VIDEOCONFERENCE MEETING

STATE OF CALIFORNIA

ENVIRONMENTAL PROTECTION AGENCY

OFFICE OF ENVIRONMENTAL HEALTH HAZARD ASSESSMENT

PROPOSITION 65

CARCINOGEN IDENTIFICATION COMMITTEE

ZOOM PLATFORM

WEDNESDAY, DECEMBER 14, 2022

10:00 A.M.

JAMES F. PETERS, CSR
CERTIFIED SHORTHAND REPORTER
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APPEARANCES

COMMITTEE MEMBERS:

Thomas M. Mack, MD, MPH, Chairperson

Ahmad Besaratinia, PhD, MPH

Jason Bush, PhD

Catherine Crespi, PhD

David A. Eastmond, PhD

Thomas McDonald, PhD, MPH

Michele La Merrill, PhD

Joseph Landolph, PhD

Dana Loomis, PhD

Mariana Stern, PhD

Sophia Wang, PhD

STAFF:

Lauren Zeise, PhD, Director

David Edwards, PhD, Chief Deputy Director

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

Amy Gilson, PhD, Deputy Director, External and Legislative Affairs

Carolyn Nelson Rowan, Chief Counsel

Esther Barajas-Ochoa, Proposition 65 Implementation Program

APPEARANCES CONTINUED

STAFF:

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

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

Gwendolyn Osborne, MD, MPH, Staff Toxicologist, Cancer Toxicology and Epidemiology Section, Reproductive and Cancer Hazard Assessment Branch

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

Rose Schmitz, MS, Research Scientist III, Cancer Toxicology and Epidemiology Section, Reproductive and Cancer Hazard Assessment Branch

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

ALSO PRESENT:

Katie Pelch, PhD, Natural Resources Defense Council

Robyn Prueitt, PhD, Gradient, American Chemistry Council

Rainbow Rubin, PhD, MPH, Breast Cancer Prevention Partners

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PROCEEDINGS

DIRECTOR ZEISE: So good morning. I'd like to welcome the Committee, staff, and the members of the audience to this December 2022 meeting of the Carcinogen Identification Committee. This meeting is being held virtually. My name is Lauren Zeise. I'm Director of the Office of Environmental Health Hazard Assessment, a department within the California Environmental Protection Agency, which is lead agency for Proposition 65 implementation, and also for the assessment of health risks posed by environmental contaminants.

We have two newly appointed members of the committee, and I'll be introducing and swearing them in shortly.

Our main agenda item for today is for the consideration of bisphenol A, or BPA, for listing as a carcinogen under Proposition 65. After the BPA agenda item, the Committee will take up a consent item on the Section 2700[SIC] list of chemicals for which testing has been required, but has been inadequate, and this is separate and distinct from the Proposition 65 list.

For the -- then the staff will present updates on various Proposition 65 regulatory and other activities. We'll be taking a 45-minute break for lunch during the meeting at around noon and take a short 15-minute break

sometime in the afternoon. The meeting is being recorded and transcribed. The transcript will be posted on OEHHA's website.

Okay. Now, we will talk about how the public can comment. Is Elizabeth or Amy, you'll be putting up the --

(Thereupon a slide presentation)

DIRECTOR ZEISE: Great. Thanks.

Okay. So during the meeting, there's the opportunity to comment on the bisphenol A item. Individuals who wish to make a comment at -- who wish to make a comment are asked to join the Zoom webinar and to fill out an online speaker request card, it's shown in -- the link is shown in the chat and also on this slide.

So you'll receive a link when you fill out the card and so maybe a possibility of people only attending by audio, so I'll read the name. That's bit.ly/ - all one word - registerCIC2022. That's how you can get the link to the speaker card and join the Zoom webinar.

You're not required to identify yourself or your affiliation in order to speak, but you may do so. If you choose to remain anonymous during the meeting, you can raise your hand, and at the time that there are calls on people wanting to speak, raise their hand, and you'll be called on to provide a comment. So if you fill out a card, we ask that you provide your name on the card and

your affiliation. Also, if you can have your Zoom name match what is on the -- on the speaker card. Okay. So when you're called on to speak, you'll need to unmute yourself, state your name again, if you wish, and your affiliation and provide your comment. And public comment will be limited to five minutes per commenter.

So now I'd like to turn to the swearing in and introducing of the new CIC members. So Dr. Besaratinia and Dr. Wang, could you please turn on your cameras. And for this segment, if the rest of the Committee could turn off their cameras.

Okay. Thank you.

So Dr. Ahmad Besaratinia is a professor of research, population and public health sciences at the University of Southern California Keck School of Medicine. He has held this position since 2013. His research focuses on genetic and epigenetic mechanisms of carcinogenesis. He received his doctorate in genetic toxicology and molecular epidemiology and his master's degree in public health from Maastricht University in the Netherlands. Prior to his USC appointment, he has held multiple positions in the Beckman Research Institute of the City of Hope. Welcome to the Committee, Dr. Besaratinia.

COMMITTEE MEMBER BESARATINIA: Thank you very

much. It's a pleasure to be here.

DIRECTOR ZEISE: And then Dr. Sophia Wang has been a professor at the City of Hope National Medical Center since 2009. Prior to joining the City of Hope, Dr. Wang was an intramural investigator at the National Cancer Institute. Dr. Wang is an epidemiologist. Her research focuses on the role of environmental and genetic risk factors for developing lymphomas and other cancers. Dr. Wang previously served as an Epidemic Intelligence Officer at the Centers for Disease Control and Prevention. Dr. Wang obtained her doctorate from the Johns Hopkins Bloomberg School of Public Health.

Welcome to the Committee, Dr. Wang.

COMMITTEE MEMBER WANG: Thank you. I'm really honored to be part of this Committee.

DIRECTOR ZEISE: Now, I'll lead you in the oath of office. So if you could please, you know, be first asked to say "I" and then state your name. And you may choose during that segment where you're asked to solemnly swear or affirm, so you can choose to either solemnly swear or solemnly affirm the oath.

All right. If you could raise your hand -- your right hand and repeat after me.

I, state your name --

COMMITTEE MEMBER BESARATINIA: I, Ahmad

Besaratinia --

COMMITTEE MEMBER WANG: I, Sophia Wang --

DIRECTOR ZEISE: Okay -- do solemnly swear or affirm --

COMMITTEE MEMBER BESARATINIA: -- do solemnly swear --

COMMITTEE MEMBER WANG: -- do solemnly swear --

DIRECTOR ZEISE: -- that I will support and defend --

COMMITTEE MEMBER BESARATINIA: -- that I will support and defend --

COMMITTEE MEMBER WANG: -- that I will support and defend --

DIRECTOR ZEISE: -- the Constitution of the United States and the Constitution of the State of California --

COMMITTEE MEMBER BESARATINIA: -- the Constitution of the United State and the Constitution of California --

COMMITTEE MEMBER WANG: -- the Constitution of the United States and the Constitution of the State of California --

DIRECTOR ZEISE: -- against all enemies, foreign and domestic.

COMMITTEE MEMBER BESARATINIA: -- against all

enemies foreign and domestic --

COMMITTEE MEMBER WANG: -- against all enemies foreign and domestic --

DIRECTOR ZEISE: -- that I will bear -- that I will bear true faith and allegiance to the Constitution of the United States --

COMMITTEE MEMBER BESARATINIA: -- that I will bear true faith in the Constitution of the United of United States --

COMMITTEE MEMBER WANG: -- that I will bear true faith and allegiance to the Constitution of the United States --

DIRECTOR ZEISE: -- and the Constitution of the State of California --

COMMITTEE MEMBER BESARATINIA: -- and the Constitution of the State of California --

COMMITTEE MEMBER WANG: -- and the Constitution of the State of California --

DIRECTOR ZEISE: -- that I take this obligation freely without any mental reservation or purpose of evasion --

COMMITTEE MEMBER BESARATINIA: -- that I take this obligation without any mental reservation --

COMMITTEE MEMBER WANG: -- that I think this obligation freely with --

DIRECTOR ZEISE: I'll repeat that. I think it's a mouthful. I'll repeat it in pieces.

That I take this obligation freely --

COMMITTEE MEMBER BESARATINIA: -- that I take that obligation freely --

COMMITTEE MEMBER WANG: -- that I take this obligation freely --

DIRECTOR ZEISE: -- without any mental reservation --

COMMITTEE MEMBER BESARATINIA: -- without any mental reservation --

COMMITTEE MEMBER WANG: -- without any mental reservation --

DIRECTOR ZEISE: -- or purpose of evasion --

COMMITTEE MEMBER BESARATINIA: -- or purpose of evasion --

COMMITTEE MEMBER WANG: -- or purpose of evasion --

DIRECTOR ZEISE: -- and that I will well and faithfully discharge the duties --

COMMITTEE MEMBER BESARATINIA: -- that I will well discharge the duties --

COMMITTEE MEMBER WANG: -- that I will well and faithfully discharge the duties --

DIRECTOR ZEISE: -- well and faithfully --

COMMITTEE MEMBER BESARATINIA: -- faithfully --
DIRECTOR ZEISE: I'll say it again. That I will well and faithfully --
COMMITTEE MEMBER BESARATINIA: That I will well and faithfully --
COMMITTEE MEMBER WANG: That I will well and faithfully --
DIRECTOR ZEISE: -- discharge the duties --
COMMITTEE MEMBER BESARATINIA: -- discharge the duties --
COMMITTEE MEMBER WANG: -- discharge the duties --
DIRECTOR ZEISE: -- upon which I am about to enter.
COMMITTEE MEMBER BESARATINIA: -- upon which I am about to enter.
COMMITTEE MEMBER WANG: -- upon which I am about to enter.
DIRECTOR ZEISE: So congratulations. We're honored to welcome you to the CIC Committee. And your deep understanding of carcinogens and your contributions in your field will really add to this esteemed body. So welcome.
COMMITTEE MEMBER BESARATINIA: Thank you very much.

COMMITTEE MEMBER WANG: Thank you.

COMMITTEE MEMBER BESARATINIA: Sorry for the technical difficulties with Zoom.

DIRECTOR ZEISE: Oh, no worries at all. Thank you.

Okay. Now, I'm pleased to introduce the other members of the Committee. And as I introduce you, if you could please turn on your camera and state your name and affiliation. And then after that, you can turn off your camera, so -- and Dr. Besaratinia, you could turn off your camera now.

COMMITTEE MEMBER BESARATINIA: Thanks very much.

DIRECTOR ZEISE: So, Dr. Bush.

COMMITTEE MEMBER BUSH: Thank you, Dr. Zeise. Yes. Jason Bush, professor and chair of Biology Department at California State University, Fresno, and adjunct professor at UCSF Fresno.

DIRECTOR ZEISE: Okay. Thank you.

Dr. Crespi.

COMMITTEE MEMBER CRESPI: Hi. Catherine Crespi, professor of biostatistics at the UCLA Fielding School of Public Health.

DIRECTOR ZEISE: Dr. Eastmond.

COMMITTEE MEMBER EASTMOND: Hi. Dave Eastmond, professor emeritus at the University of California,

Riverside. Area of specialty, genetic toxicology and chemical carcinogenesis.

DIRECTOR ZEISE: Dr. La Merrill.

COMMITTEE MEMBER LA MERRILL: Hi. I'm Michelle La Merrill. I'm associate professor of environmental toxicology at the University of California at Davis. I'm also a member of the Comprehensive Cancer Center here at UC Davis.

DIRECTOR ZEISE: Dr. Landolph.

Dr. Landolph, your camera is off and your -- good.

COMMITTEE MEMBER LANDOLPH: Hi. Joe Landolph. I'm a associate professor of molecular microbiology and immunology, associate professor of pathology, and a member of the USC Norris Comprehensive Cancer Center. And I work in the area of chemical carcinogenesis and heavy metal-induced neoplastic and morphological cell transformation.

DIRECTOR ZEISE: Thank you.

Dr. Loomis.

COMMITTEE MEMBER LOOMIS: Hi. Dana Loomis. Director of the Plumas County California Public Health Agency.

DIRECTOR ZEISE: Dr. Mack.

Dr. Mack, your camera and speaker. If you could

turn on your camera and your speaker.

So Dr. Mack might be having technical difficulties. We can turn to him in a minute again.

Okay. Great. Dr. Mack, if you could introduce yourself.

CHAIRPERSON MACK: Okay. I'll repeat. I'm Dr. Thomas Mack, epidemiologist and professor emeritus at the Keck School of Medicine and the comprehensive -- and Norris Comprehensive Cancer Center.

DIRECTOR ZEISE: Thank you.

CHAIRPERSON MACK: Is that okay, Lauren?

DIRECTOR ZEISE: Perfect. Thank you.

Dr. McDonald.

COMMITTEE MEMBER MCDONALD: Hello, everyone. Thomas McDonald, Associate Research Director at the Clorox Company.

DIRECTOR ZEISE: Dr. Stern.

Oh, Dr. Stern, you're on mute.

COMMITTEE MEMBER STERN: Thank you, Dr. Zeise. Mariana Stern. And I'm a professor in population and public health science at the Keck School of Medicine of USC and associate director of population science at the Norris Comprehensive Cancer Center.

DIRECTOR ZEISE: Thank you.

Okay. Great. So welcome, Committee. We really

appreciate your taking the time to provide your advice and judgment at this meeting. Really appreciate it.

Okay. So I just want to note that Dr. Loomis is going to be chairing the meeting today on behalf of Dr. Mack. And now, I'd like to introduce the OEHHA staff and invite them to turn on their cameras as I introduce them. So Dr. David Edwards, Chief Deputy Director of OEHHA; Carolyn Nelson Rowan, our Chief Counsel. This is Carolyn's first meeting of the CIC. Dr. Vince Cogliano, Deputy Director for Scientific Programs. And then from the Reproductive and Cancer Hazard Assessment Branch, Dr. Martha Sandy, Branch Chief; Dr. Meng Sun, Section Chief of the Cancer Toxicology and Epidemiology Section. And then staff of the Cancer Toxicology and Epidemiology Section that the Committee will be hearing from today: Dr. Neela Guha, Dr. Jennifer Hsieh, Dr. Rose -- Ms. Rose Schmitz - Rose - Dr. Karin Ricker, and Dr. Gwen Osborne. Okay. And now turning to the Office of External and Legislative Affairs, Proposition 65 Implementation Program, Dr. Amy Gilson, Deputy Director for External and Legislative Affairs. And this is Dr. Gilson's first meeting. Julian Leichty, Special Assistant for Programs and Legislation. Esther Barajas-Ochoa, Analyst for the Implementation Program.

All right. Welcome, staff.

And now, I'd like to turn it over to Carolyn Rowan for some introductory remarks about Bagley-Keene or other legal issues related to participation in this virtual meeting of the Committee. Okay. And -- great, so Carolyn -- turning it over to you, Carolyn.

CHIEF COUNSEL NELSON ROWAN: Thank you. And good morning. I just have a few points to make today before we can get underway. First, a reminder that the Bagley-Keene Act applies to this meeting, so please remember that all discussions and deliberations for this group need to be conducted during the meeting, not on breaks, at lunch, or with individual members of the Committee on or offline, and that includes phone, email, chats, and text messages.

As you know, the charge for this Committee has to do with listing chemicals, and -- under Prop 65. So you will use your own scientific judgment on the questions that are put before you. In your materials that you received prior to this meeting, there was a set of criteria developed by an earlier iteration of this Committee for listing chemicals under Proposition 65. If you have questions about the data that you're looking at for a particular chemical, please refer to those criteria. There's a lot of room for you to exercise your scientific judgment, so the intent is to provide guidance in your exercise of that judgment.

Sometimes you will hear comments regarding other information that has to do with the impact of a particular listing. For example, whether or not a warning might be required for the chemical, whether the listing will have particular impacts on sectors of the economy. While that information is helpful in the general sense, it isn't part of the criteria for this Committee. You should apply the criteria that you have available in your materials and apply your own scientific judgment on the questions that are put before you.

You will also hear about the clearly shown standard, which is part of the statute. You're required to find whether or not a chemical has been clearly shown through scientifically valid testing, according to generally accepted principles, to cause cancer. This is a scientific question and it's not a legal standard of proof. This Committee is also allowed and often does make decisions based entirely on animal evidence. A chemical that you're considering need not have been shown to be a human carcinogen and you don't need to have information about whether or not human exposures to the chemical are sufficiently high enough to cause cancer in order to list.

There's no requirement that you make a decision today on any of the questions that will be presented. In the event that you feel you have insufficient information,

you can always ask for staff to prepare additional information -- oh, sorry. In the event that you feel you have insufficient information, or you need more time to think or discuss the questions that are before you, you can always ask for staff to prepare additional information or you can ask to defer the question to another meeting.

Please feel free to ask me or any other OEHHA staff clarifying questions during the meeting. If we don't know the answer, we'll do our best to find it and report back to you. And I'll be here the whole time. If I do have to step away for any reason, Senior Staff Counsel Kristi Morioka will cover for me. So there will always be an attorney here, if you have any questions.

And with that, does anyone have any questions at this point?

Okay. Great. I'll pass it back to Lauren.

DIRECTOR ZEISE: Thanks so much, Carolyn.

Now, I'll turn the meeting over to Dr. Loomis who is the Acting Chair for today's meeting.

Dr. Loomis.

COMMITTEE MEMBER LOOMIS: Thanks, Lauren and Carolyn. Good morning, everybody. And thanks for joining us this important meeting. Appreciate the participation of all the members of the Committee and the public. So let's go ahead and get started with the primary agenda

item, consideration of bisphenol A as known to the state to cause cancer.

So we'll begin with a State presentation -- a staff presentation. And Dr. Sun, if you would lead that off please, we can get started.

(Thereupon a slide presentation).

DR. SUN: Thank you, Dr. Loomis and good morning, everyone. Welcome CIC members. I'm speaking to you today on behalf of all staff scientists of the Cancer Toxicology and Epidemiology Section. Let me first provide some background on the process by which BPA was brought to you today. BPA was brought to the CIC for consultation and prioritization in 2020. And the CIC recommended that BPA be placed in a high priority group for future listing consideration. OEHHA selected BPA for consideration for listing.

And in January of 2022, OEHHA solicited from the public information relevant to the assessment of evidence on its carcinogenicity. Information received at that time was reviewed and considered by OEHHA in the course of preparing the September 2022 hazard identification document, or HID. This document, as well as the references cited, and the public comments received on the document have all been provided to the CIC for your consideration.

The HID and the presentation you'll be hearing and seeing today are the work products of all staff scientists of our section and not just those who are speaking today. The presentation has been prerecorded and consists of two parts, with a brief Q&A session in between and another Q&A afterwards. We'd like to request that the Committee members please hold your questions until the breaks. OEHHA scientists are present at the meeting and will be able to answer any clarifying questions during the breaks.

Now, I'd like to ask Dr. Elizabeth Marder to start our recorded presentation. The first speaker will be Dr. Neela Guha, an epidemiologist.

DR. GUHA: Good morning. Today we will present an abbreviated summary of the evidence on the carcinogenicity of bisphenol A.

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DR. GUHA: We will first present background information on BPA use and exposure, then we will present carcinogenicity data from the different evidence streams listed here.

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DR. GUHA: Bisphenol A, or BPA, is a synthetic, high production volume chemical. It is comprised of two phenol rings connected by a methyl bridge. The U.S. EPA

reported domestic BPA production between one and five billion pounds in 2019. Most BPA is used in the production of polycarbonate plastics and epoxy resins. Its extensive use has led to BPA being widely distributed in the environment, even without being a persistent chemical. Human exposure occurs predominantly through consumption of contaminated food and water.

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DR. GUHA: Given its decades of extensive use in a wide range of consumer products, human exposure has occurred across all life stages. BPA and BPA metabolites can be measured in human urine, serum, and tissue. Most people have measurable levels of BPA, though in recent years NHANES and Biomonitoring California have observed decreasing trends in detected BPA following a reduction or prohibition of some BPA uses.

The level of BPA in an individual and across individuals varies over time, even over the course of a single day, due to its short six-hour half-life, multiple sources of exposure, and multiple daily exposures. This complicates exposure assessment in human studies.

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DR. GUHA: We will present evidence from epidemiology studies and then animal studies. Some animal studies cover the in utero exposure period and some

studies used transgenic models.

Next, we will present information on pharmacokinetics and metabolism. Metabolism of BPA gives rise to a complex mixture of bioactive metabolites.

Finally, we will discuss data related to the 10 key characteristics (KCs) Of carcinogens. For BPA, there are data for each of the 10 KCs, with a large volume of data on some of the KCs, such as receptor mediated effects.

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

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DR. GUHA: Fifty-one publications were identified in our literature search as human studies of cancer and BPA exposure and 26 of these were included. We included all analytical epidemiologic studies. The quality of each included study was evaluated using criteria similar to those used by the NTP Report on Carcinogens and the IARC Monographs. The studies were assessed for selection bias, information bias, and confounding, and direction and magnitude of these biases were considered. Hill guidance was also considered for issues such as consistency and temporality of the association. We excluded conference abstracts, reviews without primary data, and studies of

uterine leiomyoma, which generally do not progress to malignancy. We will present the evidence for breast, prostate, and thyroid cancers, because for these sites there were at least two studies that reported risk estimates.

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DR. GUHA: There are several considerations specific to assessing the epidemiologic literature on BPA and cancer. The general population has likely been exposed to BPA continuously across all stages in life. However, assessment of long-term levels is the greatest challenge for the studies reviewed. Considerable measurement error is possible. Misclassification of exposure would likely be non-differential and bias risk estimate towards the null, although scenarios resulting in bias away from the null are also possible.

The biomonitoring studies collected samples at a single time point. No study collected samples at multiple time points to account for the high variability in BPA levels. For the few studies estimating cumulative BPA exposure, there are also issues for characterizing exposure. Questionnaire responses generally do not correlate well with measured urinary BPA levels. Job exposure matrices are of limited utility given widespread exposure to BPA from non-occupational sources.

Most studies measured BPA post-diagnosis. It is unknown whether these measurements reflect BPA levels during a relevant time window of susceptibility. If not, true causal effects could be missed. Reverse causation could not be ruled out in these studies. Physiological or behavioral changes associated with the onset of disease and treatment may alter BPA levels. For cross-sectional studies including prevalent cancer cases, there is the concern of length-biased sampling, in which individuals with the longest lasting disease are more likely to be selected into the study. This can be an important consideration for cancers with higher survival, such as breast, prostate, and thyroid cancers. Prevalent cases could differ in characteristics related to BPA levels, such as exposure patterns or metabolism, that could affect their survival compared to the incident cases captured in case-control or cohort design. By design, a temporal association could not be established in these cross-sectional studies.

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DR. GUHA: The majority of epidemiologic studies were on breast cancer and associations with BPA were inconsistent in the 13 published studies. This forest plot includes only the 10 studies that reported a risk estimate. It is a snapshot of the highest exposure

category of BPA for each study. It's sorted by the exposure assessment method. A job exposure matrix was used in one study, while the rest performed biomonitoring. Most biomonitoring studies measured BPA in urine, the accepted standard for BPA, and all but one of these studies adjusted for creatinine to enable comparisons between individuals. The studies are heterogeneous in their characteristics.

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DR GUHA: There were two studies of thyroid cancer, both observed increased risk with BPA exposure but are limited in interpretation due to their cross-sectional design. For prostate cancer, there were three studies. Two studies reported effect estimates and both observed increased risks associated with the highest categories of BPA exposure. A third study was cross-sectional, did not report a risk estimate, and is not shown on this slide.

This concludes the presentation of epidemiologic data. Now, Dr. Hsieh will present the discussion of carcinogenicity studies in animals.

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DR. HSIEH: Thanks, Dr. Guha.

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DR. HSIEH: Carcinogenicity studies of BPA were conducted in mice, rats, and gerbils.

Eight studies were identified where treatment with BPA began at or after four weeks of age, two in mice, four in rats, and two in male gerbils. There were 17 studies in which BPA exposure began in utero or within the first week of life, five studies in mice and 12 studies in rats.

Not shown are the BPA studies conducted in transgenic mice and other animal models that I will summarize later.

The red in the table indicated the nine studies where statistically significant tumor findings were observed by trend or pairwise comparison tests, or both. Before we dive into the tumor findings, our biostatistician, Rose Schmitz, will first explain how these statistical tests were performed.

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MS. SCHMITZ: Good morning. I'll be providing background information on some of the statistical methods used in evaluating the animal cancer bioassay data in the hazard identification document.

Trend and pairwise significance tests are performed on tumor incidence data. Tumor incidence for a given tumor type is expressed as follows: the numerator is the number of tumor-bearing animals in a given treatment group and the denominator is the effective number of

animals for that group, that is, the number of animals alive at the time of first occurrence of the tumor and examined at the site.

When information on time of occurrence of tumors or time of death is not reported, the number of animals in the treatment group is used as the denominator. Like NTP, many U.S. EPA programs, and IARC, OEHHA uses the one-sided Fisher's exact test to assess pairwise significance between the control group and each treated group.

To assess the significance of dose-response trends, OEHHA has long used the exact conditional Cochran-Armitage trend test. Under the null hypothesis of no effect, it's assumed that the standard Cochran-Armitage test statistic is asymptotically normally distributed. This is reliable when sample sizes are large and balanced.

With the availability of improved computing power since the original derivation by Cochran and Armitage in the 1950s, Williams showed in 1988 that the exact conditional Cochran-Armitage test is robust to small and/or unbalanced sample sizes, such as those frequently used in animal cancer bioassays. Modern statistical software programs, such as SAS and R, contain built-in functions to run the exact conditional test and obtain its p-value. And the exact p-value is calculated using an algorithm developed by Mehta and colleagues in the

Biostatistics Division of the Harvard School of Public Health in 1992.

Dr. Hsieh will now continue presenting the tumor findings in experimental animals.

