dr. Crespi?

COMMITTEE MEMBER CRESPI: No.

COMMITTEE MEMBER LOOMIS: Dr. Eastmond?

COMMITTEE MEMBER EASTMOND: Yes.

COMMITTEE MEMBER LOOMIS: Dr. La Merrill?

COMMITTEE MEMBER LA MERRILL: Yes.

COMMITTEE MEMBER LOOMIS: Dr. Landolph?

COMMITTEE MEMBER LANDOLPH: Yes.

COMMITTEE MEMBER LOOMIS: Dr. Loomis votes yes.
Dr. Mack?
We can't hear you.
CHAIRPERSON MACK: Yes.
COMMITTEE MEMBER LOOMIS: Dr. Mack votes yes.
Dr. McDonald?
COMMITTEE MEMBER McDONALD: No.
COMMITTEE MEMBER LOOMIS: Dr. Reynolds?
COMMITTEE MEMBER REYNOLDS: Yes.
COMMITTEE MEMBER LOOMIS: Dr. Stern?
COMMITTEE MEMBER STERN: Yes.
COMMITTEE MEMBER LOOMIS: Dr. Zhang?
COMMITTEE MEMBER ZHANG: Yes.
COMMITTEE MEMBER LOOMIS: Very good.
So I count one, two, three, four, five, six, seven, eight votes to list, two votes against listing, and one abstention. So that accounts for a majority vote in favor of listing PFOS.
So with that done, we'll turn to the next part of agenda -- the agenda, which is a consent item updating the California Code of Regulations, Title 27, Section 27 triple zero, list of chemicals which have not been adequately tested as required. This is essentially a ministerial item, meaning that the Committee has asked to affirm changes in response to submissions from the

Department of Pesticide Regulation and the EPA.

So I'll ask Julian Leichty now to present this item.

MR. LEICHTY: Thank you, Dr. --

CHIEF COUNSEL MONAHAN CUMMINGS: I'm sorry, Julian.

MR. LEICHTY: Oh.

CHIEF COUNSEL MONAHAN CUMMINGS: If you could just hold for a second. Dr. Loomis, when you -- when you ask for the vote and when you summarized it, you only said PFOS, and I'm just wondering whether or not you meant to include the whole group or that -- just that one --

COMMITTEE MEMBER LOOMIS: Well, I meant to -- I meant to include the whole group, because that was the question.

CHIEF COUNSEL MONAHAN CUMMINGS: Okay.

COMMITTEE MEMBER LOOMIS: So it was PFOS, its salts, transformation, and degradation precursors. I think we can't vote on anything else, right, because that's the question in front of us.

CHIEF COUNSEL MONAHAN CUMMINGS: Well, you could -- you could split them out. I mean, you've done that before when there was a group, but I just wanted to clarify that for the record, that that's what you intended.

COMMITTEE MEMBER LOOMIS: Well, I read the question as it was -- as it was put in front of us --

CHIEF COUNSEL MONAHAN CUMMINGS: Right.

COMMITTEE MEMBER LOOMIS: -- so presumably that is what the Committee understood, that they were voting on that entire group of chemicals, named in the question.

CHIEF COUNSEL MONAHAN CUMMINGS: Right.

(Nodding heads.)

COMMITTEE MEMBER LOOMIS: I see heads nodding.

CHIEF COUNSEL MONAHAN CUMMINGS: Okay. Thank you.

UPDATE OF THE CALIFORNIA CODE OF REGULATIONS TITLE 27 SECTION 27000 LIST OF CHEMICALS WHICH HAVE NOT BEEN ADEQUATELY TESTED AS REQUIRED

COMMITTEE MEMBER LOOMIS: Okay. So I think that's what we've done. So if we're agreed on that and no one wants to revisit the vote, let's proceed with the staff presentation on the consent item.

(Thereupon a slide presentation.)

MR. LEICHTY: All right. Thank you, Dr. Loomis.

So this slide indicates the proposed change based on information received from the California Department of Pesticide Regulation. The removal of triethylene glycol detailed in the staff report provided to the Committee. I will now turn this back to Dr. Loomis.