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DR. HSIEH: Thanks.

Now, I will present the significant tumor findings observed in the animal studies. I will not present data on findings that were not statistically significant. I will start with the findings from studies where exposure to BPA began at or after four weeks of age.

In male B6C3F1 mice in the NTP 1982 long-term feeding study, the incidence of malignant lymphoma, and malignant lymphoma and lymphocytic leukemia combined was increased in the low-dose group by pairwise comparison with the control. And in the pituitary, three rare chromophobe carcinomas were observed in the high-dose group, with the increase statistically significant by the Exact trend test.

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DR. HSIEH: Moving on to tumor findings in rats from studies where exposure to BPA began at or after four weeks of age. In male Fischer 344 rats in the NTP 1982 103-week feeding study, significant increases were seen at three sites. The incidences of both leukemia and mammary

gland fibroadenoma were significantly increased in the high-dose group, with a significant dose-related trend. The incidences of testicular interstitial cell tumors was significantly increased in both dose groups, with a significant dose-related trend.

In the Hao et al. (2016), 12-week oral study in female Fischer 344 rats, the incidences of pituitary tumors, likely adenomas of the adenohypophysis, was significantly increased in the low-dose group.

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DR. HSIEH: In the following slide, I'll present the significant tumor findings from studies where exposure to BPA began in utero or within the first week of life. We will start with mice first.

Weinhouse et al. exposed female mice to BPA in utero and through lactation, then in feed from post-weaning until study termination at 10 months of age. The incidence of hepatocellular adenoma and carcinoma combined was significantly increased in the high-dose group with a significant dose-related trend.

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DR. HSIEH: Now, I will present studies in rats exposed to BPA beginning in utero or within the first week of life. These studies were conducted under the Consortium Linking Academic and Regulatory Insights on

Bisphenol A Toxicity, or CLARITY, program.

The slide gives an overview of the eight CLARITY cancer bioassays. All eight studies, I will call them study arms, used six dose levels of BPA from 0 to 25,000 microgram per kilogram per day. All eight arms dosed pregnant SD (NCTR) rats with BPA daily by gavage from gestational day six to birth of the pups. In all eight arms, the day after birth, all pups were direct -- were directly dosed with BPA through gavage.

In Arms 1 through 4 stopped dosing when the animals reached three weeks of age. In Arms 5 through 8, dosed animals every day until the studies were terminated. In Arms 1, 2, 5 and 6, the studies last until animals were one year of age. In Arms 3, 4, 7 and 8, the studies last until animals were two years of age.

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DR. HSIEH: This slide summarizes the statistical significant tumor findings in the CLARITY-BPA core studies conducted in female rats.

In Arm 3, the study with only in utero and three weeks exposure, there were increases in mammary gland adenocarcinoma, and adenoma and adenocarcinoma combined in the lowest dose group compared to control. The incidence of mammary gland adenocarcinoma was also elevated in other dose groups, but was not statistically significant. This

apparent non-monotonic response in mammary gland tumor may be related to BPA's non-canonical estrogenic activity, which will be discussed later.

In Arm 5, the continuous-dose one-year study, there was a dose-related trend in uterine stromal polyps.

In Arm 7, the continuous-dose two-year study, significant dose-related trends in tumors of clitoral gland was observed, specifically increases in clitoral gland adenoma, and adenoma or carcinoma combined.

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DR. HSIEH: This slide summarize the significant tumor findings in the CLARITY studies in male rats.

In Arm 4, the two-year study with only in utero and three weeks exposure, an increase in malignant lymphoma of the prostate was observed at the highest dose compared to control, with a significant increasing trend. A dose-related trend in malignant lymphoma at all sites was also observed. In thyroid gland, a dose-related increase in C-cell adenoma was significant by trend.

And in Arm 8, the continuous-dose two-year study, a dose-related trend in rare hepatocellular carcinoma was observed.

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DR. HSIEH: Various rare tumors were observed in BPA-treated animals in each of the eight arms in the

CLARITY studies.

For these studies, which were initiated in 2012, no ideal historical control data on spontaneous tumor incidences were identified. Two NTP studies were conducted by the same NCTR laboratory using SD rats from the same animal colony as those used in the CLARITY-BPA studies. However, the studies were initiated much earlier in 1999 and in 2003 compared to the initiation of the CLARITY-BPA core studies in 2012. They also used a non-gavage exposure route. The two NTP reports for this colony provided data for one historical control comparison. We also used two more recent databases, the Charles River (2013) and NTP (2021) databases. The relevance and the limitations of each database is detailed in the hazard identification document.

We reported rare tumors in each of the CLARITY-BPA studies when they occurred at less than one percent incidence in historical control animals in each of the three sets of historical control data, and with zero incidence in the concurrent controls.

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DR. HSIEH: Several additional issues associated with the CLARITY-BPA core studies has been raised in publications. These issues include possible exposure of control animals to BPA as a result of environmental BPA

contamination, and lack of a responsiveness of the SD (NCTR) rat colony to estrogenic chemicals and chemicals that affect thyroid gland function, the lack of an unhandled, non-gavaged control group, and the lack of ethinyl estradiol-treated positive controls in the stop-dose arms. These issues may have limited the sensitivity of CLARITY's core studies to detect carcinogenic effects.

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DR. HSIEH: This slide summarizes the tumor findings from the animal cancer bioassays we have discussed so far.

There were increases in hepatocellular tumors in male rats and female mice; pituitary tumors in female rats and male mice; and thyroid C-cell tumors in male rats; mammary gland fibroadenoma in male rats; and mammary gland adenocarcinoma, and adenoma and adenocarcinoma combined in female rats; clitoral gland tumors and uterine stromal polyps in separate studies in female rats; testicular Leydig cell tumors in male rats; leukemia in one strain of male rats, and lymphoma in another strain of male rats, and in male mice; rare tumors in BPA-treated rats in each of the CLARITY-BPA core studies, and some with multiple types of rare tumors.

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DR. HSIEH: Now, I will summarize tumor findings from studies conducted with transgenic mouse models.

In two studies using the female mouse MMTV-erbB2 mammary tumor model, BPA exposure reduced the tumor latency. In one of these studies, BPA also significantly increased tumor multiplicity, tumor volume, and tumor metastasis to the lungs.

In a mouse model with an estradiol non-responsive mutant estrogen receptor-alpha ligand binding domain, BPA induced tumor-like outgrowths in the flank muscle in six out of 15 female mice. Two of these six outgrowths were confirmed as adenocarcinomas.

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DR. HSIEH: In other animal models, exposure to BPA either before or after introduction of a xenograft or syngeneic cancer cells, or regeneration of the mammary gland organs led to increased numbers of tumor-bearing mice, increased mean tumor volume and/or tumor weight, increased growth of established tumors, and increased incidence of mammary gland atypical ductal hyperplasia and ductal carcinoma in situ.

In animal studies of BPA administered in combination with other chemicals, increased mammary tumor incidence or multiplicity and decreased tumor latency occurred in studies where BPA was administered before a

model carcinogen or after a tumor initiator, and increased prostate tumors and prostatic intraepithelial neoplasia were observed in studies where BPA was given before testosterone and 17 beta-estradiol.

This concludes the first half of the presentation. We will now have a short Q&A break for any clarifying questions from the Committee.

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COMMITTEE MEMBER LOOMIS: It looks like there's a question from Dr. Eastmond.

COMMITTEE MEMBER EASTMOND: Yes. Thank you. A large amount of data that you've summarized. It's my understanding that both for the NTP study that was the high dose study published in 1982 and then for the NTP CLARITY study that was published in 2018, both of those studies had internal review. And they had ex -- they had a peer review committee review the pathology data and the analysis in detail. And both of those concluded that there was -- they did not see that there were any clear treatment-related effects. Do you want to comment as to why you're seeing different results than they are?

DR. SANDY: So I'll turn to Dr. Meng Sun and see if she would like to respond.

DR. SUN: Yeah, I can say a few words. So, yes, Dr. Eastmond, when we report data from the -- these

studies, we look at tumor incidence. And Ms. Rose Schmitz has explained in her -- on her slide that we use effective number whenever possible to report the tumor incidence. We also look at historical control databases for rare tumors. So do you have any specific questions on the tumor incidences we presented?

COMMITTEE MEMBER EASTMOND: Well, it's just -- it's more of a general thing is that, you know, when you have -- this is a government agency testing result and independent review, external peer review, and they come out and say, yeah, we see some changes here, but given that many of these have, you know, high control valuses -- you know, spontaneous control incidence or the life table analysis don't support what we're seeing here in these tests, you know, their summary conclusions to my understanding were pretty much -- they didn't see any real -- what they thought were clear treatment-related increases.

So it strikes me when you go through all these trends, there's not a stepping back and looking and saying what do these other people that actually conducted the studies or did the primary review and evaluation reports what were their conclusions. That seems to have been ignored in going through your results. But anyway, it's just something that struck me in this -- both of these

two, because they're high quality studies generally.

DR. SUN: Dr. Sandy, you had your hand up earlier. Did you want to say something?

DR. SANDY: I believe Dr. Cogliano wishes to speak.

DR. COGLIANO: I want to say thank you very much. So I think you're right, Dr. Eastmond. This is what the NTP panels have said. But what we're doing here is presenting all of the data that we have. And the NTP Panel is sort of looking at just the CLARITY Study and whether they thought that that provided some level of evidence. We're going to be presenting as well as the NTP study. We've presented some of the other studies, as well as some of the mechanistic information that you'll hear after this question and answer break. And this is to give the Committee the full picture of evidence that exists that will go into your deliberations.

COMMITTEE MEMBER EASTMOND: Okay. Thanks, Vince.

COMMITTEE MEMBER LOOMIS: Are there any other questions from the Committee?

I can't see everybody in the gallery right now. So if there's others.

Dr. Landolph. Okay. Go ahead, Dr. Landolph.

COMMITTEE MEMBER LANDOLPH: There. Yeah, thank you very much for that interesting presentation. I've

read through this 600 page document. I'm on my third reading through it now. And I guess my simple question to the authors is in your opinion, given all this data that's present on the animal carcinogenesis studies, what I'm looking at and I'm seeing is data that is positive, occasional trend tests that are positive, dose response curves in some of these assays, and it's a very large database.

So my opinion looking at this is I would not be able to dismiss in my mind all this data that's positive. And I'd like to ask the authors, you know, the whole animal carcinogenesis studies, is that something you feel that you could do? Could you declare all this data as negative, because I don't feel that way?

DR. SANDY: So if -- perhaps I can take a start at this. This is Martha Sandy. So Dr. Landolph, we have presented and tried to summarize the data that are available, the evidence that is available from all data streams. And we've presented that to your Committee and really it's -- it's your Committee's job to make the decision, so we leave it to you.

COMMITTEE MEMBER LANDOLPH: Well, that's -- Martha -- that's fine, Dr. Sandy. And I'm quite able to do that, but I'm just asking you as the people who have lived with this data and have summarized it, is do you

think this is a negative database? I mean, I don't feel that way at all. Are you allowed to express an opinion on that?

DIRECTOR ZEISE: You know, I just want to say I think we're, you know, I think what we wanted to do was break the full presentation -- really appreciate the comments being made, but I think what we wanted to do was to present the evidence in the report. And so what we did is we're kind of halfway through our presentation. And this is a break for clarifying questions. So I think we'll have ample time to have a discussion -- you know, for the Committee to have a discussion around the evidence. We'll also include an opportunity for public comment. But I wonder if we could potentially leave that discussion for later on. It's covered under a different agenda item.

COMMITTEE MEMBER LOOMIS: Yeah, let me chime in for a moment. I think that's what we need to do. The question that Dr. Landolph is raising is important, but it's obviously central to the Committee's job here in this meeting. So let's go ahead. I see one more question from the Committee. We'll go ahead with the rest of the presentation and then we'll have a chance to discuss the Committee's opinions on the evidence.

So, if that's okay, I'm going to turn to Dr.

Crespi with another clarifying question.

COMMITTEE MEMBER CRESPI: Yeah, I do have a clarifying question. So regarding the animal studies, is it the case that the analyses that we were presented with here and also in the report were analyses that were done by the OEHHA staff rather than what was conducted by the study investigators, in particular the NTP and the CLARITY studies? Maybe staff could clarify that question and how their analyses differs from the ones that were done by the study investigators.

DR. SUN: I could try to answer that. Yes, you are correct, Dr. Crespi, in reporting the NTP 1982 studies and the CLARITY studies, OEHHA did our own statistical analysis. And Ms. Schmitz has laid out the way we do our statistical analysis, the one-tailed Fisher pairwise comparison and the exact trend test. And we have table footnotes underneath each table where we presented tumor incidence on how these tests were done and who did them.

COMMITTEE MEMBER CRESPI: Thank you.

DR. SANDY: And this is Martha Sandy. I'll clarify that -- or add to that clarification that it is our practice when we have data in published studies and published reports to look at the data and to do analyses, as Dr. Meng has -- Sun has indicated. In publications where the -- we don't have any additional information

needed to do certain analyses, such as effective number using that, then we have to rely on just what's reported in the paper, and we summarize that in the hazard identification document letting people know, the reader know, what was available to us.

COMMITTEE MEMBER LOOMIS: Thanks, Martha.

Dr. Landolph, you still have your hand up. Did you have another comment or question?

COMMITTEE MEMBER LANDOLPH: No, sorry. I just forgot to pull it down.

COMMITTEE MEMBER LOOMIS: Okay. Dr. Eastmond, it looks like you're back. Do you have another question?

COMMITTEE MEMBER EASTMOND: Yeah, just a bit of a -- well, somewhat clarifying. It's my understanding that say for the CLARITY Study, there were something like six doses. And so there were pairwise comparisons done with each of those doses, plus a trend test. And that was what OEHHA did. And I think independently, and there may have been life study tests done by NTP and others, this is somewhere -- my calculations, does that mean you're -- there are probably at least 40 tissues evaluated. So you're looking at probably 200 statistical tests for that particular study, is that correct?

Now, that's approximate, but usually it's -- you know, if you've got 40 tissues and you've got five

pairwise comparisons and one trend test, that would be 40 times six, so you're looking at 200 to 240 tests. And that's what I have to look at is looking for consistency and numbers of statistical tests that are done.

COMMITTEE MEMBER LOOMIS: So is that a question?

COMMITTEE MEMBER EASTMOND: Well, does that sound like reason -- does that sound about right, that there were roughly six doses with pairwise comparisons plus trend tests. So you're looking at something about 200 different statistical tests done for that one study.

DR. SUN: Dr. Eastmond, I wonder if you're worried about multiple comparison issues, is that --

COMMITTEE MEMBER EASTMOND: I mean that -- that basically was what it gets to is that with that many statistical tests you're going to expect a certain number to be positive by random chance.

COMMITTEE MEMBER LOOMIS: Well, this is a -- this sounds like a discussion item, so --

COMMITTEE MEMBER EASTMOND: Yeah. Oh, it's true. I mean, that's correct. I was trying to point out and ask -- clarify it, but that's fine.

DR. SUN: Maybe later on during discussion our biostatistician could explain.

COMMITTEE MEMBER LOOMIS: Is that satisfactory?

Dr. Landolph, it looks like your hand is still

up, if you could just put that down, it helps --

COMMITTEE MEMBER LANDOLPH: Yeah.

COMMITTEE MEMBER LOOMIS: -- keep track of things. Are there any more questions from the Committee before we go on to the second part of the staff presentation?

Okay. Seeing none, let's proceed then.

DR. SUN: Thank you. Dr. Marder, could you start the second half. The next speaker will be Dr. Karin Ricker.

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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 and metabolism.

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DR. RICKER: The pharmacokinetics and metabolism of BPA are well studied. BPA is well absorbed following oral or dermal routes in humans and is distributed throughout the body. BPA can cross the blood-brain barrier and placenta and it has been detected in breast milk, adipose tissues, and body fluids such as amniotic fluid. BPA has short half-lives in humans and animals, generally less than 24 hours. The serum half-life of BPA by the oral route in humans is about six hours.

Excretion is fast with some species differences. In humans, urine is the primary excretion pathway, along with feces, breast milk, and sweat. Although it has a short half-life in humans, BPA is still detected in over 90 percent of the U.S. population, suggesting daily exposure. In rodents, feces is the main excretion pathway. BPA also undergoes enterohepatic circulation in rodents but not humans.

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DR. RICKER: BPA metabolism is complex. Here is an overview. We have metabolism with conjugation to glucuronate and sulfate, delineated in the two light blue boxes here. The green boxes below show metabolites of dimerization and the rest is oxidative metabolism.

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DR. RICKER: Now, to walk you through this, let's start with the parent molecule, BPA.

BPA is metabolized in the liver, primarily via conjugation with either glucuronic acid or sulfate, leading to the formation of BPA-glucuronide and BPA-sulfate, both shown here. BPA-glucuronide is usually the main metabolite formed in humans and constitutes approximately 70 percent of excreted metabolites. The primary hepatic enzymes in humans are listed here on this slide. BPA-glucuronide can cross the placenta and can

subsequently be de-conjugated in the fetus by beta-glucuronidase leading to free BPA.

Next, we have sulfoconjugation of BPA. In humans, this reaction is primarily carried out by cytosolic sulfatase 1A1. BPA-sulfate is usually a minor metabolite and constitutes about 20 percent of excreted metabolites. BPA-sulfate can also be deconjugated by enzymes such as estrone sulfatase.

While phase two metabolism of BPA is very effective, there are several conditions or factors that can influence the extent of conjugation and thus the amount of unconjugated BPA. We have listed a few examples here. Enzyme polymorphisms of key enzymes can result in significantly lower glucuronidation. I already mentioned the de-conjugation reactions by beta-glucuronidase and estrone sulfatase. Co-exposure to other phenolic xenobiotics and/or medications can also lead to a significant reduction of BPA conjugation. People with certain diseases or at certain life stages can also have less BPA conjugation.

Now, we will turn to the oxidative metabolism. These reactions are generally catalyzed by cytochrome P450 enzymes, CYP enzymes for short. Different metabolic reactions include hydroxylations, carbon bond cleavage, dimerization, and conjugation with glutathione.

In an initial oxidation step, BPA is hydroxylated by CYP enzymes and forms the ortho-hydroxy-BPA, also called BPA catechol. The catechol is estrogenic and has been shown to induce cell proliferation of human breast cancer cells. In the next step, the catechol undergoes further oxidation to the semiquinone, and ultimately forms the BPA-3,4-quinone and its glutathione conjugate. The BPA quinone can form DNA adducts and it can undergo redox cycling during which reactive oxygen species are produced, leading to oxidative stress.

BPA itself can also be directly conjugated with glutathione. This step requires enzymatic activity from CYP enzymes and may involve a reactive arene epoxide intermediate, which is shown here.

Carbon bond cleavage of the parent molecule forms hydroquinone and a carbocation intermediate, another reactive metabolite. Downstream metabolism then leads to two compounds, isopropenylphenol and hydroxycumyl alcohol. And hydroxycumyl alcohol is also estrogenic. Further reactions of isopropenylphenol and its intermediate radical lead to the formation of the intermediate of the metabolite MBP. MBP, the chemical name is shown here on the slide. MBP is more estrogenic than BPA and has been shown to induce proliferation of human breast cancer

cells. The carbon bond cleavage also produces phenol and its glutathione conjugate.

Lastly, BPA can form dimers. Several dimers have been identified. Here, we show two dimers, one with a carbon linkage and the other one with a carbon-carbon linkage. BPA dimerization may be a two-step metabolic process consisting of enzymatic oxidation of BPA into an unidentified reactive intermediate followed by a nonenzymatic reaction between the reactive compound and the parent compound. Alternatively, there may be an aromatic radical pathway involving an aryl radical.

This concludes the metabolism section. We are now moving on to Dr. Osborne, who will discuss the data for the key characteristics of carcinogens.

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DR. OSBORNE: We organized the mechanistic data for BPA by the ten key characteristics of carcinogens, or KCs, that are used by IARC and NTP in their evaluations of carcinogenicity evidence. The key characteristics were identified by IARC based on a comprehensive review of mechanistic information for known human carcinogens in IARC Group 1.

As detailed in the HID, there is evidence on BPA for each of the 10 KCs, and some with considerable evidence. Data from human and animal, animal cells in

vitro, and acellular systems were identified for many of these KCs. A brief overview of each will be presented. You'll notice that on each slide there is a reference to the section and appendix in the HID for each KC. By far, the most evidence is related to receptor-mediated effects, so I'm going to start with KC8.

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DR. OSBORNE: Over 1,000 studies were identified for KC8. For the estrogen receptor, there is a large body of evidence from observational studies in humans and multiple experimental systems indicating that BPA modulates classical estrogen receptor-mediated effects to induce estrogenicity through several different estrogen receptor subtypes.

BPA can also modulate non-canonical estrogen receptor activities, such as the rapid onset of extranuclear responses at low-dose with non-monotonic dose-response. This could potentially explain the mammary tumor response at the lowest dose seen in the CLARITY-BPA core study number three. BPA is also observed to affect membrane-associated, G-protein coupled, and estrogen-related receptor gamma, and to induce epigenetic changes to regulate the expression of estrogen receptor alpha.

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DR. OSBORNE: Now, turning to other receptors. BPA exposure was associated with an increase in expression of the progesterone receptor in some human cell studies and most in vitro studies in non-human mammalian cells. BPA exhibited antiandrogenic activity on human androgen receptor and interfered with androgen receptor nuclear translocation in several studies in human cells and in cells from other mammals.

BPA exposure antagonized activity of thyroid hormone receptor beta in several human cell lines. And BPA altered expression of other nuclear receptors such as peroxisome proliferator activated receptors alpha and gamma, aryl hydrocarbon receptor, and pregnane X receptor, each of these in several different systems.

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DR. OSBORNE: Now, for the effects on hormone levels. BPA levels were positively associated with estradiol in male partners in subfertile couples, girls and female adolescents, and newborns.

Higher BPA levels were associated with elevated testosterone in women and girls with polycystic ovarian syndrome. No consistent findings were observed in other subpopulations. BPA decreased testosterone levels in male mice, and altered testosterone levels in female mice, but not consistently in either direction. Higher BPA exposure

was associated with increasing prolactin levels in occupationally exposed men and women. Prolactin levels were also increased in rats following BPA exposure.

No consistent associations were observed with progesterone or thyroid hormones.

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DR. OSBORNE: There are also a lot of studies for KC10, alters cell proliferation, cell death, or nutrient supply. Many studies observed BPA-induced cell proliferation in multiple types of human cells. Many studies in rats and mice have reported BPA-induced hyperplasia in multiple organs. Multiple studies report BPA decreases apoptosis, increases anti-apoptotic proteins, and decreases pro-apoptotic proteins in several human cancer cell lines.

Additional studies report BPA alters proteins involved in cellular replication or cell cycle control signaling pathways in several human cancer cell lines, increases angiogenesis in human umbilical vein endothelial cells and increases pro-angiogenesis gene expression in human cells, and increases glycolysis-based energy production in several human cancer cell lines.

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DR. OSBORNE: KC1, is electrophilic or can be metabolically activated. As mentioned earlier, BPA

metabolism generates electrophilic and reactive metabolites, which are listed here. BPA may also induce oxidative lesions in DNA as discussed in more detail under KCs 2 and 5. The metabolite BPAQ can form other DNA adducts, which has been observed in human breast cancer cells and other systems. Following enzymatic activation, BPA can also form protein adducts.

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DR. OSBORNE: Next is genotoxicity. BPA induced mutations in human fibroblasts and kidney cells in vitro. BPA increased the dominant lethal mutation rate in male rats. However, no effects were observed in bacteria, yeast, or Drosophila. The mutagenicity of BPA has not been well studied in systems other than bacteria and yeast.

Several chromosomal effects induced by noncytotoxic concentrations of BPA were observed. Studies in animals and in human and animal cells have reported increases in micronuclei, chromosomal aberrations, and various types of chromosomal abnormalities following BPA treatment. In plants and acellular systems, BPA increased chromosomal aberrations and microtubule abnormalities.

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DR. OSBORNE: A substantial amount of data on BPA-induced DNA damage are available. More than ten human

observational studies reported associations between BPA and urinary or serum levels of 8-OHdG, a biomarker of oxidative damage to DNA. Two human observational studies reported positive associations between urinary BPA concentration and sperm DNA fragmentation. Increases in DNA adduct formation, DNA strand breaks, oxidative damage to DNA, and gamma-H2AX were observed in multiple experimental systems treated with noncytotoxic concentrations of BPA. Increases in expression of proteins associated with DNA damage-control were observed in two studies in human cells in vitro and in an earthworm study.

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DR. OSBORNE: Evidence of BPA-induced oxidative stress comes from consistent findings from many human and animal studies in vivo and in vitro. More than 500 original studies were identified and this slide summarizes positive findings of various KC5 biomarkers.

As mentioned earlier, 8-OHdG is a biomarker for measuring the direct effect of oxidative damage to DNA. BPA was significantly associated with increased 8-OHdG in multiple studies of human populations at different life stages and in different locations. Increases were also seen in many animal studies in vivo and in vitro.

Significant increases of reactive oxygen or

nitrogen species were reported in many human cell and rodent in vivo and in vitro studies, some with dose-dependent increases. In human cells, increased ROS production was observed at low doses.

BPA was also significantly associated with increases in lipid peroxidation in human observational studies and multiple other data streams. In addition, significant reductions of GSH or antioxidant enzymes were reported.

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DR. OSBORNE: KC3, alters DNA repair or causes genomic instability. A few studies reported decreased capacity to repair DNA damage in human and rodent cells. Some studies reported decreased expression of DNA repair enzymes.