DR. MARDER: Dr. Loomis you are muted. I believe you were reading the questions, but you were muted.

COMMITTEE MEMBER LOOMIS: Okay. Sorry about that. So thanking Julian for that very quick but informative presentation. Again, this is a consent item, but it does require a formal vote on the following question. But before we go to that question, would any member of the Committee like to comment or ask a question about it?

Okay. Hearing and seeing nothing.

The question that requires a vote then is should Section 27000 of Title 27, California Code of Regulations be amended as indicated in the staff report?

So again I'll call your names in Alphabetical order and ask you to vote yes, no, or abstain.

Dr. Bush?

COMMITTEE MEMBER BUSH: Yes.

COMMITTEE MEMBER LOOMIS: Dr. Crespi?

COMMITTEE MEMBER CRESPI: Yes.

COMMITTEE MEMBER LOOMIS: Dr. Eastmond?

COMMITTEE MEMBER EASTMOND: Yes.

COMMITTEE MEMBER LOOMIS: Dr. La Merrill?

COMMITTEE MEMBER LA MERRILL: Yes.

COMMITTEE MEMBER LOOMIS: Dr. Landolph?

Dr. Landolph, if you're voting, we can't hear

you.

COMMITTEE MEMBER LANDOLPH: Did you hear? Okay. Yes. Sorry.

COMMITTEE MEMBER LOOMIS: Thanks. Got you.

Dr. Loomis votes yes.

Dr. Mack?

CHAIRPERSON MACK: Yes

COMMITTEE MEMBER LOOMIS: Could you repeat that. We couldn't hear you.

DR. MARDER: You're unmuted. We just -- it was a little garbled, Dr. Mack. Just repeat.

COMMITTEE MEMBER LOOMIS: Sorry, Dr. Mack. Can you say it again? We just couldn't understand it. If you're having difficulty, would it be okay for you to type it into the chat?

CHAIRPERSON MACK: Yes. I'm sorry.

COMMITTEE MEMBER LOOMIS: We heard you that time.

(Laughter.)

DR. MARDER: Thank you.

COMMITTEE MEMBER LOOMIS: Thank you.

Dr. McDonald?

COMMITTEE MEMBER McDONALD: Yes.

COMMITTEE MEMBER LOOMIS: Dr. Reynolds?

COMMITTEE MEMBER REYNOLDS: Yes.

COMMITTEE MEMBER LOOMIS: Dr. Stern?

COMMITTEE MEMBER STERN: Yes.

COMMITTEE MEMBER LOOMIS: Dr. Zhang?

COMMITTEE MEMBER ZHANG: Yes.

COMMITTEE MEMBER LOOMIS: Okay. The vote is unanimous, so the change is affirmed.

STAFF UPDATES

CHEMICAL LISTINGS VIA THE ADMINISTRATIVE LISTING MECHANISMS AND SAFE HARBOR LEVELS

COMMITTEE MEMBER LOOMIS: And now we'll move on to the next item on the agenda, staff updates. We'll have updates on Proposition 65 listings, regulations, and litigation since the last meeting. So Julian Leichty again has the first presentation on listings and safe harbor levels. Please go ahead, Julian.

MR. LEICHTY: Thanks, Dr. Loomis. So since the Committee's last meeting, we have administratively added a reproductive toxicity endpoint, developmental toxicity to the listing of bisphenol A. And we've added two chemicals to the Proposition 65 list as causing cancer. These chemicals are molybdenum trioxide and indium tin oxide.

Next slide, please.

NEXT SLIDE

MR. LEICHTY: I'll now move to the chemicals currently under consideration for administrative listing, which are perfluorooctanoic acid (PFOA), tetrahydrofuran,

2-ethylhexyl acrylate, methyl acrylate, and trimethylolpropane triacrylate, technical grade.

Next slide, please.

NEXT SLIDE

MR. LEICHTY: Turning to safe harbor levels. Since last meeting, four safe harbor levels have been adopted in regulation. No significant risk levels were adopt for p-Chloro-alpha,alpha,alpha-trifluorotoluene, Dibromoacetic acid, dichloroacetic acid, trichloloracetic acid.