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DR. OSBORNE: KC4, induces epigenetic alterations. Many studies related to epigenetic alterations that may be relevant to carcinogenesis were identified in humans and animals. Examples of some of the observed effects are shown on the slide. This includes examples of possible BPA associations with altered methylation of specific genes found to be altered in various cancers, global methylation, and microRNA expression. MicroRNAs play crucial roles in the

regulation of cancer-associated processes, including proliferation, differentiation, and apoptosis. Altered histone modifications were also observed in several human cell lines.

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DR. OSBORNE: Data on KC 6, induces chronic inflammation, comes from several human observational studies and many animal studies. In human cross-sectional studies, positive associations were observed between BPA levels and inflammatory biomarkers, such as c-reactive protein and tumor necrosis factor alpha. BPA was positively associated with increased levels of interleukin 6 in eight cross-sectional studies and one cohort study. No significant associations were observed with IL-1beta, IL-10, TNF-alpha, or CRP in the two cohort studies.

In animals, BPA exposure was associated with chronic inflammation, as evidenced by histopathology and concurrent chronic inflammation and increases in pro-inflammatory biomarkers in 12 studies. Two studies reported a negative association between BPA exposure and these biomarkers.

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DR. OSBORNE: KC7, is immunosuppressive. T and B cell cellularity or proliferation was decreased in several systems. Neutrophil chemotactic capacity was decreased in

human cells in vitro and mice. Effects were also observed on macrophages. For example, macrophage phagocytotic capacity was decreased in human cells in vitro, rodents, and fish.

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DR. OSBORNE: Dendritic cell endocytotic capacity was decreased in human cells in vitro and cell numbers were decreased in rats. BPA exposure decreased the percentage of splenocytes that were natural killer cells in mice. And IgM levels were decreased in mice and fish.

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DR. OSBORNE: Finally, immortalization of cells by BPA was reported in several systems.

These include: Cell transformation of Syrian hamster embryo cells; in human cells, increased cell invasion and mesenchymal cell markers and decreased epithelial cell markers and p21 expression, a gene involved in cellular senescence; and altered telomerase activity and expression and telomere length. In a cross-sectional study, higher urinary BPA levels were associated with shorter telo -- relative telomere length in adult women.

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DR. OSBORNE: To recap, BPA is unusual in that there is evidence for each KC with considerable evidence

for some. For KC1, electrophilicity, there is evidence that BPA produces electrophilic metabolites, DNA and protein adducts, and oxidative lesions in DNA.

For KC2, genotoxicity, there is evidence of mutagenicity, chromosomal effects, and DNA damage.

For KC3, DNA repair and genomic instability. There are a few studies that have reported a decrease in DNA repair capacity and DNA repair enzyme expression.

For KC4, epigenetics, BPA was associated with altered global and local methylation, DNA methyltransferase changes, microRNA changes, and histone modifications.

For KC5, oxidative stress, effects such as oxidative damage to DNA, increase in ROS and RNS, increase in lipid peroxidation, and decreases in GSH and antioxidant enzymes were observed.

For KC6, chronic inflammation, increases in inflammatory cytokines and tissue inflammation were seen.

For KC7, immunosuppression, several alterations were observed, including a decrease in T and B cells, decrease in macrophage phagocytosis, neutrophil chemotaxis, dendritic cell endocytosis and IgM.

For KC8, receptor-mediated effects, BPA activates estrogen receptors, antagonizes the androgen receptor, alters hormone levels, and alters PPARalpha and gamma,

AhR, and PXR levels.

For KC9, immortalization, increases in cell transformation and invasion and mesenchymal cell markers were observed, as well as decreased cellular senescence genes and altered telomerase activity and telomere length.

Finally, KC10, cell proliferation, cell death, and nutrient supply. BPA increased hyperplasia and proliferation, decreased apoptosis, increased angiogenesis, altered cell cycle control pathways, and increased glycolysis-based energy production.

And that concludes our presentation of the data regarding the carcinogenicity of BPA. Thank you for your attention and we're happy to take any questions.

COMMITTEE MEMBER LOOMIS: Okay. Thank you to the staff for that presentation. Let's see if there are any further questions from the Committee.

Okay, Dr. Eastmond, you're first.

COMMITTEE MEMBER EASTMOND: Me again. I had a question. Quite an amazing amount of information that you covered and compiled in your document. It strikes me as a phenolic compound, BPA should act as an antioxidant certainly at low doses. Did you see any -- but we're getting all these reports of oxidative damage. And it's probably the most consistent in many respects. Did you see any dose relationship between this sort of antioxidant

you would predict versus the oxidative stress when you looked at the -- analyzed the data?

DR. SUN: I'll give it a try, Dr. Eastmond. Yes, we did see dose response in some of the studies for oxidative stress, in KC 5. And if you'd like to give us some time, we can respond to you with the list of specific studies. But yes, we do see dose response and it's possibly mediated by the BPA metabolite BPA quinone, which is including KC 1 as well.

COMMITTEE MEMBER EASTMOND: I mean, would -- I mean it just struck me as unusual, because I look at the molecule, these phenolics tend to be antioxidants at low dose. And clearly, as you go to the high dose is when you get the hydroxylation and form the quinone, then you would expect oxidative stress. But anyway, it was interesting be to me that just that combination. I wondered if there was a distinct dose response. But anyway, thanks.

COMMITTEE MEMBER LOOMIS: Any other questions from the Committee?

Dr. Eastmond, you still have your hand up.

Going once.

Going twice.

Okay. I don't see any other questions. So if there are none, it's time to move on to the next segment of the meeting, and that is the Committee discussion of

the evidence.

And so we'll start first with human cancer studies. With Mariana Stern, Catherine Crespi, and myself. And then we'll move on to discussion of the studies of cancer in animals with Dr. Landolph, Dr. Bush, Dr. La Merrill. And then finally, we'll have several discussants on the 10 key characteristics of carcinogens.

Somewhere in there we'll stop for lunch, but that will just depend on how things move along. So I'll call a lunch break sometime around 12 when we come to a stopping point between the major sections.

So let's go ahead with discussion by the Committee of studies of cancer in humans. Dr. Stern, would you like to start?

COMMITTEE MEMBER STERN: Sure, I'll be happy.

So just pulling my notes here. So thank you the OEHHA team for your wonderful presentation. You make our job much easier because you've provided a wonderful overview of the epidemiological literature. So what I'm going to try to do is focus on highlighting some of the most informative studies and giving a summary of the whole picture of the studies that we review.

So as the OEHHA team highlighted, BPA has been detected in the human population, so that confirms that the exposure is widespread. However, it's not a

persistent chemical. So quantifying the exposure and documenting the association between exposure levels and cancer risk is -- has proven to be extremely challenging.

There has been two main approaches that have been used in the epidemiological studies that have been identified to measure BPA. And these were summarized before, so I'll just repeat it very quickly. One has been measuring in biological samples mostly urine, blood, and blood serum, and a few measure in adipose tissue. And aside from technical issues with the actual measurements, which some of the studies had some issues, a key challenge is that -- that the half-life of BPA is fairly short between four and six hours. So any single measurement is really not going to capture cumulative levels of exposure. It's an intermittent exposure that we're capturing.

So we're likely underestimating any possible association between BPA and cancer risk, because this challenge is likely non-differential. So we project that this is the direction of the misclassification. Another approach that has been used by a few studies are -- is to use job exposure matrices, which have been useful for other chemicals. However for BPA, they're not that useful because majority of exposure comes from diet and beverages and not really from occupational settings.

There's only one study that I'm going to

highlight, which took a different approach, which was to do a specific questionnaire around sources of exposure of BPA, such as, for example, drinking hot water from a plastic cup. And they constructed a database based on existing literature to be able to assign scores of exposure to the participants. So I'll share in a few minutes what that study found.

Another important issue that complicates our understanding of the role of BPA in cancer through the epidemiological studies is the issue of temporality. Majority of the studies measure it at the time of diagnosis or soon after diagnosis. So we don't know if that measurement is representative of what the participants were exposed to when their cancer developed. There's only a few studies that measure it in a prospective study setting.

So altogether, the evaluation of BPA's role in cancer risk through epidemiological studies is extremely challenging and possibly unreliable. And so a key concern is that we have not been able to capture the true association that may or may not exist in the population. From my perspective, my main concern is not so much that we may find something spurious - although in some studies, and I will highlight that, that might be the case - rather that we may not be finding an association that may exist

in the population.

So there were a total of 28 publications and majority were for breast cancer with 14 publications -- excuse me -- followed by prostate with three, and lung and thyroid cancer with two publications each. And then there were single publications for another set of cancer, mainly endometrial, osteosarcoma, meningioma, melanoma, gallbladder cancer, lymphomas, and one study that focused on all cancers focusing on mortality.

Studies included were from the U.S., from Europe, from China, from Korea, Mexico, and Iran. And studies differ quite a bit in how informative they are, with the most informative studies being the minority and including: those that measure BPA prior to diagnosis, which were only a handful; those that use proper methods to measure BPA adjusting levels -- to levels of creatinine, and having high levels of detection in their sample; those that consider appropriate confounders, such as body mass index, which is known to be an important confounder for many cancers, and those that have reasonable sample sizes.

So I'll talk about the studies in breast cancer first. There were three studies that measured exposure before diagnosis, so these were prospective studies where exposure was measured before patients that developed the cancer.

One study used a job exposure matrix and about 10 percent of women only reported having been exposed based on occupation. They didn't find an association in the study, although they did report a positive association when considering women who had longer time of exposure, but this was not significant.

So as I mentioned before, a key concern with this study is that we don't think that occupational settings are the main source of exposure to BPA and only 10 percent of the women were exposed. Another study was done in the context of the EPIC cohort, which is a prospective multi-center study done in Europe. This study was based in Spain. They measure BPA in serum. Only one-time measure. This is true for all studies. No study measure repeated times BPA. They did not find an association. A key concern with this study is that the level of detection BPA in serum was -- is much lower than in urine.

Finally, there was a study done within the multi-ethnic cohort, which is another population-based cohort done here in California and in Hawaii of over a hundred thousand people. And it includes five different racial and ethnic groups. They measure BPA in urine and found no evidence of an association with cancer risk.

There were 11 additional studies that measured BPA at the time of diagnosis or soon after. And these

studies differed in several aspects, which introduces a lot of variability in how informative the studies are, mainly how they handle BPA measures, some adjusted for creatinine levels, some did not, some had only a very small percent of the sample with detectable levels. And the studies differed in approaches of how to handle those samples that had detection levels lower than the level -- the threshold of detection.

Some consider total BPA, some consider only free BPA, which is known to be very low, because BPA is metabolized very quickly. Some consider important confounders like BMI, some did not. And the biological matrices used varied. Some -- majority used urine, but some used serum and a few adipose tissue.

Altogether, there were three studies that measured BPA in urine that found significant positive associations. One was a study in China, one in Iran, and one study in Mexico. The study in Iran was very small, so I don't think it's very informative.

The Chinese -- the study done in China was of moderate size, but a key concern is the fact that they did not adjust for BMI, so that estimation of a positive association could be inflated.

The Mexico study is a bit more informative. They did find a positive association. A key concern with this

study was that a lot of the women had measurements that were below the level of detection. However, they did do a sensitivity analysis where they just focused on those that had detection levels above the threshold with reasonable sizes -- sample size. And they did see a positive association among that subset. So I think that this study is the only one of this group that is informative.

There was one study in Taiwan that measured BPA in urine that also reported a significant difference in levels between cases and controls, but they did not provide proper estimates of association adjusted for confounders.

And finally, there were six studies that reported no associations. Four of them were informative, given the sample size, consideration of confounders, and use of urine samples, with one study using adipose tissue.

So in conclusion, the evidence for breast cancer is inconclusive with majority of informative studies not showing an association, but with two informative studies out of the 14 showing a positive association. So next I will move on -- move to prostate cancer. There were three studies, one measured BPA before diagnosis was done within the EPIC cohort, the same one that look at breast.

And for prostate cancer, remember for breast they did not find an association. But interestingly for

prostate cancer, they didn't find an association when looking at the BPA measurements as a continuous variable. But when they considered tertiles they did find evidence of a positive association with prostate cancer risk.

The other two studies were case control studies, one in Hong Kong and one in Ohio. The Ohio study measured BPA in urine, and they found higher levels in cases compared to controls, but they did not report any measure of association or adjustment for confounders. So that study is not very informative.

However, the Hong Kong study is interesting, because this is the one I mentioned where they constructed their own exposure database and they paired the database with a questionnaire they designed asking specific questions about exposure to diet and drinking. For example, they asked when you drink hot water with -- you know, with a plastic cup, how often do you do that, et cetera.

So they use existing literature to kind of put together a database. And they have two independent readers put together this database assigning BPA levels to the different type of containers used and the different behaviors, and then they use that to derive a score.

So an advantage of this approach is that it captures longer time exposure because it's not relying of

that one measurement. So I thought that this approach that they used was interesting, and similar to approaches that we use for dietary components, for example, in the epidemiological literature. So this study did report a positive significant association with a significant trend, you know, but it was the only one that used that approach. So you cannot compare with others. So that was it for prostate.

There were two other cancers that had more than one paper, one was thyroid cancer. There was one cross-sectional study from Italy that reported a non-significant positive association, not a very informative study, very small, and they did not consider confounders. As in China, also a modest sample size, but they did find a positive association.

And then there were two studies done in lung cancer. One was in China. It was a fairly good sized study with proper adjustment of confounders and detection of BPA in more than 97 percent of their sample, and they did report a positive association of statistical significance.

Moreover, they also look at potential modification by a polymorphism in the estrogen-receptor gene and they found a significant interaction.

Another study was from Korea. And they used

metabolomics to compare cases and controls, and they found sort of doing an agnostic search of metabolites. And among those significantly associated between cases and controls, one of them was BPA. So they found significant differential levels between the two groups.

And finally, there were six more studies in six different cancers, three reported statistical significant associations, one in osteosarcoma. However, they did not adjust for confounders, one in meningiomas, which was reasonably sized with proper adjustment. However they did not adjust for creatinine in their samples, so maybe that association estimate is not accurate.

And lastly, there was one study done in biliary duct on gallbladder cancer in Europe, which had a reasonable sample size and took into consideration appropriate confounders, but given that it used a job exposure matrix, it only identified nine people out of the 114 cases, so very small sample size. However, despite that, they did identify a positive association.

And then there were three other studies that reported no associations or no significant associations and included a prospective study within the MEC on the MEC cohort on endometrial cancer, a study in Europe on lymphomas that also used a job exposure matrix, and a study in melanomas in Europe that also used a job exposure

matrix. And finally, there was one study that used NHANES data to investigate the role of BPA on all cancer mortality and all cause mortality. They reported no association with cancer mortality, but they did report a significant positive association with all cause mortality. The importance of this study is that it used a national representative data set and they did adjust for all potential confounders.

So in conclusion, the evidence for other cancers is also inconclusive, similar to breast. And I think the most remarkable findings are for the two studies in prostate cancer, the one study in lung cancer, and the study in gallbladder cancer, which this -- even though neither of these studies were perfect, at least they had both sample size and reasonable measurement levels. And so they seem informative and they report significant positive associations.

So my takeaway from reviewing this literature is that there seems to be some evidence that is very -- it's limited for prostate, lung, and gallbladder cancer, but clearly more studies are needed, given that, you know, we only have two studies for prostate, one for lung -- two for lung and one for gallbladder. So the role of BPA on these cancers, and particularly breast cancer, based on this existing literature with all the flaws that we have

is inconclusive.

So I want to turn it over to Dr. Crespi and Loomis, if you have something more to add.

COMMITTEE MEMBER LOOMIS: Yeah. Thank you. Thank you for that very informative presentation. Let's go on to Dr. Crespi. And before we do that, I just want to remind the Committee that we'll have time for clarifying questions at the end of the discussion period. So please hold your questions until we've gone through all the different evidence streams and then we'll open it up for discussion.

So Dr. Crespi, the floor is yours.

COMMITTEE MEMBER CRESPI: Thank you. Well, Dr. Stern gave a very thorough and excellent summary of the studies. And I think that, you know, there's no reason to repeat some of the information that she's already provided.

I agree exactly with her assessment of the studies. In general, most of them I would say were inconclusive or not informative as to -- as to the question. I -- so, yeah, I found that -- I guess a few things to highlight would be that in the breast cancer studies, which -- of which there were the most -- the studies that found positive associated -- associations were the ones where the samples were collected after

diagnosis. So I think in particular there -- one would be concerned about a reverse causation and suggest some kind of a physiological connection between the cancer diagnosis and the detection of the elevated levels.

I think that some of the studies are somewhat suggestive and suggest avenues for further exploration. For example, the prostate cancer study in men in Hong Kong, which used an assessment of exposure by ingestion through the questionnaire, I thought that was an interesting approach. It was one of the few studies that tried to actually assess chronic -- you know, did at least have a chance of assessing chronic exposure to BPA, whereas the other studies all used single samples, which is not an adequate way to assess long-term exposure. So I think that study is somewhat informative, but I still think that overall the studies don't show clear evidence and don't provide a basis for concluding that there is a causal connection.

COMMITTEE MEMBER LOOMIS: Thanks, Dr. Crespi.

Well, I'll give my assessment as well and I won't try to go through study by study as I think staff documented and Dr. Stern's summary have done a really good job of presenting the evidence.

What I do want to say is that I think this is certainly one of the most challenging exposure assessment

situations that I can imagine. First of all, we have a ubiquitous exposure, so it's very difficult to find people who are not exposed at all. And it's hard to know where to look even for a gradient of exposure.

The second challenge is that the chemical is not persistent. So a single measurement or even a couple of measurements in a longitudinal study are not likely to be informative. So the challenges are really significant and I don't think they've been addressed very well in this body of literature. As my colleagues mentioned, the one study of prostate cancer in Hong Kong that used a kind of combination of questionnaires and expert assessment is really interesting. That approach to exposure assessment was promising. I think it's a -- it's a good idea and the study did find indications of positive statistically significant association for prostate cancer. That said, it's only one study.

Looking at other cancer sites, I really thought the evidence was inadequate for quite a few cancer sites that only had one or two studies each. I note thyroid, bone, whole cancer, eye cancer, lung, lymphoma, gallbladder cancer, bile duct cancer. I think that was studied along with gallbladder. Again these studies had only one study each. These cancer sites had only one study each, even though some of them found positive

associations.

The literature on breast cancer is also quite challenging. A good number of studies using different designs, different biological matrices, but all of them face the same difficulty of trying to assess exposure based on essentially single measurements except for the one case control study that used a job exposure matrix. Again, an interesting idea, but very few women had occupational exposure, so that study isn't particularly helpful either.

So breast cancer studies found a variety of associations ranging from fairly strong positive ones to negative ones. But on the whole, I see that literature also as inadequate.

So taking everything together, what I would expect, given the challenges of exposure assessment, is that the exposure data would involve quite a lot of noise, random noise. In general, that kind of exposure measurement error is expected to produce bias toward the null, but I would say it's important to remember that bias is a tendency, and that doesn't mean that it will happen in every single study. So it is also possible for random exposure measurement error, which is what I would expect in this situation, to produce bias away from the null in a single study. There are also reasons to think that there

might be some spurious positive associations as my colleagues have explained.

So, you know, overall, I think the body of human cancer studies provide inadequate evidence or inconclusive evidence as my colleagues in this group have suggested.

So --

COMMITTEE MEMBER STERN: Dr. Loomis, if I may add something that I forgot to mention in my presentation. Is that okay to chime in now?

COMMITTEE MEMBER LOOMIS: Yeah. Yes, please.

COMMITTEE MEMBER STERN: So the other concern that I wanted to highlight, particularly for breast, because breast was -- as was discussed is the main target organ that we suspect that we might see an association because of the -- of the biological pathways.

So there were three prospective studies and two of them had problems. One used a job matrix, the other one in Europe used serum. So they had lower detection levels. So the third study, which was the multi-ethnic cohort, was the one that we were hoping would provide some clarity. And they found no association.

However, one important thing I forgot to mention about that study is that most of the women at the time of enrollment were probably close to 60 year old, so they developed cancer a few years after those measurements or

sometime after that, but kind of very close to diagnosis time.

So one concern with this study and one of the reason why they may not have found an association perhaps is that it has to do with the window of exposure, right, that they were measuring BPA level with all its imperfections at a time when maybe women were no longer exposed to high levels of BPA, because maybe the relevant time of exposure is at a younger time in a women's development. And no study actually has provided those estimates, right, of -- so there are some existing cohorts now out there that potentially in the future can provide us those data, but currently we don't have that. So that's another concern, the issue of latency that may be is the critical exposure of -- to BPA is when women are adolescents or young adults. And we don't have any information about that from any of those studies.

COMMITTEE MEMBER LOOMIS: Yeah. Thanks for that. I think another interesting question is that we don't have any occupational studies really of workers with exposure to BPA from manufacturing or other uses. That would be really helpful, even though occupational exposure isn't the main source of exposure for the population at large. You know, a study of a more highly exposed group with the potential to identify exposures and perhaps quantify

exposures through methods, other than biological sampling would be really helpful, but we don't have that.

So Dr. Mack, I see you have your hand up. We will have time for questions and answers at the end of the --

CHAIRPERSON MACK: I actually wanted to add a couple points.

COMMITTEE MEMBER LOOMIS: Sure.

CHAIRPERSON MACK: But the points that both you and Mariana just made, but one is the point you made about the absence of an occupational exposure from a plant where there would be continuous exposure of substantial amount. That would be something that should have extremely high priority.

And the second point is the one that Mariana just made and that is that the best study -- the best single breast cancer study was the multi-ethnic cohort study, which was beautifully done, but because of the lack of meaning of the single urinary exposure is not informative.

I guess the third point I think I would like to make is that usually when we have epidemiologic studies in large numbers that are negative, it is substantial evidence of no relationship between exposure and disease. But in this case, the exposure is so bad on every way it's being used, that there is simply no evidence whatsoever

against a positive association. So we have to be very careful how we interpret them.

That's all the points I was going to make.

COMMITTEE MEMBER LOOMIS: Yeah, thanks. Those are really helpful points. I appreciate that.

CHAIRPERSON MACK: Well, I guess to add one other point just of curiosity. The multi-ethnic cohort, first author is Dr. Anna Wu, which has two individually interesting characteristics. One, she's a previous member of the Committee, but more importantly, she's also a previous member of the OEHHA staff, which I think is a unique circumstance.

Okay. Thank you.

COMMITTEE MEMBER LOOMIS: Thanks, Dr. Mack.

I'll just add a couple of other things, since you've opened up these issues. I would agree that the multi-ethnic cohort is probably the most informative study on breast cancer despite the methodologic limitations that we've heard about.

The other study that I was impressed with is the EPIC study in Spain. That one, as mentioned, used serum as the biological matrix. And even though detection is lower reportedly in serum compared to urine, I don't think I'm particularly concerned about that, as long as there's internal consistency. So that study did find a positive

exposure response relationship for prostate cancer. So I think that study is still reasonably informative, despite the limitations that have already been mentioned.

So Dr. La Merrill has a hand up. And if it's another comment like this, we can take it. If not, if it's just a question, maybe we'll hold until after the Committee presentation.

COMMITTEE MEMBER LA MERRILL: I just wanted -- was wondering if someone could -- maybe you, Dr. Loomis, since you mentioned it, the lymphoma study. I realize there was only one, but there is some evidence for it in the animal literature, and also I think perhaps some mechanism, so I would just like to be able to hear the future conversations in the context of knowing what that singular study -- like what you all think were the pros and cons what was the outcome of that study. Is that okay to ask right now?

COMMITTEE MEMBER LOOMIS: Yeah, I think we can take that now.

COMMITTEE MEMBER LA MERRILL: Okay. Thanks.

COMMITTEE MEMBER STERN: Yeah, I can provide my views on that study, if that's helpful.

COMMITTEE MEMBER LOOMIS: Please do.

COMMITTEE MEMBER STERN: So this was a study -- was a multi-center study done in Europe as part of the

Epilymph consortia. And so they've had a pretty good sample size, over 2,000 cases and over 2,000 controls, so that's very good. They did consider confounders. It was a multi-center study, so it was representative of the population.

Now, the concern with the study is that they use a job exposure matrix to estimate exposure. And as we discussed before, for BPA, that doesn't seem to be very applicable, because this is at the general population, not among workers of specific factories, right? So we're trying to see whether people in population happen to have a job that happened to have a bit of exposure to BPA, and that proportion is low.

And we know from other studies that majority of exposure in the human population is coming from beverages and from diet. So they have very few people that actually had exposure. So to give you a sense, out of the 2000 and a -- they had 2,178 cases. Out of those, only 19 cases had a positive exposure to BPA through occupation, and only 17 controls out of the 2000 controls.

So they -- their estimate of association was 1.55. So it was a positive association, but it wasn't significant. The confidence interval included the value of one. So we consider these a null study. So that's what I can share. So it's very underpowered to detect

something because of the amount of people that are exposed. So unfortunately, the study is not very informative in that regard. It was a well-conducted study. There are no other significant flaws in how they handled the analysis. I just think it was underpowered.

COMMITTEE MEMBER LOOMIS: Yeah, that's helpful. So this is a -- it is quite a large study. It's well done, looking at a lot of different exposures in relation to lymphomas, but not particularly informative by itself in this particular situation, in my opinion.

Okay. At this point, let's -- well, it's getting close to lunch time, so let's see what the Committee's preference is. We could go through the discussion of animal cancer studies and then break for lunch, or we could take a break now. What's -- what would your preference be?

Let's just say continue through the animal cancer studies, who would like to do that?

Let's see I only see one hand up, which might mean --

COMMITTEE MEMBER STERN: I think the animal studies are going to take a little bit of time, right? So maybe better to break before --

COMMITTEE MEMBER LOOMIS: Well, there's a lot of evidence.

COMMITTEE MEMBER STERN: -- so that we can -- yeah, not, have to hurry.