Next slide, please.

NEXT SLIDE

MR. LEICHTY: We have lastly proposed safe for level -- a safe harbor level for one chemical, 1,3-dichloropropene for the inhalation and oral routes.

And I'll now turn things to Carol.

OTHER REGULATIONS AND LITIGATION

COMMITTEE MEMBER LOOMIS: All right. Carol, please go ahead.

NEXT SLIDE

CHIEF COUNSEL MONAHAN CUMMINGS: Okay. Good afternoon again. For our other regulatory actions besides the safe harbor levels, we've been primarily working on safe harbor warnings for various chemicals, but we've also done a couple of other things. As you may recall, last

meeting, we were in the process of wrapping up some changes to the warnings for alcoholic beverages. It wasn't the content of the warning, it was the way to provide the warning that took into account that companies are now selling alcohol over the internet and through apps. So that became effective April 1st of 2021.

We also have two regulations that are being considered for approval by the Office of Administrative Law. One is a regulation that would establish concentration levels for certain foods that are cooked or heat processed. And the first set of concentrations would be for acrylamide in those foods. And as I said, it's under review for -- hopefully for approval and filing.

We also have at the Office of Administrative Law what we call tailored warnings for cannabis and THC products. There's four different versions of the warning depending on the type of -- mostly the route of exposure whether it's smoking, edibles, topical, that sort of thing. So we've adopted warnings and methods for providing warnings for those two chemicals.

We are in the process of modifying our safe harbor warnings that we call short forms. We have longer warnings, then we have this short form. And we determined that the short-form warnings needed some modifications, including restricting the use of them to small products or

packages, which was our intent, but the regulation didn't actually say that. And we are adding some requirements to name at least one chemical, even in the short-form warning. So currently, we're looking at the public comments on that and hope to have a decision about our next steps on that regulation soon.

We have two other tailored warnings that we fairly recently proposed, one for acrylamide in foods. And that would of course cover those that aren't covered by the cooking or heat processing regulation. There will be foods that are above the concentration levels that we plan to adopt there. And so this -- that's what this is for.

And the same goes for glyphosate there. We don't anticipate that most consumer products will need a warning, but there will be some, and so we have proposed warning language for glyphosate.

Okay. Next slide.

NEXT SLIDE

CHIEF COUNSEL MONAHAN CUMMINGS: And just to update you briefly on litigation. Our litigation list is getting shorter, but more complicated. So we have the two cases in blue are actually in the federal courts. We haven't been in federal court very much under Prop 65, but we currently have these two. I should say "we" means the

State, because we are not, as OEHHA, part of these two case. But certainly Prop 65, given that we implement it, we have an interest in both of them.

As you'll see on the slide here, the -- this litigation is about providing warnings for glyphosate exposures and acrylamide exposures from food. And this -- these cases were part of the impetus for us to propose the specific warning language that I mentioned on the prior slide

The arguments in the cases are that providing a warning for these chemicals under Prop 65 would violate the company's First Amendment right against compelled commercial speech. Both of them, or at least parts of them, are in court -- of the Ninth Circuit Court of Appeal, other parts are still in the trial courts.

We have the very long running Council for Education and Research on Toxics versus Starbucks case, which, as you may recall, has been on our list for some time. It was -- it's been about 10 years in litigation. It was recently decided by the trial court and is now on appeal in the California court -- courts of appeal. And it has to do with whether warnings are needed for coffee.

As you may recall, we adopted a regulation last year, or maybe it was 2019, that determined that a warning is not required for coffee, even though there's acrylamide

and other chemicals in coffee.

But that's still -- that case is on appeal. We have this case -- the Physicians Committee for Responsible Medicine I think was already on the list last time. And that is a request by this group for us to list processed meats as carcinogens under Prop 65, which we have declined to do. And we are in early stages of that case. We're negotiating discovery requests from PCRM.

And lastly, we did resolve another long-running case of the American Chemistry Council versus OEHHA, which had to do with the early listing of BPA as a development toxicant. And after the trial court and court of appeal upheld that listing, the -- I believe that the -- it was the State Supreme Court declined to hear the case, and so now it's final, and we did relist bisphenol A for developmental effects.