COMMITTEE MEMBER LOOMIS: So it seems to me the consensus of the Committee is to break now. Let me check with the staff and make sure that that's okay. Whenever we break, it will be for 45 minutes.

DIRECTOR ZEISE: Yeah, I think that is fine. And I think in breaking, Carolyn Rowan will give a Bagley-Keene reminder, so it's fine if you want to break.

CHIEF COUNSEL NELSON ROWAN: Okay. If that's the consensus. Before we break, I'd just like to remind the members that during breaks, you aren't allowed to talk amongst yourselves about the subject matter of the meeting. That includes phone calls, texts. In fact, my recommendation would be that you also not talk to third parties regarding the same information. If you do, you should disclose the fact that you had a discussion with someone and give the content of that discussion, so that it's part of the public record. It's just best to chat about something else over the lunch break.

And that's all I have.

COMMITTEE MEMBER LOOMIS: Okay. Thanks. So our break is for 45 minutes. That means we come back at 12:40. So we'll see you all back here at 12:40 for discussion of cancer studies in animals.

Thanks.

(Off record: 11:55 a.m.)

(Thereupon a lunch break was taken.)

AFTERNOON SESSION

(On record: 12:40 p.m.)

COMMITTEE MEMBER LOOMIS: Okay. I hope everybody had a good lunch. Let's resume, if the next discussants are here.

Dr. Landolph, are you ready to go?

COMMITTEE MEMBER LANDOLPH: Yes, sir, I am, Dr. Loomis.

COMMITTEE MEMBER LOOMIS: Okay. Let's then proceed with discussion of cancer studies in animals. It's a -- it's your microphone.

COMMITTEE MEMBER LANDOLPH: Okay. You want my picture too?

COMMITTEE MEMBER LOOMIS: Yes, please.

COMMITTEE MEMBER LANDOLPH: It says you cannot stop your video, because the host has stopped it.

Nope, still the same.

COMMITTEE MEMBER LOOMIS: Okay. Well, why don't you just go ahead and speak and someone will probably get your camera turned on in a moment.

COMMITTEE MEMBER LANDOLPH: Okay. Thank you. So first I'd like to thank the staff, as many people have done before for the enormous amount of work that went into compiling this 500, 600 page document. And I think they did a pretty good job on the animal carcinogenicity

studies too.

So I read over them. I want to go through them, and just tell the court reporter I'll be on page 27 in Roman numerals, and so you can probably just copy a lot of this down from the document itself.

So they said, the staff did carcinogenicity studies of BPA have been conducted in male and female Fischer 344 rats, female Sprague-Dawley rats, male and female Sprague-Dawley (NCTR) rats, female Wistar-Furst rats -- Furth rats, male and female B6C3F1 mice, male and female Agouti C57black/6J:C3H/HeJ mice, female CD-1 mice, and male gerbils.

Statistically significant tumor findings are the following.

I first adopted the hypothesis that this was not a carcinogen. And let's see if that's true or not. So the staff found that from the literature, which they did a very extensive literature search. In the alimentary system, there were hepatocellular tumors in male Sprague-Dawley (NCTR) rats, and female Agouti C57Black et cetera mice. So that's positive.

In the endocrine system, they found pituitary tumors in female Fischer 344 rats and male B6C3F1 mice, thyroid C-cell tumors in male Sprague-Dawley (NCTR) rats.

Then in the mammary gland, they found in the

literature fibroadenomas in male Fischer 344 rats, adenocarcinoma and adenocarcinoma and adenoma combined in female Sprague-Dawley (NCTR) rats. And these they say were all statistically significant tumor findings.

Then in the reproductive systems of the females they found clitoral gland tumors and uterine stromal polyps. Those stromal polyps are not malignant. And they found reproductive systems of males, testicular interstitial, (Leydig), L-e-d -- y-d-i-g cell tumors in male Fischer 344 rats.

They also found lymphohematopoietic system in that system, leukemia in male Fischer 344 rats, lymphoma in male Sprague-Dawley NCTR rats and male B6C3F1 mice.

In addition, the staff noted that multiple types of rare tumors were observed in several studies in male and female Sprague-Dawley NCTR rats. I looked through that data. Most of them were ones, here and there, scattered throughout. And then they said there's more data on the animal tumor findings, which they listed below. In the female and the male Fischer 344 rats, which was 103-week feeding study in BPA treated male Fischer 344 rats, the incidence of mammary gland fibroadenoma was significantly increased in the high-dose, (2,000 parts per meter -- parts per million) grouped by pairwise comparison with control, with a significant dose-related trend.

Great.

They did 103-week feeding study in BPA-treated male Fischer 344 rats. The incidence of testicular interstitial, (Leydig), L-e-y-d-i-g, cell tumors was significantly increased in both dosing groups (1000, 2000 ppm), by pairwise comparison with controls, with a significant dose-related trend.

And in the 103-week feeding studies in BPA-treated male Fischer 344 rats, the incidences of leukemia was significantly increased in the high-dose, (2000 ppm), group by pairwise comparison with controls, with a significant dose-related trend, NTP 1982.

Then they discussed the tumors in the female rats. And they noted that in a 12-week oral study in BPA-treated female Fischer 344 rats, the incidence of pituitary tumors, likely adenomas of the adenohypophysis, was significantly increased in the low-dose group at 50 milligrams per kilogram per day.

Tumors in the male Sprague-Dawley (NCTR) rats. In the two-year continuous-dose study in male Sprague-Dawley NCTR rats exposed to BPA in vitro and from PND1 until study termination - this is the CLARITY-BPA core study number 8 - the incidence of rare hepatocellular carcinomas was increased with a significant dose-response trend. My star there for emphasis.

In the two-year stop-dose study in male Sprague-Dawley NCTR rats exposed to BPA in utero and in gavage from postnatal day one to postnatal day two - the CLARITY-BPA core study number 4 - the incidence of thyroid C-cell adenomas was increased with a significant dose-related trend. I note that that's not a malignant tumor but it's increased with a dose-related trend.

In a two-year stop-dose study in the males Sprague-Dawley NCTR rats exposed to BPA in utero and via gavage from postnatal day one to postnatal day 2, CLARITY-BPA study number 4, the incidence of malignant lymphoma of the prostate, dorsal/lateral lobes, was significantly increased in the high-dose group, 25,000 micrograms per kilogram per day, by pairwise comparison with controls, with a significant dose-related trend. The incidence of malignant lymphoma from all sites was increased with a significant dose-related trend, NTP 2018.

In the one- and two-year studies in male Sprague-Dawley NCTR rats exposed to BPA in utero and after birth for different lengths of time (Arms 2, 4, 6, and 8 in CLARITY-BPA core study) multiple types of rare tumors were observed in multiple organs in treated groups of each of the study Arms, except for Arm 6 where only one rare type tumor was observed with none in concurrent controls.

Then they discussed the tumors in the

Sprague-Dawley NCTR rats on page XXIX. And they said in a two-year stop-dose study in female Sprague-Dawley NCTR rats exposed to BPA in utero and via gavage from postnatal day one to postnatal day two, which is CLARITY-BPA core study 3, the incidence of adenocarcinoma of the mammary gland, and the incidence of adenomacarcinoma and adenoma combined was each significantly increased in the 2.5 microgram per kilogram per study group, and they referenced NTP 2018.

Next, they said in the one-year continuous-dose study in female Sprague-Dawley NCTR rats exposed to BPA in utero and from postnatal day one until study termination, which was (CLARITY-BPA core study number 5), the incidence of uterine stromal polyps was increased with a significant dose-related trend NTP 2018.

Then they said in the two-year continuous-dose study in female Sprague-Dawley NCTR rats exposed to BPA in vitro -- in utero and from postnatal day one until study termination (CLARITY-BPA core study number 7) the incidence of clitoral gland adenoma, and adenoma and carcinoma combined was each increased with a significant dose-related trend. That's important.

Next, they said in the one- and two-year studies in male Sprague-Dawley NCTR rats exposed to BPA in utero and after birth for different lengths of times (Arms 1, 3,

5, and 7 in CLARITY-BPA core study) multiple types of rare tumors were observed in multiple organs in treated groups in each of the study arms, NTP 2018.

The tumors in the B6C3F1 mice they said in -- regarding these, in a 103-week feeding studies in BPA-treated male B6C3F1 mice, the incidence of chromophobe carcinoma of the pituitary gland was increased in the high-dose group, 5000 ppm, with a significant dose-related trend, NTP 1982.

Then they said, in the 103-week feeding study in BPA-treated male B6C3F1 mice, the incidence of malignant lymphoma, and malignant lymphoma and malig -- and lymphocytic leukemia combined was significantly increased in the low-dose (1,000 parts per meter -- per million) by pair comparison with controls, NTP 1982.

Then they talked about tumors in the female Agouti mice. In the 10-month studies in these mice exposed to BPA in utero and via lactation, then in feed from post-weaning until study termination, the incidence of hepatocellular adenoma and carcinoma combined was significantly increased in the high-dose group (50 parts per million), with a significant dose-related trend, (Weinhouse et al. 2014).

And I'm going to skip the rest of that, because it's important, but it's not as important as those primary

studies. So I was going to say for me personally, as one of the members of the Committee, I took that to indicate that there is a significant amount of animal tumor data that is positive and where the trend is dose dependent, and it's in males and females, and it's in rats and mice of different species.

So therefore, for me, unless I hear something different, that convinced me that the animal studies are positive in rats and mice of different species. So although no study is perfect, nevertheless, the weight of those positive studies convinced me that BPA is indeed an animal carcinogen, in particular rodent carcinogen.

And I can stop there.

COMMITTEE MEMBER LOOMIS: Okay. Thank you, Dr. Landolph. Let's go on with the discussion and turn to Dr. Bush.

COMMITTEE MEMBER BUSH: Yeah, thank you, Dr. Loomis and thank you Dr. Landolph for prepping the discussion here. I want to thank the OEHHA staff for their Herculean effort, for delving into all of this data and creating this HID. So hands off to the teamwork there. And I have read the public comments from all four submissions. And I must say that some do raise compelling questions and statements.

And so I'm going to start with Table 7. Dr.

Landolph did a good -- great job setting the stage here. My take on this is a little bit more pessimistic, I suppose. And let me explain why. So Table 7, which is page 54, eight studies. And really the only studies of value that I see there are from the 1982 NTP results with rats and mice. The other four studies that were there had too few animals and I question whether there's sufficient statistical power there.

So delving into those, you know, four reliable studies on Table 7 really we're seeing a marginal increase in leukemias in males, p-value of 0.02, 26 percent of the controls actually have this as well, and we only see this trend in the high dose. Fibroadenomas were probably a little more convincing, but there's only four of 34 animals found with this kind of tumor. And the Leydig tumors, you know, are common to the F344 strain, and so almost 75 percent of the controls got these tumors as well. So there's some data there, but I think it's marginal. And then when it comes to the rare pituitary carcinoma in the B6 mice, again there was marginal increase when I'm looking at those trends.

So we've got this data set. And then along comes the CLARITY Study, okay? When I first got wind of this, a number of years ago, you know, I was excited. This was going to be a well-designed long-term cancer study. We

were going to learn lots of cool stuff, and finally, you know, be definitive on BPA. We're going to show that it's the smoking gun once and for all. And then, you know, what happened?

If we look at these different Arms, you know, looking at Arms 1 through 6, many different endpoints, but from a macro view looks like mixed results to me. There's some suggestive data, but I don't see it as being clear. There's some common themes like hyperplasia. Presumably that's some atypical hyperplasia, but nothing is a clear dose response in my mind.

And, you know, it's okay to say, well, that's Arms 1 to 6. You know, but Arms 7 and 8, here we have the penultimate two-year chronic rodent cancer bioassay. This now is going to be definitive. And what happened? I mean, there are some common biological phenomena, but again it's not clear.

I'd also mentioned that some of the public comments indicate that, you know, the statistical approach used in some of the analysis, it raised questions for me as well. So I do appreciate the description at the beginning by OEHHA staff and the biostatistician discussing the methodologies there.

So we have to balance this with the conclusions of the NTP itself, so the Camacho 2019 paper, where they

determine that there's a possible relationship between the increased incidences of lesions in the female reproductive tract and male pituitary and exposure to the 25,000, the highest dose level. That's not very convincing of their own study, okay, alluding back to some of the comments that Dr. Eastmond mentioned previously.

You know, so is there a problem with this study? I do thank OEHHA for identifying the shortcomings of the CLARITY Study as others have described in the literature. There certainly are some limitations that were brought up in the initial presentation. I do share some of those concerns, but, you know, this still represents our best most robust study and I still believe that the results are mixed, and still leaves some outstanding questions. So then what else do we have left in the animal studies?

Well, we've got these -- there are the other rat studies from Table 26. These are, I think for the most part, are of little value due to the small numbers, the short exposure times, and the lack of lifetime study duration. Now, that's not to say that there isn't something here, particularly when we consider the -- that common theme of hyperplasia. So maybe there's something there.

I'll -- a few more notes here. Moving into the mice studies, similar problems. Low numbers in -- with

five studies of any utility and none of them went beyond one year. Again, hyperplasia is coming up, particularly in the endometrium and some possible hepatic effects, but the numbers are too small and we're only seeing this in the high-dosed animals.

The transgenic studies, various endpoints there. Suggestive at best and sporadic with no clear dose-response relationship that I can see. That common theme again emerging of hyperplasia. I didn't give really any weight to the xenograft studies. You know, because of the established cancer cell lines, which I always feel have limited value. And then the final group of studies, looking at BPA before or after carcinogen treatment, there are various endpoints that, you know, one can pick, but nothing common. And so I see those results as mixed as well.

And on page 101, OEHHA states again the limitations. They're small numbers, short BPA exposure, and only one organ tissue in many of these studies. So, you know, where's the utility there. There isn't a lot. So, you know, cherry picking the data a little bit I think can be problematic from a false positive perspective.

So that would be my summary of the animal studies and I will yield my time to the other Committee members.

COMMITTEE MEMBER LOOMIS: Okay. Thank you, Dr.

Bush.

So third discussant, Dr. La Merrill, what would you like to add to what we've already heard?

COMMITTEE MEMBER LA MERRILL: Sure. So thank you all for your great summary over at OEHHA. And my prior -- the colleagues here prior summaries have been very helpful. And I'll try not to be redundant in my comments.

I've kind of organized my thoughts more around the outcome rather than the individual study. So with respect to the individual outcomes, I think I just want to point out a part of the trends in cancer biology that are I think quite important. And that is, you know, many decades ago President Nixon declared a war on cancer. And in response, NCI put a lot of effort into trying to, you know, better understand and treat cancers. And after quite a bit of time, they found that their methods weren't really quite working, and so they came up with the Mouse Models of Human Cancer Consortium in the late nineties to address the fact that, you know, rodent tumors are not the -- that are spontaneous are not really the same as human tumors, and that if we want to do with malignancies of humans, we need to have better models.

And so I think, you know, that field has really moved forward in thinking about having rodent tumors better recapitulate the pathologies that you see in

humans. And there's certainly been a lot more success in that effort, as opposed to, for example, the NTP studies, where we're still looking for spontaneous tumors. And I think that across the board what I will say is I did not perceive, apart from the presentation of some rare pathologies which I'll get to, that BPA modified the presentation of the type of pathology, and that each model, whether or not it's a spontaneous rat or mouse, or a transgenic, or the use of a carcinogen, or the use of a xenograft basically produces the pathology of a tumor at that site that you would expect based on that model. And I don't see evidence of bisphenol A modifying it so much.

The evidence that I think presented, in general, apart from some rare things, was really changes in incidence, changes in latency, changes in growth, and changes in metastasis. So that's a kind of general impression I wanted to share with you all and kind of put it into context of how I think about modeling cancer.

So there was several studies that reported lymphomas. We have the NTP 1982 study, where we saw the male B6C3F1 mice had an increased in malignant lymphoma among the lower dose they tested. So they had 1,000 ppm of BPA in that study and saw 8 of 47 of those male mice with this malignant lymphoma. Only 2 of 47 had it in the controls and that was at 3 of 45 in the highest dose group

at 5,000 parts per million.

The next and only other study in whole rodents that looked at -- that observed lymphomas was the CLARITY Study that we heard about. And let's see here, we have the stop-dose two-year study - so just looking at the early window of susceptibility - saw an increase among 25 mg per kg per day group, which was the highest dose group. And they didn't see them anywhere else, but there were four in that high dose group. And so that individual group was significant statistically and also contributed to an increased -- a significant trend of this malignant lymphoma with a p-value of less than 0.01. And this is notably an uncommon neoplasm in Sprague-Dawley rats. And the controls were within historical ranges is how they defined less than one percent the historical range was part of the definition that OEHHA provided to us.

And then in addition to that in the CLARITY, there was the observation of a different kind of rare tumor, which is called a histiocytic sarcoma, and these are often considered to be related to lymphomas. So I wanted to point that out. And that was also in the same dose group.

With respect to leukemia, another hematopoietic cancer type, we saw in the 1982 NTP study, the males had increased leukemia in the high-dose group. There were 23

out of 50 of the male F344 rats that had 2,000 parts per million of BPA in their food had leukemia, whereas only 13 of 50 of the controls had it. So it practically doubled, and that was also a significant trend with a p-value of 0.02. Again, the controls were in the historical range. This wasn't observed in the females. Although, you could say that there was a trend, where each group had 50 females and the controls had 7 leukemia -- 7 female rats with leukemia. The middle group, it went up to 13, and then the high-dose group it went up to 12. So in the presence of BPA in females, it kind of doubled, but it was not significant.

Then further evidence for leukemia also came -- sorry, I'm just skimming here. I just want to point out in the NTP 1982 study of mice, there was no evidence of the leukemias being significant, but there was a bit of a trend in terms of there was none in the control group and there was one in the middle-dose group and two in the higher-dose group. So, you know, rare events are hard to statistically capture, so it's a bit underpowered perhaps.

And then in the CLARITY Study, you know, it's done many years later in 2018, so you're getting a little more fine understanding of diagnosing or calling IT leukemia, so they called you granulocytic leukemia rather than non-otherwise specific, which is what we found in

1982 NTP. The male Sprague-Dawleys, or the NCTRs, of that CLARITY, we saw each dose group have one of these granulocytic leukemias, but not in the controls. And again, that's a rare tumor in those as well.

So we're seeing that across two species, two studies and they're getting increased leukemia. There's a lot of studies related to mammary gland pathology and trends in terms of onset and growth and metastasis. And I think it really -- as I, you know, was talking a bit, beginning as a -- as a great example of this kind of you get what you would expect with the model. So when you have a spontaneous rat mammary tumor, you don't tend to get much more beyond a hyperplasia. It's not -- they don't tend to make malignancies and they don't mimic the pathology really of human breast cancers all that well.

But we do see hyperplasia. And let's see here, the CLARITY Study in the female two-year that I think was already brought up. It was also a similar thing that came up when someone used a pump to deliver bisphenol A osmotically. They also later saw adenocarcinomas in that pump model. They changed the dosing around a little bit with the pump model, expanded the window from in utero to lactation, and again basically saw hyperplasias and adenocarcinomas at a later time point, which was only postnatal day 140, so six months. You know, the average

length of their life is several years.

So, you know, the scope in terms of I know it was brought up about the sample sizes. I mean, I think low sample sizes are really going to bias your results towards the null, right, because you have less power to detect effects. So similarly, if you're not looking for as long you have -- less opportunity to observe an overmalignancy.

We also had the Wistar-Furth rat model, so a different strain or substrain of the rats. And they too had hyperplasias and also described some DCIS. And those female rats -- sorry, ductal carcinoma in situ, so basically, it looks like a cancer, but hasn't done the invasion part, so it's a pre-neoplasm you could say.

Then in mice, there's a couple studies. You know, obviously, there's a limitation with the relevance of an osmotic pump as a route of exposure, but these folks used gavage and a gestation period that was kind of similar to the rat study. They observed lipoma in the mammary gland. And, you know, through three and eight months of age weren't observing any mammary gland tumors. But by 14 months, there was some of this hyperplasia that I brought up before.

And then when you move into a transgenic model, that mimics the HER2-positive human breast cancer, and that one is called MMTV-Erbb2 for short. It has a much

longer name. They use drinking water BPA delivery. And this model is kind of the gold standard and research on HER2-positive human breast cancer it gets mammary adenocarcinomas. And they're capable of metastasis. And then -- in that study, they were able to observe increased tumor multiplicity and tumor volume, which is kind of a surrogate for growth, in addition to significantly increased lung metastasis. And that was at both doses that were used in that study by Jenkins 2011.

And then there was another study that used the same mouse model, but instead used subcutaneous dose. So not as gold standard in terms of mimicking like human condition, but they, too, saw a reduced latency. And it went from 37 and a half weeks or so in the control group to 35 weeks in the 50 nanogram per kilogram group and down further to 32 weeks in the 500 nanogram per kilogram group.

And those were significant and then they saw increases in some non-lesion items, but that are consistent with kind of more mechanistic understanding, so things like -- but I'll just mention them here, since we're talking about that study, and that was increase in terminal end buds, which are full of pluripotent rapidly providing -- proliferating cells during proliferate -- excuse me, during puberty and they also measured increased

proliferation of the epithelium from those mice exposed to BPA.

There was another study in mice that looked at hyperplasia or saw increased hyperplasia in DCIS with bisphenol A. Then in CLARITY, we heard about that already, but basically there was one fibroadenoma and there wasn't really much in the way of neoplastic lesions, so -- in that spontaneous rat model on -- not really anything going on at all.

There was a couple different studies, maybe five or six that used a carcinogen either DMBA or MMU as a Co-exposure with bisphenol A. Excuse me. And most of those studies they saw an increase in the mammary tumor incidence. A of handful them saw an increase in tumor multiplicity. I don't think tumor multiplicity is as relevant to the human condition, because women don't usually present with multiple independent tumors when they get diagnosed. And this was -- excuse me here -- both in female rats and in mice using these co-exposures. It was reported that there was decrease in mammary tumor latency. And a couple of the studies indicated that there was higher proliferation in the lesions.

Several of the studies did not report the pathology. I thought the pathologies were typical of what you see using DMBA and MMU. So, for example, DMBA usually

produces squamous cell carcinomas that are not really considered very similar to human. So these studies are, you know, supportive secondary evidence, but I wouldn't hang my hat on them if it was the only information we had.

And then there's a couple xenografts with BPA exposure before or afterwards. And I do see increased growth of these xenografts, which are human breast cancer cells implanted on mice, suggesting, you know, BPA can be a promoter. And then -- yeah, I think I'll just leave that as the end of the mammary.

There's a couple of studies that addressed hepatocellular carcinomas. So in the CLARITY Study, there was an increase incidence of that in the dose groups, but -- that were higher. So this is a rare carcinoma to find in rats. They saw 2 of 24 in the 250 microgram group, 1 of 24 in the 2,500 microgram group, and then in the 25,000 microgram group, there was 3 of 19 male NCTR rat that had this rare hepatocellular carcinoma. But none of these lesions were observed in the lower doses of that CLARITY or the control, so that was a significant trend at 0.01.

And then in the Agouti C57 Black 6 spread to the C3H/HeJ dietary BPA was used in the Weinhouse Study that our first speaker talked about, where we saw hepatocellular carcinomas in all the BPA treated groups

and none in the controls. And again, that was a significantly increasing trend, so we have two species where we have a significant trend of a rare tumor and none in the control. So I think that was noteworthy.

There's a fair bit of prostate tumor research that's gone on in a number of studies through the years. Most of this comes out of Gail Prins' lab. I don't want to get into the details of every single one, but I will I say that -- let's see here if I can -- sorry, just lots of notes here.

There was one study that didn't come out of her lab in 2003, the Ichihara study, the F344 males had been evaluated up to 65 weeks old. They had no prostate tumors or preneoplastic lesions in dose groups ranging from 50 to 120,000 micrograms per kilogram per day.

The Prins' lab tends to use this Sprague-Dawley model instead. So they did not report any BPA-related neoplastic or preneoplastic effects in any region of the prostate as part of CLARITY, but OEHHA reported that when they looked at the supplemental data in a table of that peer-reviewed publication, and this is in Table 23 of our workbook. There is a statistically significant increase in preneoplastic, high-grade, prostatic intraepithelial neoplasms which are referred to as PINs. And this was evidenced by a significant trend, but it was

prostate-region specific.

And then Prins like to use this -- a pump system, where they provided testosterone and estrogen to more mimic the human condition of an aging human man. And in those cases, they observed that BPA increase microinvasive carcinomas and PIN. So there were several studies that of -- among their group that was found that using this hormone supplemented situation.

Okay. Sorry. I'm just going down here.

There was also a xenograft of a human prostate cancer cell line that's commonly used called LNCaP, and they had increased growth when exposed to BPA. And then if BPA was -- excuse me. If the rats were exposed to BPA during or after a human prostate xenograft that also increased the grade of PIN and -- in that testosterone, estrogen model that Prins uses. I believe I might have said that was a pump and actually it's more correct to call it a pellet, so excuse me.

NTP in 1982 observed the increase Leydig cell tumors that we heard about before, so I won't touch on that. There was a couple of reports of pituitary tumors across female rats and male mice, so the female F344s had increased incidence of pituitary adenomas in the low dose group at 50 mg per kg in the NTP 1982 study. So that was at a p-value of 0.05.

They saw none -- none of these pituitary adenomas in the control group. In the 50 mgs group, they saw four out of 10 of these rats had a pituitary tumors. Only 1 of 10 of the rats at the 200 mg dose group got them and then 3 out 10 got them in the 400 group. So not a linear dose response, but an absence in the controls, but not the treated.

And then with the male B6C3F1 mice that the NTP 1982 study used, they also saw an increase incidence in pituitary tumors, however they were a different subtype called chromophobe carcinomas. These appeared in the high dose group, none in the controls, and kind of an intermediate amount in the middle dose group. So just barely reaching an increased trend significantly with a p-value of 0.046. So a little bit of evidence of pituitary tumors increased in two species.

Then there's a handful of uterine, reproductive, and gonadal type female lesions. I think most of these are not really -- well, some of them are not neoplasms or pre -- necessarily preneoplastic. But I'll just point out that in the -- in the CLARITY Study, there were two observed fibrosarcomas of the clitoral gland. And in the BPA, two and a half and 250 mg per kilogram dose groups among animals that didn't have those clitoral lesions that were described earlier. So there were -- there seemed to

be -- you know, that's a rare one.

Then there was other study that looked at subcutaneous BPA being provided to CD-1 mice. And there wasn't really any significant changes. So overall, I think that category of the -- you know, the gonadal region we'll call it, I thought that, in general, it was fairly unremarkable, but I did want to point out the fibrosarcomas.

I last want to just highlight a few things about miscell -- what I call miscellaneous rare tumors. I went through -- you can find a summary of those on Table 25, but I would like to point out that it's missing osteosarcoma and histiosarcoma. So I went through each of the individual tables of CLARITY that were provided related to rare tumors in particular, where I wanted to see if there were any that appeared in both sexes in order to make me feel more confident that they might not just be simply spurious results.

And what I found was that we had, as noted in Table 25, the males from the one-year perinatal chronic or, you know, where they start in the perinatal period and proceed through the rest of the study. They had small intestine carcinoma observed. And the females from the two-year chronic continuous dose study that started in the perinatal period, they also had small intestine

adenocarcinoma observed. And then when looking at just the female and males from the two-year chronic study, they had the -- they had the common histiocytic sarcoma, which can arise de novo, but is actually also known to arise from B-cell lymphoma. So again tying back to the evidence that there might be something going on with rodent lymphoma risk related to BPA exposure and then the two-year stop dose in males had osteosarcoma as did the female two-year continuous dose study.

So I thought that it was interesting that we had a couple of the rare tumors appear more than once across both sexes of the rats. And I think I will stop there. So thank you for listening to my overview.

COMMITTEE MEMBER LOOMIS: Okay. Thanks, Dr. La Merrill.

Let's see whether any of the other assigned discussants have anything to add that we haven't heard already.

Okay. It seems there's nothing else, so we'll move on to the assigned discussion of the 10 key characteristics of carcinogens. And we'll take these mostly in order, but Dr. McDonald has number 1 and number 5. So while you have the microphone, Dr. McDonald, if it's not too confusing, I'll just ask you to do both of those and then we'll go back to the established order.

COMMITTEE MEMBER McDONALD: Sure, that would be fine.

I also want to acknowledge the work done by OEHHA to synthesize the data on bisphenol A. Once again, you've managed a herculean lift. The amount of studies and information on this chemical is daunting, and so thank you for pulling this all together. I also want to thank the public comments of U.S. FDA, ACC, NRDC, and PIA.

The case of bisphenol A is a difficult one. The epidemiology data are troublesome, because of exposure assignment. The animal cancer data are suggestive, but the largest pivotal study, CLARITY 70 -- 7 and 8, where you have life-long exposure and you really should see effects, instead the effects are unremarkable.

Yet, we have a rather large mountain of mechanistic data that shows bisphenol A causes a wide range of effects, including DNA damage, oxidative stress, altered hormone states, changes in cell function, immortalization, proliferation.

So these mechanistic traits or key characteristics of a carcinogen are going to be discussed in the next 10 sections. And the first one is whether bisphenol A is electrophilic or can be metabolically activated. So a key characteristic is electrophilicity, that is whether the molecule itself or more likely or more

often the metabolite of the chemical is reactive or electron seeking, that is whether the chemical or its metabolite bind to electron rich cellular macromolecules like, DNA, RNA, lipids, proteins forming addition products, which we usually refer to as adducts. Binding to DNA is good evidence of electrophilic activity.

So bisphenol A can be metabolized by the cytochrome P450 enzymes and peroxidases, which Dr. Ricker very nicely walked us through this morning. These pathways are quantitatively minor, less than 10 percent, but they still probably carry all of the concern. These pathways form a variety of electrophilic compounds. The most notable is the bisphenol A-3,4-quinone, often referred to as BPAQ. There's a semi-quinone intermediate, an arene epoxide intermediate, an isopropene phenol radical, and then there's another electrophilic compound that then dimerizes to bisphenol A. And with all this redox cycling and quinone formation, you get a lot of reactive oxygen species formed as well.

The DNA adduct studies have mostly focused on the quinone adducts, the primary ones are with guanine and adenine. So bisphenol A-3,4-quinone, or BPAQ, has formed DNA adducts that have been identified as 3-hydroxy-bisphenol A-N7-guanine and 3-hydroxy-bisphenol A-N7 adenine. So the DNA adducts have been measured

following treatment with BPA in various systems including -- including human in vitro, animal in vivo, and in vitro, and, of course, in cell-free systems.

Importantly, DNA adducts have been measured in human cells in vitro at low concentrations. For example, De Flora et al. in 2011 measured DNA adducts in both normal and prostatic tumor cells, with fairly low concentrations of 200 nanomolar and also down to 1 nanomolar when treating long-term. There's an increase that it was not quite significant, but close.

There are also studies that have measured DNA adducts of bisphenol A following oral and intraperitoneal dosing of rats and mice. Unfortunately, these studies used very high doses, 200 mg per kg, and there are no other lower dose studies that were summarized.

These studies found DNA adducts in the liver of rats, and both DNA adducts in the liver and mammary gland of mice of CD-1 mice. Interesting, the same adducts were found in liver and mammary gland epithelial cells. So DNA adducts are not a required step for carcinogenesis, but they certainly demonstrate that these metabolites are electrophilic and capable of DNA damage.

N7-guanine adducts in particular are very good biomarkers of internal exposure of activated carcinogens. There are some researchers though that have questioned the

biological significance since they do not persist and they form readily and not likely to be mutagenic. But usually when you have these adducts, they're accompanied by many others that are potentially mutagenic, as well as we have a lot of reactive oxygen species being generated along the way.

So with respect to oxidized DNA, there's a significant evidence that bisphenol A causes oxidative DNA changes, which are believed to be due to the reactive oxygen formation, reactive oxygen species. So I'll discuss DNA oxidized bases in the next section in oxidative stress, which will now be very soon. But the reactive oxygen species and the DNA oxidation probably underlie a lot of the DNA strand breaks and other genotoxicity that you'll hear from the next discussant.

Let me make one more point on this topic is that bisphenol A, because it forms quinones, it loves to bind to cysteine residues on proteins. In a recent study for example Hu, H-u, et al. in 2022 examined protein adducts in the liver of treatment of rats with single high dose or repeated lower dose. And modified proteins included superoxide dismutase, catalase, glutathione transferase. And these, of course, are important because these are the key antioxidant protective enzymes that protect against the oxidative damage.

So just in sum, bisphenol A is an electrophilic chemical with the potential to cause DNA and protein adducts, as well as reactive oxygen species. So that's that section.

Okay. So shall I move on to oxidative stress then, Dr. Loomis?

COMMITTEE MEMBER LOOMIS: Yeah, go ahead.

COMMITTEE MEMBER McDONALD: All right. So oxidative stress key characteristic of carcinogen number 5. Another key characteristic of carcinogens is oxidative stress. And that, as you all know, is really the imbalance between reactive oxygen species, or ROS, or reactive nitrogen species relative to antioxidant properties. So these reactive species may add to carcinogenicity through DNA alterations, changes in cell type or control, but it really is the cell's ability to maintain the balance between oxidation and reduction that's important for cell development, growth, and survival.

We, of course, during normal metabolism, generate reactive oxygen species and we have many antioxidant molecules, enzymes, efficient and regulated pathways to scavage these species and prevent toxicity. So really it's when you get the host behaviors or chemical exposures that tip that balance that leads to toxicity.

So reactive oxygen species can be formed during the metabolism of bisphenol A, probably through the redox cycling of these quinones and semi-quinone metabolites. They also could be formed through other oxidation reactions. So in the bisphenol A studies of oxidative stress, there are a number of biomarkers that are used, mostly for oxidative DNA damage. They assess 8-hydroxydeoxyguanosine. You know, and as noted in that Steffensen 2020 review, this marker is easy to measure, but it does have the weakness of high inter- and intra-day variability because of many confounding sources, such as food, exercise, smoking.

Some other studies looked at lipid peroxidation or oxidative damage to lipids, and were -- these were often measured using the markers of malondialdehyde or 8-isoprostane. And then other studies used general markers, such as glutathione levels, glutathione dimers as well as changes in the function or titer of protective enzymes, such as glutathione transferase, glutathione peroxidase, superoxide dismutase, catalase, and others.

I should step back just briefly. You know, we really should take some caution when applying this key characteristic in particular, because oxidative stress is caused by many non-carcinogens as well. Any chemical that causes systemic toxicity or inflammation, you know, can

cause inflammation and you often see changes in these same markers as well.

So I think we should focus on oxidative stress as it relates to the potential mechanisms, especially at non-toxic doses and the potential outcomes such as genetox, and receptor and cell signaling.

So bisphenol A has induced reactive oxygen species in hundreds of studies in humans and animal cells in vitro, including low concentrations at or near human expected levels in some populations. In animals in vivo, again quite -- including quite low doses on the order of low microgram per kg, induced ROS in many tissues and cell types.

In human observational studies, we must control and consider the factors such as co-exposures, disease state, and smoking status. And also some of the human observational studies have the same limitation that we saw in the epi studies, where, you know, some use single-spot urine samples for exposure assignment. However, many others use multiple exposure time points, so that really -- that really strengthened their studies.

There were 13 observational studies, six showed no or negative association, but the vast majority were positive, and these did include some studies that had repeated urine samples to improve exposure assignment.

With respect to human in vitro, there's over two dozen studies, bisphenol A in human cells that reported significant changes in a variety of cell types. These included lymphoblastic cells, breast cancer cells, colon cancer cell lines, neurons, kidney, blood cells, liver and lung cells.

Interestingly, some of these studies showed that ROS not only forms and can be measured increased in the cytosol, but also in the mitochondria. So bisphenol A metabolites do accumulate in the mitochondria and they lead to energy shutdown, cell death, which of course then kicks up cytokines and can lead to inflammation.

Animal in vitro, there were many, many animal in vitro studies that showed increase in ROS markers in a dose response fashion in the blood and in the tissues, including ovary, liver, brain, testis. Also, increases in these markers, including malondialdehyde were seen in animals given greater than 5 mg per kg, but there were a few studies that showed markers elevated even after low doses on the order of microgram per kg.

Let me just give you one example that is one of the longer term studies in this group. Wang et al. in 2019, it was a 10-week drinking water study. It's a good example in mice. Longer term oral intake at 50 micrograms per kg induced ROS markers in the serum, colon, and liver,

as well as corresponding decreases in the activities of the enzymes that protect against oxidant status, such as superoxide dismutase and catalase.

There were clear increases in inflammatory cytokines, there were clear reductions in mitochondrial function in the tissues, and there was a clear increase in Caspase genes being expressed, as well as functional enzyme activity in the liver and colon suggesting BPA-induced apoptosis. I thought that was interesting just because there's quite a number of studies that looked at in vitro activities of apoptosis in cancer cells, such as that reviewed by Nomiri in 2019, where they showed BPA inhibited apoptosis in some studies, where actually inducing apoptosis in others.

One of the key review papers that OEHHA highlighted was that of Amjad in 2020. It summarized numerous animal studies that had been conducted where bisphenol A induced oxidative stress that was alleviated by co-exposures to a variety of antioxidants like catalase, small molecules like vitamin A, C, and E, melatonin, lycopene, ginseng. Nearly all of the antioxidants reduce bisphenol A oxidative stress, lipid peroxidation, and DNA damage. I think it just really points to the complexity of studying bisphenol A effects in humans. And there's this constant always the

interbalance between that oxidation and reduction that's always going on.

All right. I'm almost through here. I've just got animal in vitro. There were about three dozen studies in rodent cells from a variety of tissues, almost all found significant increase in ROS markers. For most -- for some cell types, high micromolar concentrations cause cell toxicity or cytotoxicity. But there were -- actually, the majority of the studies in mammalian cells showed lower non-cytotoxic dose still resulted in ROS formation.

So in sum, I think it is clear that bisphenol A causes oxidative stress. It causes oxidative stress at high doses, but also importantly it does so at lower doses as well that are noncytotoxic. Bisphenol A induces reactive oxygen species that appear to be involved in altering cell signaling pathways, promoting cell proliferation and survival, as well as DNA damage.

That's it. Thank you.

COMMITTEE MEMBER LOOMIS: Thanks, Dr. McDonald.

So let me just point out that it is 10 minutes to 2 and remind the remaining discussants that you can assume that we've all looked at the report and data to the extent we need to. So please just summarize your observations about the studies and the key takeaway messages that you

think the Committee should be aware of.

We'll go on now to Dr. McDonald with key characteristics 2 and 3.

I'm sorry, Dr. Eastmond.

COMMITTEE MEMBER EASTMOND: Thank you. And I'll try to move through this fairly quickly.

So key characteristic 2 is really does the agent exhibit genotoxicity? And there is evidence that bisphenol A is genotoxic at multiple endpoints in vitro. Although, the results are somewhat more mixed than it seemed presented in the document to me. For example, it was -- the document says it causes mutations. And where -- so if you look at this, it's negative in many -- the Ames test in salmonella bacteria. It's been tested many times. It's been negative. Negative in yeast. It was negative in four mutation assays in standard tests in animal cells, but it was positive in two non-standard tests in human cells.

It was also positive in one dominant lethal study in rats and negative in one. So you get this sort of mixed path -- picture, but there's enough evidence here that it does look like it is positive certainly in vitro, and that's for chromosomal damage, DNA strand breaks, adducts as well and oxidative damage to DNA as indicated by Dr. McDonald.

The evidence for genotoxicity in vivo is limited and is more problematic and I'll give a couple of examples. So about 20 years ago, there was a very high profile study by Pat Hunt and colleagues that reported that bisphenol A caused aneuploidy in -- and related effects in germ cell. And it's in the document. However, that -- there was a group from Europe that actually had funding from the European Commission to work on that exact same type of study. And I should say there are only about a handful of labs in the world that do these types of studies. So it was actually very fortuitous that this other group by Pacchierotti et al. had funding to repeat the study by Hunt, and they were unable to repeat it.

And so the repeat study is also in the document, but you don't see it in the context. The one was quite dramatic sort of result, but the follow-up result by a very reputable group of investigators was not able to repeat that work.

And then there's some other issues that come up in vivo, where you have one group in actually what I consider actually quite a poor study, but reports chromosomal damage at very low concentrations of bisphenol A. Similar results are not seen at much, much higher doses, thousand times higher doses by, you know, result labs that are considered to be quite reputable. So you

get this sort of issue. It's kind of a messy pattern, but certainly there's some evidence for genotoxicity.

Let me -- I'd like to put this, if I could, in a little bit broader context, since most of my career I was involved looking at genotoxicity related to phenolic compounds. And Tom McDonald was involved in some of this many years ago, but -- so the metabolism and toxicokinetic information to indicate to me that positive results when they are seen would likely be much more common or restricted to the high doses of bisphenol A. If you think about the toxicokinetics and metabolism that was presented, it's very similar to other phenolic compounds in that initially when the body is exposed or cells are exposed to these phenolic compounds, phase 2 conjugation takes place, so that basically you have conjugation with glucuronidation and sulfation occurs, and that really predominates.

But as you get to higher concentrations, then you start seeing bioactivation by cytochrome P450, monooxygenases. And these will form reactive intermediate such as your quinones. But generally, there's fairly substantial levels of reduced glutathione, which will conjugate with this so -- or plan to activate that.

But as you go up to higher doses or higher concentrations, then you'll start seeing more covalent

binding to macromolecules, such as proteins and DNA. And that's sort of the common sort of classical toxicology perspective. And that's the way I look at this or interpret. And that seemed to be consistent with the evidence.

So this suggests to me that when -- that there should be a sort of strong nonlinear component to the dose response curve. And indeed, the United Kingdom's Committee on Mutagenicity concluded that the dose responses of similar compounds, hydroquinone and phenol are likely to exhibit a threshold response, just because of these multiple protective mechanisms in vivo.

Another point I'd like to point out is that this phase 2 metabolism, which tend to be quite efficient is found for phenolic compounds both in the intestine and in the liver. So it becomes important when you evaluate studies to identify the route of exposure, so that, you know, is this relevant to sort oral exposure or is this a unique sort of thing. So when you talk about osmotic pumps implanted -- they are -- the compound is reaching systemic circulation without directly going through the intestine or the liver. So you might expect to see somewhat different results than if the compound was given orally.

So in sort of summary, I think there is certainly

evidence that -- and I should say, Tom -- Dr. McDonald went through the evidence for -- there's oxidative damage to DNA in multiple studies reporting this as well. So there is certainly evidence that bisphenol A is genotoxic in vitro, but I would consider the evidence in vivo to be much more limited, certainly for traditional endpoints. And that's kind of my summary for key characteristic 2.

Key characteristic 3, it alters DNA repair or causes genomic instability is indicated in the report. Overall, there were a relatively small number of studies that looked at the ability of bisphenol A to alter DNA repair or cause genomic instability. And a few of them reported that bisphenol A decreased capacity to -- for cells to repair certain types of DNA damage and is various cell types. And a few others reported decreased expression of DNA repair enzymes.

So I consider these evidence in this area to be fairly limited. So for the -- there's maybe some suggestion there, but it's not certainly convincing by any means that bisphenol A may cause some effects on DNA repair, but it's not -- again, it's sort of in a limited evidence or suggestive evidence category.

So that's really my comments for those two key characteristics. I'm happy to answer questions if people have them or maybe we'll wait till later.

COMMITTEE MEMBER LOOMIS: Yeah, let's move through all the key characteristics and then we'll open it up for questions. Okay.

Next up, Dr. Besaratinia, key characteristic 4.

COMMITTEE MEMBER BESARATINIA: Thank you. Let me get to my notes. Well, I want to also recognize the work of all contributors to this nearly 600-page report. I'm sure it was a major undertaking and lots of work went into that. The document is a good read and it reviews a large body of work.

As we heard today, the literature on the cancer causing potential of BPA is quite rich. By focusing on the epigenetic effects, the report identifies, if I read it correctly, 413 articles published in this topic. I myself did a quick PubMed search and found 128 review articles only on this topic. This is quite astonishing considering that investigating the epigenetic effects of this chemical only gained momentum about 16 years ago. So that was basically due to publication of two seminal studies, one by the Prins group in 2006 and the other one by Jirtle's group In 2007. This latter study I'd recommend inclusion of this second very important study, which was published in PNAS, somewhere appropriate in the report.

Following the publications of these two studies,

there has been a flurry of research into the epigenetic effects of BPA and other endocrine disrupting chemicals. The report summarizes many of these studies, and the presentation given earlier today highlighted some of the findings of those studies.

I'm not going to repeat what is written in the report or was presented today, but just to give a brief overview of my gathering from reading the literature on my own and reading the report. My take is that there is basically three distinct, but often interrelated epigenetic modifications that are associated with BPA exposure. Among these apparent DNA methylation is the most studied one.

Relatedly, studies on DNA hydroxymethylation are also beginning to emerge. These studies have been performed in vitro, in vivo, and in human populations. To a much lesser extent, studies on histone codes and non-coding RNAs have been also performed in cell cultures treated with BPA or in tissues and organs of animals treated with this chemical. The histone modification studies have focused on a few active or repressive histone marks. Occasionally, measuring the -- occasionally, measuring enzymes that catalyze these reactions and sometimes quantifying the expression of the associated genes.

Likewise, studies on long non-coding RNA, specifically microRNAs and long non-coding RNAs, and BPA exposure have mainly been in vitro and in vivo experiments, and fewer human studies are there in the literature.

I'm not going to go through the histone modification or non-coding RNA studies, as many of these studies are extension of the original DNA methylation studies. And most of the comments that I will make for DNA methylation studies will also apply to those other studies.

As for DNA methylation studies, a large number of in vitro, and in vivo experiments, and human studies have shown that exposure to BPA is associated with either gain or loss of DNA methylation in a single gene or multiple genes. The report refers to these studies as individual gene methylation studies. There have also been reports of association between BPA exposure and DNA methylation at a global level. These are referred to as global methylation studies in the report.

What I would like to note is that with the exception of perhaps a couple of studies, the global studies as they're referred to in the report are not truly genome-wide studies, because they either use methylation array, which interrogate only a small fraction of the CpGs

of the epigenome of the genome, at best less than two percent or they use Elisa or immunoprecipitation or other enrichment-based method to analyze specific repeat elements as a proxy for the CpG content of the entire genome. So as it stands, there is a need to study the effects of BPA on the whole epinome perhaps using more advanced techniques, such as NGS based platforms.

Based on the in vitro and in vivo data, there is evidence that exposure to BPA is associated with apparent DNA methylation, both individual genes and in gene panels. This associations are mostly cell type dependent as is shown in cell culture experiments. They have also been shown to be tissue specific or sex specific in some animal studies.

A wide variety of cell types from different species have been treated in culture with BPA at varying doses, mostly in the nanomolar to micromolar range. Following the treatment, some but not all of these cell types show changes in methylation status, for example in the promoter region of a gene or in repeat elements. Again, methylation changes are detectable in some but not all doses. Also establishing a dose response relationship has not been straightforward.

Pathway analysis of the differentially methylated genes has been performed in several of these studies. And

there's also enrichment of nuclear pathways that are implicated in cancer, neurodevelopment, and metabolism, and reproduction among others.

Let me see. Several of these studies have also measured the expression of enzymes that catalyze DNA methylation, both overexpiration and underexpression of DNA methyltransferases, both the de novo and the maintenance DNMTs have been observed in in vitro and in vivo experiment. Their relationship between enzymes level and the methylation status of the tested gene has not been direct as can be expected.

More or less, similar findings have been reported from animal studies after in utero or lactational exposure to BPA. Again, I want to underscore the tissue specificity and sex dependency of the effects that have been reported in most of these animal studies.

As for human studies, the focus has mostly been on mother-child pairs or adolescents and adults with environmental exposure to BPA. There are also studies in adults occupationally exposed to this chemical. Although associations between DNA methylation status and BPA exposure have been found in some of these studies, the results need to be interpreted quite cautiously. As we heard all day today, the main concern is the reliability and precision of exposure data for BPA in human studies.

To make matter more complicated and complex, there is the issue of epigenome plasticity which can significantly impact the human study. As you all know, the epigenome can change by both physiologic and pathologic conditions, developmental stage, normal aging, exposure to a wide range of chemicals and agents, lifestyle factors, diseases. These all can affect the epigenome. So it's tremendously challenging to account for these factors in the epigenomic studies in human population.

In the case of BPA, this situation might be even more complicated considering the persis -- pervasiveness of this chemical in the environment. It's complex pharmacokinetics, particularly on -- in its short life -- half-life and rapid excretion and most importantly lack of long-term exposure biomarkers for this chemical.

I'll briefly mention some examples of the limitations of the published studies in humans. For instance, in mother-child pair studies, spot urine samples from mothers they're collected for BPA measurement in order to find this association with DNA methylation in fetal tissues, placenta, cord blood, or peripheral blood from offspring two years up to 14 years after birth.

Again, as we heard all day today, the accuracy and representativeness of a one-time measurement of BPA in

mother's urine is at best questionable, especially when it's used to estimate the gestational exposure or the newborn's exposure years after birth.

A further complication is the continuous exposure of these newborns to other sources of BPA and the constant alterations of their epigenome as they continue to grow. The same concerns also apply to studies in boys, and girls, and adults whose urine or serum samples were taken at a single time or twice a year in order to make an average for annual BPA exposure.

Also, in many studies, a major concern is the use of heterogeneous tissues or mixed cells for methylation analysis, despite the fact that epigenetics -- epigenetic marks are mainly cell type specific. For instance, the use of whole blood or placenta tissue in many studies is a significant limitation, considering that blood is comprised of various cell types. Methylation changes that are associated with BPA exposure can simply be caused by changes in blood cell composition as a result of exposure to not only BPA or -- but also other chemicals and stressors.

And a further concern is the use of potentially compromised study subjects. For example, women receiving reproductive medication or undergoing IVF treatment the epigenetic changes that are reported in these women could

simply be attributed to those therapeutic and not necessarily BPA exposure.

So putting all these together, one can argue that drawing conclusion from the results of human studies that are published so far is very challenging considering the quality of the available data and the design of those studies.

So one option would be to consider future studies that are better designed and sufficiently powered and preferably done in well-characterized population. Of course, this is not going to be an easy task considering the cost, time, and efforts that would be needed to carry out these studies, and the wait time to get the results.

The alternative, and perhaps a more realistic approach, would be to -- if one wants to reach a faster conclusion would be to focus on the available data from in vitro and in vivo studies. And this should be, of course, complemented with some follow-up studies, for example using banked specimens that are already available from many of those published studies. For example, one can consider the functional consequences of the epigenetic changes that have been reported to be associated with BPA. This is a very important area that is unfortunately very understudied up until now.

Along those lines, I think the report mentions

the CLARITY Project. Also another source is the target program that was funded by NIH several years ago. And one can maximize the use of banked specimens from those projects for preferably multiomic studies. And doing so we may contemplate, you know, integrated analysis of both epigenome and transcriptome in order to find a functional role of BPDAS -- BPA-associated epigenetic changes. And this can help us place this information in a wider context, which is the gene dysregulation and human disease, particularly human cancer.

So I think I'll stop here.

COMMITTEE MEMBER LOOMIS: Thanks, Dr. Besaratinia.

We'll move on to Dr. Wang with key characteristics 6 and 7. And again, I remind the discussants that we don't need a study by study description, but a summary of the key points that you think the Committee should be aware of, particularly your assessment of the strength of the evidence of each of these characteristics.