That's all I have, unless you have questions.

COMMITTEE MEMBER LOOMIS: Thank you, Carol. Are there any questions?

DR. MARDER: Dr. Eastmond has his hand raised, Dr. Loomis.

COMMITTEE MEMBER EASTMOND: Yes, I have a question. Carol, thanks for that overview.

CHIEF COUNSEL MONAHAN CUMMINGS: Uh-huh.

COMMITTEE MEMBER EASTMOND: Over the years, we've

been asked to hang on to paperwork that we had related to some of these cases.

CHIEF COUNSEL MONAHAN CUMMINGS: Um-hmm.

COMMITTEE MEMBER EASTMOND: And I have forgotten which ones we're suppose to have. Could you send us out an email reminding us, which --

CHIEF COUNSEL MONAHAN CUMMINGS: We will.

COMMITTEE MEMBER EASTMOND: -- materials, we were supposed to be hanging on to. I mean, it's been years and years.

CHIEF COUNSEL MONAHAN CUMMINGS: Sure.

COMMITTEE MEMBER EASTMOND: So I never can quite keep track of it. Thanks.

CHIEF COUNSEL MONAHAN CUMMINGS: Okay. Yeah, I don't think you have very many, but we'll send you a list.

COMMITTEE MEMBER EASTMOND: Thanks.

CHIEF COUNSEL MONAHAN CUMMINGS: Um-hmm.

COMMITTEE MEMBER LOOMIS: Any other questions?

Okay. I can't see everyone on this screen.

DR. MARDER: No more questions or at least no more hands raised indicating questions.

SUMMARY OF COMMITTEE ACTIONS

COMMITTEE MEMBER LOOMIS: Right. Okay. If there are none then, we will move to the very last item on the agenda. And with that, I'll go back to Director Lauren

Zeise to summarize what we've done today.

DIRECTOR ZEISE: Okay. Good afternoon.

So the Committee voted to add perfluorooctane sulfonic acid (PFOS) and its salts and transformation and degradation precursors to the Proposition 65 list. The vote was eight yes, two no, and one abstain. So the chemicals will be added to the Proposition 65 list as known to cause cancer.

Then the second item was the consent item, section 2700[SIC]. And it was amended per as indicated in the staff report and the vote was unanimous.

I guess I'd like to close by just thanking the audience, the public, for their participation in the meeting and preparing with us their views. And also we really do appreciate the written public comments we receive. It really helps with the whole body of evidence and helps the Committee to consider it. So thank you very much for all of that input.

Then I'd like to thank the Committee for participating in the meeting today. Understand the amount of time it takes, taking time out of your very, very busy schedule, so we really very much appreciate it and all the preparation that goes into these meetings. Thank you.

And thank you, Dr. Loomis for chairing the meeting today. We appreciate that. And then I'd really

like to thank the staff for all the effort to put the document and this meeting together, and it was really gratifying to hear the comments on our hazard identification documents. So thank you, staff, for all of that effort and for all that went into this meeting.

And with that, I'd like to wish you all a good, and healthy, and Happy Holiday, and looking forward to a very good 2022. And we will be seeing you in the next year. And with that, I'll turn it back over to you, Dana.

COMMITTEE MEMBER LOOMIS: Thank you, Lauren.

Well, I would just like to close by echoing all those comments. Thanks to the members of the public who took the time and effort to read the documents, and comment, and to listen into the meeting. Thanks to the Committee members for all the work taken to review and work through the evidence. Really a very impressive job. And thanks especially to all of the OEHHA staff for compiling these materials. It really was a heroic effort. A lot of information on this particular substance that was not at all easy to sort through. So thanks for all of that.

And in order to wish all of you a happy and healthy holiday, it's my pleasure to declare this meeting adjourned.

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(Thereupon the Carcinogen Identification Committee adjourned.)

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 24th day of January, 2022.

JAMES F. PETERS, CSR
Certified Shorthand Reporter
License No. 10063