COMMITTEE MEMBER WANG: Okay. Can you hear me alright?

COMMITTEE MEMBER LOOMIS: Yes.

COMMITTEE MEMBER WANG: So the first topic is chronic inflammation. So there was a handful of studies

that were referenced in the report. I think this reflects that not -- there isn't a whole lot in human studies that have been conducted on chronic inflammation and BPA. These studies, the reports indicated that they reported an association. I would -- I would rephrase that and say that these studies suggest a link between inflammatory markers and exposure to BPA. And I think the major limitation in these human studies or epidemiologic studies is in the definition of what we consider chronic inflammation, which presumes long-term inflammation.

And I think the major issue in defining this outcome is that the outcome assessment in many if not all the studies have made it a single time point, where any assumption of chronicity in my opinion cannot be made.

So the way I interpret these studies that were referenced is that they have evaluated inflammatory markers, but not necessarily chronic inflammation. So this leads to the first major limitation of the delineated studies, which is study design. The majority are cross-sectional in nature, meaning that the exposure and outcome are measured simultaneously and at one time -- one time point. So we really cannot make any assumption about the chronicity of inflammation as an outcome, but we also cannot make any assumptions about causation. They're simply correlative studies.

The second limitation of the reported studies is the consideration of covariates. Some but not all of the studies have accounted for relevant covariates. And the ones that have included covariates in their models, they all consider somewhat different covariates. And I'll just point out that there are actually a number of post-characteristics and medical conditions that have been associated with inflammatory and other immune markers. And these include key cancer risk factors, such as obesity, diabetes, NSAID use or other medication use, et cetera.

Other characteristics such as the co-activity has also -- have also been associated with immune marker measurements. So for some of the studies that have reported correlations that did not account for -- you know, many of these covariates, the interpretation of the results is difficult.

There was one thing that actually I found interesting about some of the studies that were presented, in that there were curious associations that, you know, in the overall studies, they perhaps didn't observe and associate -- a link, significant odds ratio, but that many of the significant associations were actually reported among population subsets, such as women with PCOS, or within diabetic individuals, or among post-menopausal

women.

On the one hand and likely, these could just simply be spurious findings, but on the other hand, it made me wonder whether the question that was being asked by many of these studies is not quite the right one, that maybe we ought to be focusing on which susceptible populations there might be for BPA exposure, that there may, in fact, be a biological basis for concern for specific populations at risk.

So someone who is obese or there's a diabetic in the population that already experiences chronic inflammation due to those conditions, might expose to BPA exacerbate that level of inflammation? Now, I'll concede that there is actually no evidence in the data presented to suggest that, but that's just another way of looking at it that we may consider in the future.

The final limitation of the human studies is that power from any of these studies is uncertain. There was, you know, for example, a cross-sectional study of 76 men in Italy, 200 adults in Korea, 176 healthy newborns in Cyprus, 40 women with PCOS compared to 20 controls in Italy, 60 adults in South India. There were some larger studies, you know, upwards of 400 people. But still, the population, as you can see, is very heterogeneous in terms of what we're looking at. And for the most part, the

sample sizes are likely to be inadequate.

So moving on to animal studies, there were many, many more animal studies on BPA and what I would consider chronic inflammation. And indeed animal studies, longer term BPA exposure was, in fact, measured, and chronic inflammation as measured within tissues and various organs, in fact, were reported.

I think most noteworthy is that there were important dose-dependent associations with severity of inflammation increasing with BPA dose. There was a number of animal models that were reported. Long-term exposures were reported over -- from over weeks to over months and that were assessed. And there was -- even though these animal studies were also heterogeneous, because there were many more of them and because they were covering many more exposures from weeks to months and from different doses and different routes of exposures all coming up with similarly consistent associations. I found the animal studies to be a bit more robust than the -- or a lot more robust than the population or epidemiologic studies.

The biomarkers of inflammation were also measured in different ways, including in serum at different time points, mRNA expression at different time points, as well as directly in tissue based on inflammation cell infiltration in the liver, kidney, lungs, prostate lung.

So in general, I would say that the human evidence is weak to modest, but that the animal evidence of linking to chronic inflammation is much more robust.

Moving on to immunosuppression, I won't spend a whole lot of time on this category, because they're really very -- compared to the other categories, there were very few studies to evaluate. The report suggests that there was significantly -- that there is an association with immunosuppression. You know, in my read of the data, I would say there's probably insufficient evidence. There's not -- certainly, it's not null. Certainly, there is the studies that they cited. There appears to be suggestions of an association with immunosuppression with BPA exposure.

I guess where I had a little bit more difficulty in interpreting the results is that there -- I don't know if it's a biological phenomenon, but unlike -- you know, we'll just contrast to the inflammatory studies, of which there were numerous and they were -- they covered, you know, many different types of exposures, many different types of outcomes, over time, the immunosuppression studies, it's not clear whether these studies, because there's so few, whether they are spurious associations. There -- and they blanketed sparsely the different types of, you know, ways of measuring immunosuppression, so

there are much fewer studies on dendritic cells than are natural killer cells, there are IgM, and many more studies on macrophages, and neutrophils, and T and B-cell proliferation.

But even among those for which they are -- I mean, there's two ways to look at it. One is that because they're looking at all these different outcomes and there are studies popping up for each of these outcomes that, you know, one could conclude that perhaps there is consistency in the association for immunosuppression. But the other way of looking at it is that there really wasn't, you know, any dose response relationship, but I don't know if I'm interpreting that correctly, that, you know, in -- you know, there is different dosing for BPA. And in some, you know, don't -- many of the reports will say there was significant association for this level, but not at this higher level or, you know, I can -- a number of studies do that.

And so it's unclear whether there's no dose response or whether there is a threshold effect, right, so that maybe high BPA exposure you tip the balance on immunity to actually inflammation rather than immunosuppression. So it's both sides of the coin. And, you know, none of these studies actually look at both sides of the coin.

So I think because of the sparsity of the study on immunosuppression, it's difficult to interpret would be my conclusion and I'll end there.

COMMITTEE MEMBER LOOMIS: Very good. Thank you, Dr. Wang for a nice concise and informative summary.

We'll go on, key characteristic 8. Dr. La Merrill, you have that one, receptor-mediated effects.

COMMITTEE MEMBER LA MERRILL: Hi. All right. Sorry. I just had the sun come in.

Okay. So receptor-mediated effects, I think that the evidence is overall strong here. There are a tremendous number of studies looking at bisphenol A, its ability to bind and modulate the activity of estrogen receptors, both the, you know, canonical nuclear receptors of alpha and beta, but also the membrane receptors and another cytosolic ER receptor called GPER or GPR30. And the studies have been done in, you know, cell lines in multiple species using gold standard techniques.

And generally speaking, BPA appears to be an agonist of these receptors, like ER-alpha and GPER. However, for beta -- the ER-beta BPA can behave as an antagonist. One of the things that happens with estrogen receptor is the effect of a ligand can depend on the tissue context or other contexts. For example, the chemotherapy tamoxifen can protect against breast cancer

by antagonizing in the breast, but can promote uterine cancer due to differences and cofactors that are part of the binding complex of ER at the nucleus. And so interestingly estradiol itself also at ER beta kind of has antagonism properties, so that BPA can antagonize at ER betas consistent with how the natural ligand estradiol works at that receptor.

And ER expression in -- sorry, lymphomas -- lymphoma cells that are human B-cell lymphomas and characterized as ER alpha negative and ER beta positive, which is the predominant distribution of ER expression in B-cell lymphoma patients and cell lines and so forth. That BPA exposure in the -- in these B-cell lymphoma cells, it did suppress the growth in the human cells and also in the mouse cells, which is consistent with basically how estradiol would work in that context, but not really consistent with what I described earlier with respect to the increase in lymphomas being reported in the animal studies.

There's some evidence that BPA can be an antiandrogen. In the human system it seems to interfere with the translocation of AR in several independent studies of human cells in vitro. And thyroid hormone receptor has been evaluated and I didn't find that -- any compelling evidence related to BPA's ability to modulate

the activity of thyroid hormone receptor. I didn't see any -- for example, typical gold standard binding assays for that.

But OEHHA group was kind enough to summarize other receptors, including aryl hydrocarbon receptor and two PPARs, alpha and gamma. I didn't find that there was consistent evidence of the expression -- excuse me, the activity of either of those three receptors being modulated by bisphenol A. We also had a summary of the possibility that bisphenol A could modulate the expression levels of hormones or the receptors I brought up.

There could possibly be a role of BPA in increasing the expression of PXR, a receptor that was increased in association with BPA exposure in a study of infertile women and men, and also in fertile men, but not fertile women. So it's also been shown in female fish. Excuse me, it was absent in female fish, but also present in male fish, and -- but not seen in non-human in vitro models otherwise.

So I'm not -- I think that evidence is overall probably pretty week. I would also say that there's inconsistent evidence for estradiol, progesterone, testosterone, thyroid hormones, thyroid receptor, and androgen receptor being associated with bisphenol A. In human studies it's certainly been measured, but I think

we've all discussed exposure assessment issues, but also I think outcome. You know, there's a lot of temporality to the circulating levels of these hormones for people. So I think it's just -- it would be very surprising if there was actually an association that represented biology that could be detected in the context of experiments that we've seen.

Just a little more evidence suggesting that there might be an effect on testosterone levels. I can get into that if someone wants, but my take on it was that it was not particularly important.

Prolactin levels of the hormone was positively associated with BPA in occupational studies of both sexes, and in several rat studies. But nonoccupational BPA studies, the prolactin evidence was inconsistent. So I thought that that could potentially be some evidence of something real going on, since the occupational studies address some of the, you know, issues that we've discussed in the previous conversations, and then with the rat studies supporting by, you know, having better control of confounding and exposure.

Then just to touch on the AHR part of things, there was studies looking at several mouse tissues, showing AHR protein was elevated, specifically male mouse testes, spleen, kidney. And those were three separate

independent studies, and then in the human hepatocellular line, which is really a cancer cell line HepG2.

And the AhR was measured as RNA in three cross-sectional studies in humans where it was also increased. And I don't know what to think about that. I don't -- I wouldn't really care about the cross-sectional, so much on their own, because of all the things that are wrong with that kind of study. But in combination with the cell and animal evidence, there might be something to that as well.

And then lastly, I'll just touch on the PPAR gamma expression levels. There's increased PPAR gamma RNA, mostly identified. We just haven't looked at the protein has much. That RNA of PPAR gamma has been increased in experiments with human adipocytes, monocytes, and liver cells, as well as three different types of mice. And in those cases, it mostly liver. And one of the three mice studies also had testes data. And then there were a few mouse studies showing increased PPAR gamma at the protein level in a couple different tissues, liver, and testes of mice.

So overall, I would say that the evidence is strong, mostly based on the ER story, but I wanted to at least share with you all the receptors, in case it's of interest related to some of the whole organs and

phenotypes we're discussing.

Thanks.

COMMITTEE MEMBER LOOMIS: Thank you.

Let us move on now to key characteristic 9, and Dr. Landolph has that one, Immortalization.

Let's see, are you there, Dr. Landolph? It looks like you're still muted.

Do you need a minute to get ready?

What we'll do is skip on to key characteristic 10, cell proliferation and nutrient supply, and Dr. Bush has that one. Set let's just skip forward, Dr. Bush, please, to yours.

COMMITTEE MEMBER BUSH: Absolutely. Yeah. Thank you, Dr. Loomis. Okay. So key characteristic 10 alters cell proliferation, cell death, or nutrient supply. As the document states, there are over 200 relevant studies in human cells in vitro. Full disclosure, I did not read all 200. I did not get that granular. I did read the three comprehensive reviews and followed up as necessary.

In general, I viewed the cancer cell line data of less value. As we know, transformed cells, and particularly these long established cell lines, already represent an artifactual system. So I'm also speaking as someone who uses these cell lines all the time in my own lab.

So I gave more value to studies utilizing normal cells or noncancer cell lines. As the HID document states, a number of these studies report no increase and others reported decrease in cell proliferation. Of note, most of these studies used concentrations of BPA orders of magnitude more than what the physiologic concentration should be expected to be in the range of 0.5 to about 4 nanomolar.

And so there is going to be an effect. And there are many studies that report that BPA increases proliferation in various cell types sometimes at a low dose. But this does indicate that BPA's effect may be impacted by cell type, the BPA concentration and both extrinsic and intrinsic factors. In terms of apoptosis, many studies in human cancer cells demonstrating that BPA alters apoptosis signaling pathways and decreases apoptosis, but there are also negative results as well.

Similar to cell cycle control and cellular replication, there is data to support a role there. There are a handful of studies that show BPA promotes angiogenesis and angiogenic pathways, and even metabolic -- the metabolic switch towards increased glycolysis.

So I'm going to summarize quickly here. As part of this key characteristic 10, there was also evaluation

of the in vivo rodent studies and the cumulative data. They're correlating BPA with proliferation in the context of hyperplasia. That was -- those conclusions ranged from some stat -- not statistically significant changes all the way to strongly supportive.

So for KC 10 in total, it seems that the way the evidence is presented, there is support for a moderate to strong consensus of key characteristic 10. And I will end there and let Dr. Landolph tell us about key characteristic 9.

COMMITTEE MEMBER LOOMIS: Okay. Thanks.

Dr. Landolph is back on screen, so let's jump back to KC 9, immortalization.

COMMITTEE MEMBER LANDOLPH: Okay. Let me get to it.

So immortalization is a part of carcinogenesis. You can't have cancer if you don't have immortalized cells, because otherwise they'll just senesce or die out.

So the data here is pretty thin. There are two studies that reported BPA could induce cell transformation in SHE cells, and two other studies in SHE cells, and one in A31-1-13 clone of BALB/c-3T3 cells that did not find significant alterations to cell transformation, so they kind of cancel each other out. BPA did increase cell invasion in three human primary cell lines. And then

increases in mesenchymal cell markers were observed in three human cancer cell lines and one human epithelial cell line after exposure to BPA. And one study observed a decrease in cellular senescence gene in the human cancer cell line.

Higher urinary BAP levels -- BPA levels in one study were associated with shorter relative telomere length in adult women. Five studies characterized alterations to the telomerase expression activity or telomere length after BPA exposure in human cells.

Two studies performed in mammary human cells found decreases in telomerase activity hTERT mRNA expression, or telomere length after exposure to BPA. Three studies performed in human cancer cell lines found increases or no alterations in telomerase expression activity. So it's kind of a mixed bag. I'm not too wild about the BALB/c-3T3 -- I'm sorry, the BALB -- the SHE cell transformation assay. I know Carl Barrett have used it to study the temporal acquisition of transformed phenotypes. But I've talked to friends who have used this or tried to use it, and sometimes they get the same transformation frequency, but they score different events. So I'm a little bit skeptical about how reflective that is.

I do know you do get immortalization after you

get transformation of colony, so it can do that, but you kind have got these studies canceling them out. So I would say the more interesting studies are probably in telomerase activity area, but this database is pretty thin.

So I would say, yeah, it can cause cell transformation, but the studies -- in some studies, but they're canceled out by other studies. I think the most interesting data is the studies in the primary human cells, where the telomerase activity is decreasing and hTERT expression or telomere length after exposure to BPA, and three studies performed in human cancer cell lines found increases or no alterations in telomerase activity and expression activity.

So I think that database is kind of mixed. And I don't think it conclusively shows immortalization, some studies being positive, some studies being negative. So I would say there's not a lot of data here at all for causing immortalization in my opinion.

COMMITTEE MEMBER LOOMIS: All right. Thank you, Dr. Landolph. So that brings us to the end of the discussion of the key characteristics. We have some time set for Committee discussion right now. And the way I'd like to do this is first to call on the other discussants who reviewed and reported on the animal and mechanistic

data and see if there is any additional information that they'd like to bring forward or any perspectives that we haven't heard yet on the data that have been summarized by other discussants.

So Dr. Bush, hand up there. Go ahead.

COMMITTEE MEMBER BUSH: Thank you, Dr. Loomis.

So by my count for the key characteristics, I got about six or seven of these key characteristics that I think folks would generally -- would say had strong associations, and maybe key characteristic 3, 7, and 9 would be limited.

And I want us to be careful there. You know, development of the key characteristics is certainly a great utility to the community. You know, it's definitely valued and provides that framework, that a diagnostic framework to build upon when it comes to carcinogens, but there's also emerging data, you know, indicating that there needs some -- needs to be some revision of these key characteristics. And I'm going to point to a 2019 review by Krewski and others. In fact, our own Vince Cogliano was on that paper, where they looked at the 86 agents known to cause cancer in humans.

And so we're looking at the group one agents. And on average, the group one agents have about four of these key characteristics. None have 10. Only about 20

have six or seven, as we've indicated for BPA here. And, you know, those group one agents include asbestos, and plutonium, and tobacco. So, you know, I say this to perhaps help guide the conversation in terms of what these key characteristics represent.

So with a little bit of caution.

COMMITTEE MEMBER LOOMIS: Thanks. The points are well taken.

We'll go on to Dr. La Merrill.

COMMITTEE MEMBER LA MERRILL: Yeah, I just wanted to ask a question. Probably, Dr. Stern, you could address it the best. There is several analy -- meta-analyses of adults and kids, as well as actually experimental rodents indicating that BPA is associated with increased risk of adiposity. And, of course, in rodents, you know, it's experimental.

So I was wondering if we're conceiving of BMI as a mediator rather than a confounder, how might that change your perspective on some of the epidemiology studies you reviewed? I think breast cancer certainly is associated with obesity and in prostate and gallbladder as well.

COMMITTEE MEMBER STERN: Yeah, that's a -- that's a great point. And there are -- and I can look through my summary and point those out, but there were a few studies, only a handful, that actually explore that possibility.

And they look for potential effect modification of BMI, as a surrogate for obesity on the association between BPA and cancer risk. And actually, they did not see evidence that BMI was an effect modifier.

The other studies either did not consider BMI at all, and that was a problem, particularly for breast cancer, because as we know obesity is a risk factor for breast cancer. And some of the studies did consider it as a confounder. So they adjusted for it, but they may not consider the potential effect modification role.

So only a few studies look at that. And I -- if I remember correctly - I'm want to double check now - they did not find evidence that there were differences -- different associations by BMI status. But only a handful of studies looked at that. A majority did not consider it.

COMMITTEE MEMBER LA MERRILL: Um-hmm. And no one did mediation analysis, so --

COMMITTEE MEMBER STERN: No. No. But by doing the effect modification, we can kind of infer at a potential mediation. If we did see, for example, that around women with higher BMI the effect of BPA is stronger for like breast cancer risk, then we can kind of speculate that, you know, further analyses could look at that, but only a few studies look at that, so -- and there was not

proper mediation analysis done in any of the studies.

COMMITTEE MEMBER LA MERRILL: Okay. Thank you.

COMMITTEE MEMBER LOOMIS: Okay. Dr. Wang has a hand up as well. Go ahead, please.

COMMITTEE MEMBER WANG: Yeah. I just wanted to reiterate -- actually, I wanted to jump on to what Dr. Bush had along the same lines. You know, the -- for some of the epidemiologic evidence or the human studies that I alluded to for my section on chronic inflammation, it's not that there were -- and I think Dr. Mack has done this previously as well. It's not that they were null studies necessarily, it's that they're -- the study design or the studies were -- are not adequate. They're not -- you know, they're not designed in a way to assess exposure adequately or their outcomes adequately. So I think that's what we have to consider. It's not that there are, you know, a slough of null associations that we're working with.

And I did have one question for Dr. Stern. You know, I didn't see and I didn't hear in the summary, but I thought I saw in the literature, can you confirm, are there -- were there no studies on children or like in utero exposure and then childhood cancers?

COMMITTEE MEMBER STERN: No, there were no studies, either of those. All studies were in adult

populations.

COMMITTEE MEMBER WANG: Okay.

COMMITTEE MEMBER CRESPI: There was one study of osteosarcoma --

COMMITTEE MEMBER STERN: Oh, that's true with younger -- yeah.

COMMITTEE MEMBER CRESPI: -- which most of them were pediatric patients.

COMMITTEE MEMBER STERN: Yea, that is true. The study in osteosarcoma had adolescence, I think, yeah, but no studies of exposure in utero.

COMMITTEE MEMBER WANG: Thank you.

COMMITTEE MEMBER LOOMIS: Okay. Dr. Eastmond, another comment.

COMMITTEE MEMBER EASTMOND: Yeah, I just thought I'd expand a little bit on that question I asked earlier. But it's more of my perspective, but when you have lots of multiple studies and include -- indeed, the CLARITY Study has seven different arms, all of these have many, many types of statistical analysis, literally hundreds and hundreds. What I start looking for is rather than statistical significance on any one test, but looking at sort of do we see reproducibility and consistency? And I think that's really important.

And in some cases, I think it's important to go

back to the original study. And that's why I referred to that NTP 1982, if you go back and read what they commented about, specific tumor types and their interpretation, and the same thing with the CLARITY, and reading also the FDA letter that was submitted recently in the public comments. You know, it talks about some of the issues related to statistical analysis and how this was done in combining and their interpretation.

You know, for me, I think it's very -- this is helpful to look at, and looking for consistency. And I haven't seen it yet, but maybe others see that. Anyway.

Thank you.

COMMITTEE MEMBER LOOMIS: Okay. Thanks.

So that's an important question. But the way I'd like to organize the discussion here is just that we have a public comment period coming up, and then another Committee discussion period after that. And I'd like to hold discussion that's leading to a listing decision for that next Committee discussion session.

So if there's a different question from members of the Committee, let's take that now, but kind of focus on the evidence that's been presented already, rather than the listing decision.

So Dr. La Merrill, does your comment fit into that category?

COMMITTEE MEMBER LA MERRILL: Yeah. Dave Eastmond asked about consistency and I wanted to remind him that in the NTP 1982 study, the male B6C3F1 mouse had increased malignant lymphomas, as did, of course, the CLARITY Study. And so I agree with this idea to look at consistency. It's a nice criteria to contribute, but we do have two independent studies in two species with a malignant lymphoma, so I just want to clarify that.

COMMITTEE MEMBER LOOMIS: Thanks. Important point.

Dr. Wang

COMMITTEE MEMBER EASTMOND: Was that in the rat, by the way?

COMMITTEE MEMBER LA MERRILL: I'm sorry. I didn't hear the question.

COMMITTEE MEMBER EASTMOND: I thought the one in the 1982 study was in the rat.

COMMITTEE MEMBER LA MERRILL: In my notes it says B6C3F1 mice, but I can double check the --

COMMITTEE MEMBER EASTMOND: Okay. I'll look too.

COMMITTEE MEMBER LOOMIS: Okay. Dr. Wang.

COMMITTEE MEMBER WANG: So I hope this belongs here, but, you know, I do share some of the reservations that Dr. Eastmond has expressed in -- you know, in reading -- I mean, I was -- so I appreciate the

statistical overview at the beginning of the presentation, but in my mind, it would be helpful to see a rebuttal of, you know, many of the points that were made in the FDA letter. I don't know if that's appropriate here, but...

COMMITTEE MEMBER LOOMIS: Well, let's take that one up after the public comments.

Okay. Dr. La Merrill, you still have your hand up if you have something else that you wanted to bring up?

COMMITTEE MEMBER LA MERRILL: No, I apologize. I'll use the chat to put in the point.

COMMITTEE MEMBER LOOMIS: Okay. Okay. Good. Any other questions about the evidence or additional points that the Committee would like to bring forward right now?

Okay. So the next agenda item is public comments. And we probably should do a survey and see how many comment cards we've got before we start.

DR. GILSON: Hi, Dr. Loomis. We've received six comment cards.

COMMITTEE MEMBER LOOMIS: Okay. So --

DIRECTOR ZEISE: Dr. Loomis before -- Dr. Loomis, before going in, I think Vince Cogliano had his hand up and wanted to just clarify one point that was raised in the Committee discussion --

COMMITTEE MEMBER LOOMIS: Sorry, I didn't see

that.

DIRECTOR ZEISE: -- following the comments. Yeah.

COMMITTEE MEMBER LOOMIS: Yeah.

DIRECTOR ZEISE: Vince.

DR. COGLIANO: Thank you. I had a -- I my hand up just for a little bit, because I think -- I think you've got it, but the key characteristics paper that I was a coauthor on, there were quite a few results in that. And I think the idea is that really we didn't find any of the group one carcinogens that had all 10 key characteristics. And the most -- the average was about, as Dr. Bush said, around four or so. And there were some with more, but there were also some with less, so -- but we don't really look at it as how many key characteristics. It's -- the key characteristics tell us how an agent might cause cancer. What are some of the major pathways or events that are going to be involved, but definitely we don't need all 10. That's all.

Thank you.

COMMITTEE MEMBER LOOMIS: Okay. Thank you.

So if there's nothing else, before public comments. So we have six cards. Speakers are limited to five minutes each. That's about 30 minutes or less. So I'm going to suggest that we go ahead with public comment

and then call a break after that, and return to Committee discussion, if that sounds okay to the staff and Committee members.

Any objections?

Okay. So Elizabeth has put up the procedure for public comments. Just really briefly, one has to be registered for the Zoom webinar in order to make a comment orally. You can do this in two ways. You can fill out a speaker card. You can see the URL for that here on the form or you can raise your hand in Zoom. And then when you're prompted to speak, unmute yourself, and remember to lower your hand again when you finish speaking.

So the staff will keep time. I'm not sure who's doing that, but they'll let you know when your -- the end of your five minutes is approaching. If you haven't finished, and at the end of five minutes, the microphone will be cut and we'll move on to the next speaker, if you haven't finished.

So I don't have access to who has submitted a speaker card, so I think Dr. Gilson will go ahead and call on the speakers in the order in which they registered.

DR. GILSON: That's right. Thanks, Dr. Loomis. So first up, we have Robyn Prueitt. If you're here, can you -- I'll go ahead and unmute you. And if you can put up your hand, it will make it a little easier for me to

find you and allow you to talk. There we go. You should be able to go ahead.

DR. PRUEITT: Okay. Great. Can you hear me?

DR. GILSON: Sure can.

DR. PRUEITT: Great. Well, thank you for the opportunity to speak today. My name is Robyn Prueitt and I'm a board certified toxicologist at the environmental consulting firm Gradient. And today I'm speaking on behalf of the American Chemistry Council.

So the OEHHA guidance criteria for identifying chemicals for listing as known to the State to cause cancer indicate that if the weight of the evidence clearly shows that a chemical causes invasive cancer in either humans or animals, then that chemical may be listed.

Upon review of the body of evidence included in the OEHHA hazard identification document for BPA and considering the strengths and limitations of the reviewed studies, BPA does not meet the criteria for listing. As discussed in more detail in the written comments submitted by ACC, the epidemiology studies of BPA in cancer have multiple limitations that can bias the results in either direction and not solely toward the null as indicated in the hazard identification document.

Despite the limitations of the epidemiology studies, the results across analyses of specific cancer

types are inconsistent and do not clearly show that BPA causes invasive cancer in humans.

The evidence from experimental animals also does not clearly show that BPA causes invasive cancer. The majority of the animal studies reviewed in the hazard identification document have significant limitations, such as short study durations and small numbers of animals per dose group, and these studies are of limited utility for assessing BPA carcinogenicity.

In contrast, the chronic rodent carcinogenicity study conducted by NTP in 1982 and the CLARITY-BPA core study are well conducted high-quality studies that evaluated BPA over a wide range of doses. The NTP study reported increased incidences of a few types of tumors in male animals, but these do not provide strong evidence for BPA carcinogenicity.

Consistent with the conclusions of the study authors, it is more likely that the cancer types observed in this study were chance findings or common spontaneous tumor types in aging male rats. The hazard identification document fails to mention the statistically significant decrease in adrenal tumors in rats which suggests that the large number of tissues and endpoints examined in this study, as well as the multiple statistical tests used may have led to false positive or negative findings that are

due to a lack of adjustment for multiple comparisons rather than to BPA exposure.

The CLARITY-BPA study reported very few statistically significant increases in the incidence of malignant tumors and rats that are likely the result of chance fluctuations in incidence or false positive findings due to lack of adjustment for multiple comparisons. Despite the reliable evidence from this study that is consistent with a lack of BPA carcinogenicity in rats, the hazard identification document presents a biased review of the study that appears to be aimed toward a conclusion of carcinogenicity for BPA. This was also noted in the written comments submitted by the FDA.

For example, the OEHHA authors conducted their own statistical analyses of the CLARITY Study data without any rationale for doing so. And this practice can lead to the reporting of false positive results. The OEHHA authors also used unreliable historical control data sets to attempt to identify rare tumors, but this analysis is inappropriate and goes against the evidence that these tumors are spontaneous and not statistically increased compared to the concurrent controls.

The hazard identification document also discusses several issues that have been brought up in the literature

regarding the CLARITY study such as background contamination with BPA and controls, potential insensitivity of the rat strain to known estrogenic chemicals, and the lack of an unhandled control group. However, the hazard identification document did not mention that all these issues have been addressed by the CLARITY-BPA study authors and have been shown to not limit the ability of the study to detect carcinogenic effects.

Consistent with this, the FDA made the following statements in the comments that they submitted to OEHHA. I quote, "Numerous errors and incorrect or inappropriate analyses of the CLARITY-BPA core study results have been identified. We recommend OEHHA consider these issues for reanalyses as the current methods applied by OEHHA lead to an unsupported conclusion of positive..." -- "...potential positive carcinogenicity of BPA. FDA's multiple evaluations examining carcinogenicity and the results of the CLARITY-BPA study do not support classifying BPA as a carcinogen.

With regard to mechanistic evidence, the hazard identification document focused on providing any --

DR. GILSON: One minute left.

DR. PRUEITT: -- any positive evidence for each of the 10 key characteristics, but did not weigh the evidence for or against each as a plausible mechanism for

BPA carcinogenesis. The 10 characteristics are also shared by many non-carcinogenic substances, so the existence of evidence for these characteristics for BPA in certain studies does not provide strong evidence that BPA is carcinogenic.

So overall, the available studies of BPA do not provide clear or consistent evidence that BPA causes invasive cancer in humans or animals. Therefore, they do not meet the OEHHA criteria for listing BPA as a carcinogen and BPA should not be listed as such.

Thank you.

DR. GILSON: Thank you very much.

Dr. Loomis, back to you or we can take the next comment.

COMMITTEE MEMBER LOOMIS: Yeah, just go ahead. I don't know who the speakers are, so if you would just go ahead with the next one, when each finishes, that would be perfect.

DR. GILSON: Okay. Wonderful. So next up, we have Katie Pelch and I'll go ahead and prompt you to unmute.

Are you able to unmute yourself?

Oh, I see. Go ahead when you're ready.

Let's see, you should have permission to talk, but I'm not hearing you. Okay. We'll try to come back to

you.

COMMITTEE MEMBER LOOMIS: Yeah, let's go to the next speaker.

DR. GILSON: So the next speaker is Rainbow Rubin. And Rainbow had to leave, so they provided a public comment that I'll read on their behalf. This is from Rainbow Rubin, PhD and MPH, Director of Science with Breast Cancer Prevention Partners.

"Evidence from animal and in vitro studies has suggested an association between increased incidence of breast cancer and BPA exposure at doses below the safe reference doses that are the most environmentally relevant. BPA may increase mammary tumorigenesis through at least two mechanisms, molecular alteration of fetal glands without associated morphological changes and direct promotion of estrogen-dependent tumor cell growth. Both results indicate that exposure to BPA during various biological states increases the risk of developing mammary cancer in mice.

"In human breast cancer cases, urinary BPA concentrations have been positively correlated with breast adipose tissue BPA in the case group. BPA mimics both the structure and the function of the hormone estrogen and disrupts endocrine function at very low doses consistent with its nonmonotonic dose response curve.

"There is no evidence to suggest that reverse causation is the mechanism of action in breast cancer, as suggested by a Committee member. Just because no study accurately captures BPA exposure during vulnerable stages of development doesn't mean BPA is not a concern. Just because study results are inconclusive does not preclude us from protecting the population from BPA based on the precautionary principle.

"Considering the structural and functional overlap between BPA and estrogen, establishing a causal relationship in humans is extremely difficult due to multiple and variable exposures. As Dr. Mack said, there are no evidence against a positive association. Today, we heard ample evidence that BPA is a carcinogen, mutagen, and reproductive toxin.

"Please move to add BPA to the Prop 65 list".

All right. Now, I see Katie's hand is up again, so let's try again here.

Please go ahead.

MS. PELCH: Can you hear me?

DR. GILSON: So we hear -- this sound is breaking up a bit. Try again.

MS. PELCH: Okay. Can you hear me?

DR. GILSON: Yes.

MS. PELCH: Okay. Thank you. I am Dr. Katherine

Pelch. Thank you for having me here today and for allowing me to provide comments.

I am a scientist at the Natural Resources Defense Council where I specialist in the hazards and risks -- (inaudible) exposure to BPA. (Inaudible).

DR. GILSON: Excuse me, if I can cut in here. The sound quality is pretty sketchy.

MS. PELCH: Okay. Can I try to call in?

DR. GILSON: Go ahead, yeah.

MS. PELCH: Okay. I will hang up and I'll call back in a moment.

DR. GILSON: Okay. Great. Thank you.

COMMITTEE MEMBER LOOMIS: Okay. Let's -- maybe we can go on to the next speaker then.

DR. GILSON: Very good. So the next speaker is Luisa Camacho. And if you can raise your hand, that will facilitate my unmuting you or allowing you to unmute yourself. All right. I'm not seeing them here. This was Luisa Camacho with the FDA.

So let's go on again. So the last two speaker card submissions were from anon, so anonymous. If you're here and you would like to provide oral comment, please go ahead and raise your hand and I will allow you to unmute yourself.

All right. Seeing none, I'll summarize what anon

provided in the public comment card. So there are two submissions. The first one says, "Presentations have ignored public comments submitted to the OEHHA document". And then the second comment also from anon is that, "Public comments appear to be hidden from consideration", and then they provide the website where public comments are posted.

So to hopefully address these points, the speaker request card is to indicate if you would like to provide an oral comment during the hearing. So written public comments regarding the hazard identification document were -- that were submitted during the public comment period are for the CIC and were provided to the CIC as part of hazard identification materials before them today.

And these comments are publicly available on our website.

Now, until Katie Pelch calls back in, that rounds out the public comment cards that were submitted.

COMMITTEE MEMBER LOOMIS: Okay. I guess we can see if anyone else has their hand up to make a comment who hasn't submitted a card yet.

DR. GILSON: If you'd like to provide public comment, but didn't submit a speaker request card, please raise your hand in Zoom at this time.

All right. No one has their hand up.

COMMITTEE MEMBER LOOMIS: Okay. And Katie Pelch hasn't called back in yet, I guess.

DR. GILSON: Oh, let's see. I have a hand up here from Katie, Chair, if we can try again.

COMMITTEE MEMBER LOOMIS: Okay. Let's try.

DR. GILSON: Okay. So you should now be able to unmute yourself and provide your comment.

MS. PELCH: Can you hear me now?

DR. GILSON: Yes.

MS. PELCH: Okay. Perfect. Thank you so much. Sorry about all the technical difficulties. I'm Dr. Katherine Pelch, I am a scientist at the Natural Resources Defense Council, where my expertise is in providing hazard assessment and risk assessment for chemicals like BPA.

So I just wanted to start off by thanking the OEHHA staff and the CIC members for undertaking this very Herculean effort to evaluate the evidence for BPA and want to encourage the CIC to consider the guidance that says that the mechanism of BPA -- or understanding the mechanism for how BPA may be a carcinogen is not necessary. Rather, it is important to look at the entire body of the evidence.

And I think that we have heard today through OEHHA's immense efforts to catalogue the data, that there are numerous studies that show that BPA has the potential

to be a carcinogen, both the animal evidence and the mechanistic evidence. And we also heard that it is not necessary for BPA to meet all 10 key carcinogen -- or key characteristics of a carcinogen, but we did hear strong evidence that BPA is meeting several, perhaps six or seven, of these key characteristics.

So I just wanted to quickly echo my -- the comments that I submitted in written form. I apologize, as I'm driving right now, so hopefully you are able to hear me, and want to encourage the CIC to list BPA as a carcinogen.

DR. GILSON: Thank you.

COMMITTEE MEMBER LOOMIS: Okay. Very good. Let's do a final check and see if there are any other hands up for public comment.

It doesn't look like it, right?

DR. GILSON: Right.

COMMITTEE MEMBER LOOMIS: Okay. Well, it's a good idea to take a break sometime, and we're past the time program for that on the agenda. So if there's no objection, I'm going to suggest we take 15 minutes right now and reconvene promptly at 3:30.

Okay. So I'm not hearing any objection, so the Bagley-Keene warning still applies. Carol is not here, but I think we all heard it. So anyway, 15-minute break.

(Off record: 3:16 p.m.)

(Thereupon a recess was taken.)

(On record: 3:30 p.m.)

COMMITTEE MEMBER LOOMIS: Okay. It is 3:30. And we need to move through the rest of the agenda, so let's resume.

The next agenda item is again Committee discussion. And I'm going to use the Chair's position to pose a couple of issues that seem critical to me. So others may have a different opinion, but as I reviewed the human evidence of carcinogenicity, it is inadequate overall.

And so that means that the strength of evidence in animals and the strength of the mechanistic evidence becomes key in making a decision. And I will just say that the human evidence being inadequate doesn't necessarily mean that BPA doesn't cause cancer in humans, but we have to follow the evidence that we have. And as all of the discussants have pointed out, the human evidence -- human epidemiologic studies have significant limitations that might be resolved by future research, but at this point, we have the literature that we have.

So my questions for the experts who reviewed studies of animals and mechanisms are really about how strong the animal evidence is. We've heard three

different perspectives on it, but I'm kind of looking for the key summary of the strength of the evidence from all of those whose expertise is in that area. Mine is not.

I will say I'm not particularly concerned about multiple testing for reasons that I won't get into unless somebody really wants to discuss that. And I don't really have an expectation of monotonic dose response, because from what we've seen in the whole body of evidence about BPA is that the effects are often non-linear, so that's yet another challenge. And then regarding the key characteristics, my question again for the people who have spent a lot of time with that literature and whose expertise is in that area is where is their strong evidence in exposed humans, if that exists?

So we'll go ahead and open it up to the rest of the Committee now.

Okay. Good. Dr. La Merrill.

COMMITTEE MEMBER LA MERRILL: Hello. Prior to the public comments, Dr. Eastmond and I were discussing the malignant lymphoma data and I was able to confirm that in the 103-week feeding study in BPA-treated male B6C3F1 mice, it was not rats. It was mice. And the NTP 1982 study, the incidence of malignant lymphoma alone, as well as the combination of malignant lymphoma and lymphocytic leukemia combined was significantly increased in the low

dose group by pairwise comparison.

We also have evidence that the leukemia and the male F30 -- or excuse me, 344 rats of the NTP 1982 study had a significantly increasing trend of leukemias at 0.02 p-value. Their high dose group pairwise comparison was based on 23 out of 50 leukemias in the high dose group versus 13 out of 50 leukemias in the controls.

And in the CLARITY Study, the male Sprague-Dawley rats of NCTR substrain had one granulocytic leukemia observed in each dose group at 2.5, 25, and 25,000 micrograms per kilogram per day of bisphenol A, but not in the others, and that was considered a rare tumor. So we've got two independent rat studies and one that have leukemia. There was a mouse study with male B6C3F1s that had the leukemia as not significant with 0 out of 44 observed in the control group, 1 leukemia in the 1,000 parts per million group, and 2 leukemias in the 5,000, but that increasing leukemia incidence did not reach significance. So we have two independent rat studies for that.

And then with respect to the lymphoma study, we have the NCTR rats in the two-year observation period also having an increase in malignant lymphoma in the 25 milligram per kilogram group at point -- at p-value less than 0.05. And that was an increasing trend that was

significant at a p-value of less than 0.01 in the CLARITY Study. And this is an uncommon neoplasm across SD rat strains.

And in addition to that comment I made earlier to clarify about the male B6C3F1s having an increased malignant lymphoma, so we have two malignant lymphomas -- or, excuse me, two strains -- or two species with malignant lymphomas. The other malignancy that was brought up was the lung metastasis of the mouse mammary cancer model ErbB2, which is highly relevant to human breast cancer as a HER2 positive model. And they found that the 2.5 exposure group for BPA had over 25 percent of mice with lung metastases, whereas their control looked like it was maybe about five or six percent with lung metastases, and just summarizing a bar graph that they provided in that in Jenkins et al. November 2011 paper. And the BPA 25 dose group also had a percent of lung metastases at over 15 percent, so in comparison to about six percent or so in the controls. And those two dose groups were significantly different from the controls.

COMMITTEE MEMBER LOOMIS: Thank you.

I'll just go through the other members of the committee in the order in which I see their raised hands on my screen. So Dr. Eastmond, you're next.

I think you're muted.

I can't hear you.

Still can't hear you. You're muted.

COMMITTEE MEMBER EASTMOND: Unmute. Okay. Can you hear me? I've lost my screen.

COMMITTEE MEMBER LOOMIS: Now, I can.

COMMITTEE MEMBER EASTMOND: But basically -- so as pointed out, there's a marginal increase in leukemias and lymphomas that occurred at the low dose in the NTP 1982 study. It was not increased at the higher dose and it was not a significant trend. So if you look at the abstract of the NTP bioassay, and let me quote, in male mice, there was an increased incidence in leukemias or lymphomas, 2 of 49, 9 of 50, 5 of 50, but this increase was not statistically significant.

And then they're end -- so we can get into more details if you want, but that's -- essentially that's what the -- actually bioassay itself, the abstract says of the NTP bioassay. And I hope I can get the picture back here somehow.

Am I still on?

COMMITTEE MEMBER LOOMIS: Yeah, we see you.

COMMITTEE MEMBER EASTMOND: Okay. I can't see anyone.

COMMITTEE MEMBER LOOMIS: Okay. Well, I'm going to ask you a question anyway.

COMMITTEE MEMBER EASTMOND: Okay.

COMMITTEE MEMBER LOOMIS: In my preliminary remarks, I did allude to numerous observations that many effects of BPA seemed to be non-linear. So does the lack of a statistically significant trend still bother you knowing that?

COMMITTEE MEMBER EASTMOND: Actually, it does in this case. The real concern about the non-linearity of bisphenol A is brought up really in the low dose region, where people are concerned about non-monotonic effects. These are clearly in the high dose region, high and very high. So the fact that you don't have a clear dose response, for me, is kind of a different subject here entirely, because we're not in that portion of the dose response curve.

COMMITTEE MEMBER LOOMIS: Yeah. Thanks.

Okay. Other members of the Committee? I don't see any other raised hands.

So any interest in further discussion or questions for the discussants before we move on to a decision?

COMMITTEE MEMBER EASTMOND: Dana, I'm going to log off and log back on, because I can't see anything at the moment. It's very peculiar.

COMMITTEE MEMBER LOOMIS: Okay. We see a couple

of hands coming up, Dr. McDonald and then Dr. Mack.

COMMITTEE MEMBER McDONALD: Great. Yeah, one of the public comments by Robyn Prueitt sort of reminded me of a comment I wanted to make earlier on the historical controls in the CLARITY Study. I'm really not convinced that we have relevant historical controls for that study and it sort of makes me leery about the whole rare tumor analysis.

You know, OEHHA had nicely summarized three data sets of normative data to compare. And they've really talked about the strengths and limitations. But, you know, some of that date is outside the EPA recommended five-year window. And what's really concerning most to me is that the CLARITY studies were fully gavaged studies. I mean the dams were dosed by gavage, the early postnatal life, which is really stressful to the young animals was gavage, as well as gavaged through adulthood.

However, the historical controls, included animals from non-gavage dosing or from studies that had mixed gavage, dietary, and drinking water. I think it should be noted that FDA in their public comments to this Committee also highlighted the quote inappropriate application of historical control data, and ACC also commented to this effect.

You know, FDA was mostly concerned about genetic

background. And they also were really pointed to the differences in the rodent diet. Anyway, I just -- I just feel that the rare tumor analysis, at least from the CLARITY Study, should be sort of given less weight towards our clearly shown criteria.

DIRECTOR ZEISE? Hi, Dana. Now you're muted.

COMMITTEE MEMBER LOOMIS: So I am.

Dr. Mack, you're up next.

CHAIRPERSON MACK: Actually, I put my hand up just because I want to push Joe Landolph to give us his bottom line. You asked the three of them to do so and I only heard from one.

COMMITTEE MEMBER LOOMIS: Very good.

Dr. Landolph has his hand up and you're next.

And you're still muted, Dr. Landolph. So if you're speaking, we can't hear you.

COMMITTEE MEMBER LANDOLPH: Sorry. Can you hear me now?

COMMITTEE MEMBER LOOMIS: Yes.

COMMITTEE MEMBER LANDOLPH: Okay. Sorry. Yeah, I read this 600-page document a number of times over. And it's pretty interesting. It reminds me of the way I was trained growing up, you know, as a scientist. And the doggone thing is metabolized. It's glucuronidated. It's metabolized and epoxides are formed, free radicals are

formed. It's genotoxic. Dr. Besaratinia indicated in that section that I also read that the epigenetic effects are occurring. They're very complicated, but they do occur and that's another route to carcinogenesis. Oxidative stress, Dr. McDonald covered pretty nicely. There's chronic inflammation.

So I think this is a very complicated chemical. I think it operates probably through a number of different mechanisms to cause carcinogenesis. I don't think we've, by any means, settled that yet, but it's got a lot of potentially carcinogenic mechanisms.

Yeah, the animal data -- there's a couple studies I didn't like, because they had high backgrounds, like one had 13 in the controls. But there is also a lot of animal data there that's positive, and some of it is statistically significant for trend tests or pairwise comparisons et cetera. In fact, I was reading it into the record on purpose to refresh people's memories about the enormous amount of work that the OEHHA had done in formulating this document and all the things they had found. And I don't think they operated with a lot of biases. I think they just put things together. I was trying to drag them out and was kind of stopped from doing that.

So this looks like a classical chemical. It's

metabolized by P450. It's glucuronidated. You get oxidative stress. You get a bonus of epigenetic effects. You get some chronic inflammation, so -- and I -- I'm going to jump over to a safety issue for one thing. I really don't like the fact this chemical is all over the doggone place. And I think it behooves the chemical industry, and I say this as a -- as a chemist, which was my training, to be more responsible in doing environmental impact reports, before they put this stuff all over the place.

So I'm going to jump back now just to the science. I think this is a carcinogen. I think the animal data is sufficient for us to convict it as a carcinogen. And I think the mechanisms are beginning to become clearer. They're not totally clear yet. So I think that my training tells me I'm going to vote to make this a carcinogen just from my own personal vote and for my own personal reasons. And it's mutagenic too. So there's a lot of properties about this chemical that are deleter -- are dangerous and can contribute to carcinogenicity as well as the animal data.

COMMITTEE MEMBER LOOMIS: Okay. Dr. Mack, you still have your hand up. Did you want to say something else?

CHAIRPERSON MACK: Yeah, I still -- I'm not one

of the animal people, so perhaps you want to ask Dr. Bush first, but then I have a comment.

COMMITTEE MEMBER LOOMIS: Yeah. Dr. Bush has his hand up right now, so let's go right over to you.

COMMITTEE MEMBER BUSH: Yeah. Thank you. So I very much appreciate Dr. Landolph and Dr. La Merrill's perspective. I agree there is something here. There is -- there is some convincing data, but when I look at the animal data, I'm seeing things that are too inconsistent to warrant a definitive decision on this chemical at this time.

I mean, I'm going to remind everyone there is, as the HID document indicated, there's 4,000 hits, 1,300 references. There are no slam dunks here. The -- there is a lot of circumstantial data. How many more studies are going to be necessary to find this as being a carcinogen? I question many of the -- the veracity of many of these animal studies, the CLARITY Study being the pièce de résistance and that was inconclusive as far as I'm concerned.

Yes, there are some suggestions of association with some cancers. But in my mind, it doesn't meet the criteria for clearly invasive cancer.

COMMITTEE MEMBER LOOMIS: Thank you.

And Dr. Mack, you wanted to say something else

after that.

CHAIRPERSON MACK: Yeah. Speaking as an epidemiologist, I have a couple comments before -- which are not directly pertinent to the decision, but I'll make them first.

First comment is this stuff is ubiquitous and it's contact sensitive. That means that plastic of the wrong kind being touched has the potential to transmit the agent. So that means that if the agent does have danger, it's likely to be very wide spread danger.

Second point is that for breast cancer and for some of the other cancers it's very clear that early exposure is important. And early exposure to a touch sensitive agent is perhaps a real problem with children and children -- all the way up through puberty. So I'm especially concerned that we make the right decision about this particular agent.

And to me, now that I've said that, again that's not relevant to the decision, because that's not in the line that's required. But to me, given that this stuff is estrogenic, it magnifies estrogens. It affects estrogen receptors and progesterone receptors. And it looks to me, from what the animal people have said, that there's a real probability that it does, in fact, under some circumstances, cause neoplasms. So my inclination is to

say that this should be listed.

Thank you.

COMMITTEE MEMBER LOOMIS: Thanks, Dr. Mack.

Let's do a quick survey of the rest of the Committee, see whether anybody else wants to comment before we proceed to a decision.

Dr. Landolph, you still have your hand up. Did you have something else?

You're muted, but if you don't have anything else to say, you could just put your hands -- hand down.

COMMITTEE MEMBER LANDOLPH: Let's see. Yeah, I just had a small thing to say. I think Tom and I are fairly close on this issue. I expressed and I do share his worry about the ubiquity of this material. I think it's probably been made ubiquitous in an irresponsible manner and I'd like to see this kind of stuff stopped, if possible. That's outside the purview of our committee, I understand. But I think Tom and I are on the same page. I think this chemical looks like a carcinogen. It behaves like a carcinogen. It's metabolized and detoxified like a carcinogen would be. It's genotoxic. It's epigenetic -- posing epigenetic effects. So I again indicate that I'm fairly close to Tom's position and I'm going to vote to list it as a carcinogen for all the animal data and the other reasons I just enumerated.

COMMITTEE MEMBER LOOMIS: Okay. Thanks.

Dr. La Merrill, your comment.

COMMITTEE MEMBER LA MERRILL: I just wanted to ask a procedural question of the OEHHA staff. I've had the guidance criteria in front of me as I reviewed the literature and had this meeting with you all today. And I was just curious about the part -- obviously, there's some guidance on how do we look at the quality of a study, which I think have been addressed well. We've talked also about malignancies and malignant potential. There's a point in the guidance criteria where it suggests that we should look at tumors being found to occur in significant excess in the two genders of a species, or in two distinct species, or in two different experiments carried out in two different laboratories under different protocols.

And I'm just curious how that's been applied in the past. And, you know, particularly with respect to rodents and, you know, is there a sense in here that if you look at the further language there, it says that a single study in once species might be considered to provide sufficient evidence of carcinogenicity. Another part says evidence of carcinogenicity in animals derived from dah, dah, dah.

So I was wondering is there a feeling about whether or not something that's an animal carcinogen would

be listed as a carcinogen? I'm just curious about the role of the inadequate human versus the animal data/mechanistic data.

Thank you.

COMMITTEE MEMBER LOOMIS: So would the staff like to answer that question? Maybe Lauren's --

DIRECTOR ZEISE: Yeah, why don't I -- you know, this is -- just I want to start by saying this criteria was developed by the Committee and has been used by the Committee. So it's -- it's the Committee's criteria that were developed in Committee process.

And the Committee has already listed a number of chemicals based on animal evidence alone, so that has happened. And I guess what I would -- and potentially -- I don't know if someone else from OEHHA wants to raise an issue, but it might make sense to -- Dr. Mack was involved in developing these criteria, so with respect to some of the points you raise, Michelle, I wonder if Dr. Mack would like to weigh in.

CHAIRPERSON MACK: My computer is not working well, so I can't raise my hand, but you wanted me to comment on her question.

COMMITTEE MEMBER LOOMIS: Yes.

DIRECTOR ZEISE: Yeah, particularly the animal.

CHAIRPERSON MACK: Well, first of all, the animal

description of the two species, two sexes, good studies, rare tumors, those aspects are all pretty standard. And Joe I think played a role in revising anything that I wrote with respect to the criteria.

With respect to the no human but only animal, this was written with the recognition that human data is, first of all, very difficult to get, and epidemiologic data is always suspect, and it takes a really lucky circumstance to be able to get completely convincing human data.

Second of all, the actual wording of the Proposition 65 did not refer to humans. It said causes cancer. And we've judged several different compounds to be carcinogenic tentatively without any good human data, for the obvious reason that there was none and would not be any, but the animal data was very convincing.

So in this case, the animal data is not terribly convincing, but it exists. And in light of the other circumstances, especially the carcinogen -- the -- I'm sorry, the carcin -- carcinogen criteria, I don't have any problem with what I told you before.

Does that answer your question, Lauren?

DIRECTOR ZEISE: Yeah, thanks.

COMMITTEE MEMBER LOOMIS: Thank you, Dr. Mack. That's very helpful.

Dr. McDonald, one more comment.

COMMITTEE MEMBER McDONALD: Yeah, I just wanted to add a real quick point. I put my hand up when I heard about the ubiquity comment. Just -- I don't think it's been said today, but bisphenol A already appears on the Prop 65 list for repro and development. So I just want to make -- you know, make it clear that this should be focused on the cancer and not whether or not it should be listed.

COMMITTEE MEMBER LOOMIS: Thank you.

Now, are there any members of the Committee who haven't spoken yet who have a comment or question before we move to vote?

Dr. Wang.

COMMITTEE MEMBER WANG: So I hate to bring us back, but can some -- can someone from the OEHHA staff just remind me why the CLARITY data were reana -- I mean, I know that there was a comment made that some studies were reanalyzed. I mean, it still bothers me a little that the different results presented from the original report. I mean, there are a number of points made in the FDA document that I would -- it would be helpful for me to hear, you know, somewhat a summary of a rebuttal.

DR. SUN: Dr. Loomis, if it's okay, I can say a few words.

COMMITTEE MEMBER LOOMIS: Yeah, please do.

DR. SUN: Yes. Thank you, Dr. Wang, for the comment. I can say a few things regarding the FDA comment. And our biostatistician can chime in as well. I just want to clarify regarding the historical control critique. The FDA comment gave us, they pointed out that the Charles Rivers and the NTP -- the two second databases are inappropriate to be used. It seems too that they prefer the NTP 2008 and 2010 database. Whereas, in fact, our document, we use a more stringent criteria. So the rare tumor needs to fulfill the criteria for all three of these databases to be considered rare. So rare tumor is defined as less than one percent occurrence. And we only presented those that are not shown seen in concurrent controls. So that's the point.

And regarding the statistical test that OEHHA performed and how they're different from the NTP and NCTR reports, I'd like to ask Rose Schmitz to say a few words. But I'll start by saying that it is OEHHA's practice to use the effective number when they are available. In all the past HIDs, we would do this analysis when the data are available to us.

So Ms. Schmitz, are you available to talk?

MS. SCHMITZ: Sure. Can you all hear me?

COMMITTEE MEMBER LOOMIS: Yes.

MS. SCHMITZ: Okay. Yeah. So as Dr. Sun pointed out, one reason why there might be a discrepancy between the -- say a p-value or, you know, some significant result in what's presented in the hazard identification document versus in the report is that we use effective number when we can. So we're actually looking at the original animal data and taking into consideration when each tumor of that type was first observed and what animals were actually alive at the time of the first occurrence of the tumor, and what animals were examined at the site. You know, for various reasons sometimes a tissue can't be examined and so those animals would also be excluded from the denominator as would animals who didn't survive until the occurrence of the first tumor. So I think, does that -- does that answer your question about why the results may be a little bit different?

COMMITTEE MEMBER LOOMIS: Does that answer your question?

COMMITTEE MEMBER LA MERRILL: Can I ask Rose just a clarifying question on her last point?

MS. SCHMITZ: Um-hmm.

COMMITTEE MEMBER LA MERRILL: Rose, when you said the you also exclude animals that didn't have -- survive until the first tumor, do you mean an animal that died at a tumor-free state or do you mean in the cohort, like if

it's incident -- if the whole cohort is incident free?

MS. SCHMITZ: Yeah. So we look at for each tumor site, so suppose we're looking at, you know, lymphoma in male rats or something or in one experiment we're going to look at when the tumor was first observed in any dose group within that experiment and then any animal at any dose group who didn't survive until the first occurrence of that tumor would be removed from the denominator, does that make sense?

COMMITTEE MEMBER LA MERRILL: (Nods head).

COMMITTEE MEMBER LOOMIS: Does that answer the questions?

COMMITTEE MEMBER WANG: (Thumb up).

COMMITTEE MEMBER LOOMIS: Hearing no further comment, we have entered our last hour, so we do need to move along. And so with that in mind, I want to say if any member of the Committee is not prepared to vote now and needs more discussion before we move on? If you feel like we need to talk about it some more, please speak up or raise your hand, otherwise we'll move on.

Okay. I am not seeing a request for further discussion. So let's proceed to vote on the listing decision. So the question before the Committee is specifically this, has bisphenol A been clearly shown through scientifically valid testing, according to

generally accepted principles to cause cancer?

So I'll now call on each member of the Committee to vote and we'll record your votes. So we're going in alphabetical order.

Dr. Besaratinia, how do you vote?

Can't hear you.

COMMITTEE MEMBER BESARATINIA: I'm sorry. I said my vote is no.

COMMITTEE MEMBER LOOMIS: Dr. Bush?

COMMITTEE MEMBER BUSH: A quick comment. I very much want to say yes. I don't work for the plastics industry. I appreciate what Dr. Landolph and Dr. Mack have said. My concern is that this does not meet the scientific threshold. No other authoritative body has indicated that BPA is a carcinogen. Our own FDA says that it isn't. My vote is no because of that.

COMMITTEE MEMBER LOOMIS: Dr. Crespi, how do you vote?

COMMITTEE MEMBER CRESPI: My vote is also no. And Dr. Bush summarized what my sentiments and my thoughts are. I just feel like it's not seeing the threshold of clearly shown -- evidence clearly showing. And yeah, so I'll leave it there.

COMMITTEE MEMBER LOOMIS: Dr. Eastmond, your vote please.

COMMITTEE MEMBER EASTMOND: My comments are similar to those of Dr. Bush and Dr. Crespi. No. I just don't think there's sufficient evidence yet.

COMMITTEE MEMBER LOOMIS: Yeah. Dr. La Merrill

COMMITTEE MEMBER LA MERRILL: Yes.

COMMITTEE MEMBER LOOMIS: Dr. Landolph.

COMMITTEE MEMBER LANDOLPH: Yes, for all the reasons I already enumerated.

COMMITTEE MEMBER LOOMIS: Dr. Loomis votes no for reasons similar to those articulated by Dr. Bush. And I will say, I am concerned about this ubiquitous chemical, but I just don't think the data are there to list it at this point.

Dr. Mack?

CHAIRPERSON MACK: Yes.

COMMITTEE MEMBER LOOMIS: Dr. McDonald?

COMMITTEE MEMBER McDONALD: I vote no for the same reasons stated earlier.

COMMITTEE MEMBER LOOMIS: Dr. Stern?

COMMITTEE MEMBER STERN: I'm going to say yes for the reasons Dr. Mack and Landolph explained. I understand the concern that it's not a clear -- the evidence is not clear as far as the carcinogens, but I think the key characteristics are convincing. And even though the epidemiological data is not as informative as we want it

to be, I'm concerned about a couple of studies that were well done and report the positive association. I feel with more time, we'll see that more of those may show up. So I'm concerned about this.

COMMITTEE MEMBER LOOMIS: Dr. Wang, your vote, please.

COMMITTEE MEMBER WANG: I'm going to say yes, mostly because I'm convinced by the mechanistic data and I don't -- I don't think it needs to satisfy every single Component, so I don't want there to be sufficient human data before we make a decision.

COMMITTEE MEMBER LOOMIS: Okay. Thank you. The Committee has voted, and as I count it, there were five yes votes. So, that is not enough to add the chemical to the list. That we would require six votes. And I'll ask Dr. Gilson or whoever on staff is counting votes to verify what I've just said.

DR. GILSON: Yes, that's correct.

COMMITTEE MEMBER LOOMIS: Okay. So BPA won't be added to the list at this time. However, you know, given the concerns of the Committee and comments that have been made about the current state of the evidence, I can imagine this one coming back at some future time as evidence continues to accumulate.

So we'll move on to the next item, that is the

consent item, update on the California Code of Regulations Title 27, Section 27000, a list of chemicals which have not been adequately tested as required. So this is one of the duties of the Committee to review this question and to affirm the changes in response to submissions to the Department of Pesticide Regulation. U.S. EPA has indicated there are no changes. This is basically a ministerial duty of the Committee, in that we rely on information provided to OEHHA by the Department of Pesticide Regulation and the U.S. EPA in order to identify the chemicals that need to be added or removed to this Section 27000 list.

And so at this stage, I'll invite Julian Leichty to give the staff presentation on this item.

MR. LEICHTY: Thank you.

(Thereupon a slide presentation).

MR. LEICHTY: All right. So thank you for that, Dr. Loomis. Proposition 65 requires the State to publish and update annually a list of chemicals that are required to be tested under State or federal law for carcinogenicity or reproductive toxicity and that have not yet been adequately tested as required. This can be found in Title 27, Section 27000 of the California Code of Regulations and is commonly referred to as the Section 27000 list, separate and distinct from the Proposition 65

list of chemicals known to cause cancer, reproductive toxicity. This Section 27000 list has no regulatory impact. It does not require that any testing be done. Rather, it's a source of information concerning chemicals that need further testing pursuant to State or federal law.

To update the list, OEHHA requests information from the California Department of Pesticide Regulation and the U.S. Environmental Protection Agency's Office of Pollution Prevention and Toxics and Office of Pesticide Programs each year.

This year, OEHHA staff reviewed these responses and identified one recommended change to the Section 27000 list, removal of bromadiolone.

Based on information received from DPR, data requirements for this compound have been fulfilled and further carcinogenicity and reproductive toxicity testing are not required. The letter from DPR along with additional background, response letters from U.S. EPA, a mock up of the proposed change are all -- and are all available in the staff report provided to the Committee and posted online. The proposed change is also shown on this slide.

As Dr. Loomis mentioned, this is a consent item and a ministerial duty of the Committee, in that the CIC

and DARTIC us the information provided by DPR and U.S. EPA to identify the chemicals that need to be added to or removed from the Section 27000 list. We ask the Committee members to vote in favor of the proposed change, so we can update the list.

And I'll now turn it back to Dr. Loomis for the vote.

COMMITTEE MEMBER LOOMIS: Okay. So this is a consent item. If there are any clarifying questions, we can take those now.

I'm not seeing any, so we'll proceed to a vote. This does require a roll call vote. So the question we're voting on is should Section 27000 of the Title 27 of the California Code of Regulations be amended as indicated in the report?

So again, we'll go through the Committee members in alphabetical order.

Dr. Besaratinia?

Can't hear you if you're speaking.

COMMITTEE MEMBER BESARATINIA: I'm sorry, is there an abstinent vote for this?

COMMITTEE MEMBER LOOMIS: I couldn't hear your question. Sorry.

COMMITTEE MEMBER BESARATINIA: Oh, I'm sorry. Is there an abstinent vote on this? I'm assuming that it

would amount to a no.

COMMITTEE MEMBER LOOMIS: You can -- you can abstain, if you wish, or vote no. You can do whatever you want.

COMMITTEE MEMBER BESARATINIA: Yeah. Unfortunately, I haven't had the chance to read this, so -- study this, so I'm not going to vote on this.

COMMITTEE MEMBER LOOMIS: Okay. So you're abstaining, is that correct?

COMMITTEE MEMBER BESARATINIA: Yeah. Yeah.

COMMITTEE MEMBER LOOMIS: Okay. 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?

Don't hear you.

COMMITTEE MEMBER LANDOLPH: Oh, Yes. Yes.

COMMITTEE MEMBER LOOMIS: Yes.

COMMITTEE MEMBER LANDOLPH: Yes.

COMMITTEE MEMBER LOOMIS: Thanks. Got it.

Loomis votes yes.

Dr. Mack?

CHAIRPERSON MACK: Yes.

COMMITTEE MEMBER LOOMIS: Dr. McDonald?

COMMITTEE MEMBER McDONALD: Yes.

COMMITTEE MEMBER LOOMIS: Dr. Stern?

COMMITTEE MEMBER STERN: Yes.

COMMITTEE MEMBER LOOMIS: And Dr. Wang?

COMMITTEE MEMBER WANG: Yes.

COMMITTEE MEMBER LOOMIS: Okay. So we have more than six yes votes, so the change is affirmed.

Okay. Assuming the staff agrees with my tally of the votes, we'll move on to staff updates.

The next item is an update of the proposition listings, regulations, and litigation that have taken place since the last meeting of the Committee. And again, Julian Leichty will present this.

(Thereupon a slide presentation).

MR. LEICHTY: Thank you.

So I'll be providing an update on Proposition 65 development since the last CIC meeting. I'll start by going over the chemicals or endpoints added to the Proposition 65 list or under consideration for potential listing, as well as data call-ins requesting information on chemical toxicity. Then I'll review adopted and proposed safe harbor levels.

After that, I'll turn it over to our Chief Counsel Carolyn Rowan to provide an update on other regulatory actions and significant Proposition 65 litigation.

Next slide, please.

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MR. LEICHTY: Since the Committee's last meeting, five chemicals have been added to the Proposition 65 list, PFNA and its salts were added as reproductive toxicants and trimethylolpropane, triacrylate, technical grade, tetrahydrofuran, methyl acrylate, and 2-ethylhexyl acrylate were added as carcinogens.

Additionally, the cancer endpoint has been added for the following chemicals previously listed for reproductive toxicity, perfluorooctane sulfonic acid and its salts and transformation and degradation precursors following the Committee's decision last year, and Perfluorooctanoic acid, PFOA.

Next slide, please.

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MR. LEICHTY: Four potential cancer listings are under consideration antimony and trivalent compounds, 1-bromo-3-chloropropane, 1-butyl glycidyl ether, and Glycidyl methacrylate are under consideration for listing administratively under the Labor Code mechanism.

The DARTIC's -- and next, the DARTIC's 2022 meeting was held in October and consisted of a workshop on zebrafish data in development and reproductive toxicity health hazard assessment. No listing decisions were considered. Early in the year, OEHHA issued a data call-in on bisphenol S to request information related to its reproductive toxicity. This information is used in the preparation of the hazard identification document.

Next slide, please.

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MR. LEICHTY: Since the Committee's last meeting, cancer no significant risk levels were adopted for oral and inhalation exposures to 1,3-dichloropropene, (1,3-D), and became effective October 1st, 2022. OEHHA also proposed a no significant risk level for antimony trioxide and is reviewing comments received on the proposal.

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

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CHIEF COUNSEL NELSON ROWAN: Thanks, Julian, and hello again. I have a few updates on Proposition 65 regulations and litigation.

Since the Committee last met, OEHHA has adopted a number of new safe harbor warning regulations. The safe harbor warning for cannabis smoke and delta-9-THC exposure became effective on October 1, 2022. Those regulations

provide non-mandatory specific safe harbor exposure warning methods and content for retail products that can expose consumers to cannabis smoke or delta-9-THC via inhalation, ingestion, or dermal application. And also for environmental exposures to cannabis smoke, and delta-9-THC businesses where smoking of cannabis, or vaping, or dabbing of delta-9-THC occurs.

The content identifies the chemical route of exposure and provides specific information to consumers about the risk of using cannabis products including cancer, and while pregnant, the impact exposures can have on an unborn child.

OEHHA has also adopted a new safe harbor warning for glyphosate. That regulation provides safe harbor guidance for businesses that cause exposures to glyphosate from consumer products that require a warning. The warning language reflects the range of opinion by authorities on the carcinogenicity of glyphosate. It was approved on September 1 and will become effective the first of the year.

OEHHA has also adopted a new safe harbor warning for acrylamide in food. And that regulation provides safe harbor warning content for businesses that cause exposures to Proposition 65 listed chemicals in foods and beverages that require warnings. OAL approved that regulation on

October 26th and it will become effective the first of the year as well.

Also, on November 3rd, OEHHA resubmitted a final regulatory package to the Office of Administrative Law for a proposed regulation regarding exposures to acrylamide in cooked and heat processed foods. This regulation provides that a manufacturer of a food does not expose an individual to acrylamide within the meaning of proposition of 65, if the manufacturer reduce the levels of acrylamide to the lowest level currently feasible as defined in the proposed reg. It also sets forth concentration levels in foods that are deemed to comply and OAL is currently reviewing the final package.

Any questions on those regulation updates?

Okay. Next slide, please. I also have few litigation updates for you.

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CHIEF COUNSEL NELSON ROWAN: First, the Physicians Committee for Responsible Medicine versus Newsom case. This is a challenge to OEHHA's decision not to list processed meats. And we're in the discovery stage right now. Oh, I see -- I think I see a hand there.

Dr. Eastmond, did you have a question?

COMMITTEE MEMBER EASTMOND: Probably more relevant after you finish this part.

CHIEF COUNSEL NELSON ROWAN: Okay. So as I was saying, we're in the discovery stage right now for the PCRM versus Newsom case.

There's also the National Association of Wheat Growers versus Bonta litigation. That case involves a First Amendment challenge for the glyphosate warning requirement. The challenge centers on the argument that because only the IARC have identified the chemical as a carcinogen and other agencies, including U.S. EPA, have said it is unlikely to be a human carcinogen, there can be no warning with -- that would not be misleading. So the district court determined that required warnings for glyphosate exposure violated the First Amendment, limits on compelled speech. And the Attorney General's office appealed that to the Ninth Circuit. The case was on hold while OEHHA prepared a new regulation. And now that OEHHA's new regulation is final, the parties recently filed supplemental briefs in the Ninth Circuit addressing the adoption of that new reg. So now the court will decide whether to send the matter back to the district court or proceed to oral argument.

There's also the Cal Chamber versus Bonta case, which involves another First Amendment challenge, which in that case is a challenge to the safe harbor warning for acrylamide. The district court previously granted a

preliminary injunction and the Ninth Circuit affirmed. That case is back with the trial court now. Although, there's been little activity since a new judge was assigned, the Attorney General's office recently filed a notice informing the court of our new acrylamide warning regulation.

And finally, in the Council for Education and Research on Toxics versus Starbucks case, this is the case where CERT challenged the OEHHA regulation on coffee as part of a long-running enforcement action. Recently, the case was argued in September and last month the Court of Appeal issued a decision affirming the trial court's decision upholding the coffee regulation. CERT recently filed a petition for review with the California Supreme Court. So we'll see what happens with that.

And that's -- those are my updates on significant Proposition 65 litigation.

Dr. Eastmond, did you have a question?

COMMITTEE MEMBER EASTMOND: Yeah, I did. Well, it's more of a housekeeping thing. But over the last 10 years or so, we've been asked to hang on to various documents related to the various litigation. We never seem to be told when we can get rid of them. It would be helpful if you could let us know which ones we need to still hold on to and which ones we can throw away.

I mean, send it out later, because I know this is not off the top of your head. But it would be useful to -- at some point be able to get rid of some of these.

CHIEF COUNSEL NELSON ROWAN: Sure. Yeah, I'd have to check the litigation hold list and -- but we can -- we can provide you an update on that.

COMMITTEE MEMBER LOOMIS: It looks like there's another question.

COMMITTEE MEMBER BESARATINIA: Can I -- can I ask a quick question. Out of curiosity, I just want to see what was the ruling on the fourth item regarding the warning for acrylamide for coffee? And I see that it was against Starbucks and how is it going to affect other franchises?

CHIEF COUNSEL NELSON ROWAN: So the ruling in that case, the CERT versus Starbucks case, upheld OEHHA's coffee regulation. So OEHHA had adopted a regulation essentially saying that chemicals formed in coffee from the roasting and brewing process don't require a warning under Proposition 65, because of special circumstances related to the chemical mixture of the coffee. So that was upheld in this Court of Appeal decision. So it -- that would mean that warnings are not required.

COMMITTEE MEMBER BESARATINIA: Okay. Thank you.

COMMITTEE MEMBER LOOMIS: Are there any more

questions?

CHIEF COUNSEL NELSON ROWAN: Okay. Thank you.

COMMITTEE MEMBER LOOMIS: Thanks, Carol. Thanks, Julian.

We'll move to the last agenda item then and go back to Director Lauren Zeise. But before we do that, I would just like to thank Lauren and the entire OEHHA staff for really a Herculean effort to put together all of the vast material for this meeting. It's -- it was a huge job and they've really done admirably with that. And I see members of the Committee nodding and clapping their hands. So thanks to all of you for really great background work.

So, Lauren, your turn to summarize what we've done and wrap-up the meeting.

DIRECTOR ZEISE: Okay. All right. So the Committee considered at length and deliberated at length on whether to add bisphenol A to the Proposition 65 list as a carcinogen. By a vote of five yes and six no, the Committee declined to list bisphenol A.

The Committee also voted on a consent item. And they voted to remove bromadiolone from the Section 2700[SIC] list that's published in the California Code of Regulations. The vote was 10 yes, one abstention. And so the chemical will be removed from that list.

So I think I want to give thanks and

acknowledgement for the extensive work that the Committee did to prepare for this meeting. It was a huge document, very complex. It took a lot of time and effort I'm sure to work through this document. And it was pretty obvious that the Committee prepared and considered it very carefully, so we really appreciate your effort on that.

And, of course, I want to add my thanks to the staff for all of their work to put that document together, and also to the audience and commenters today.

We do have a final item. And that is that Dr. Mack -- Dr. Thomas Mack has informed us of his intention to resign from the Carcinogen Identification Committee after his 30 years of service as Chair of the Committee.

It's a tremendous service to the People of California.

I'm going to try not to get choked up.

(Laughter).

DIRECTOR ZEISE: So Dr. Mack came to the Committee in -- early in 1993, he began as Chair of the CIC. So this is Dr. Mack's last meeting. And I thought -- we wanted to step back and take some time and -- you know, for the Committee members to express their thanks to Dr. Mack and -- that wish to and that have -- and wish him well and also for staff at OEHHA.

I thought maybe a little history lesson first.

And that's that the Governor's -- the Proposition 65 statute places the responsibility of the Governor -- on the Governor to cause the Proposition 65 list to be published. And as you all know, you're all appointed by the Governor.

And originally, under the Deukmejian administration, when we started this, there was one committee. It was called the Scientific Advisory Panel, the SAP. And they considered whether to put carcinogens on the list and also developmental and reproductive toxicants. So we had that committee. Proposition 65 is kind of a complex -- very complex. The evidence continues to become more complex. And so under the Wilson administration, the decision was made to make two committees, the Carcinogen Identification Committee and the Developmental and Reproductive Toxicant Identification Committee. So we have two committee meet -- to committees to add chemicals to the list.

So in 19 -- early in 1993, the question was, well, you know, with all the attention on Proposition 65 and a number of things that were going on in the background, it was really important to get an esteemed -- esteemed committees together. And, of course, this Committee has continued in that.

So we were looking for a Chair for the Committee.

And, you know, Dr. Mack had been part of the a lot of work at IARC, the supplement 7, which re -- basically did a lot of well-considered -- I can't -- I can't remember how many carcinogens, but relooking at a large number of carcinogens and Dr. Mack was a rapporteur for some of the IARC monographs. And he had created this LA Cancer Registry and also the Registry of -- International Registry and California Registry of Twins to study chronic diseases and had a tremendous notoriety in publication records, so we asked Dr. Mack. And so he agreed.

I remember the meeting with Dr. Mack very well, because I had not -- not much before that point in time given birth to my son and I brought him down to LA and he stayed with my parents and I went to meet Dr. Mack. And he's now 30. We just celebrated his 30th birthday.

So anyway, Dr. Mack agreed. You know, esteemed physician and epidemiologist, so he served under five governors. He -- you know, Pete Wilson, Gray Davis, Arnold Schwarzenegger, Jerry Brown, and Gavin Newsom. So all five governors. And I think it's a testimony to Dr. Mack's skill as a -- and brilliance as a Chair and epidemiologist to have been able to span as Chair of the CIC all those different administrations.

So, you know, and all the while also you all now see how much work this committee can be ahead of a

meeting. And, of course, Dr. Mack has had this very esteemed career at USC as well. So I think I can speak on behalf of the -- this administration, California EPA, and OEHHA in thanking you, Dr. Mack, for your long service to the -- to the State and as Chair -- as Chair of this Committee. So just thank you so much. Really appreciate it. And --

(Applause).

DIRECTOR ZEISE: Yeah. And so I think I'll turn it over to Dana and you want to facilitate the Committee. I know a couple of staff have something to say as well and maybe Dr. Mack wants to close.

CHAIRPERSON MACK: Thank you very, Lauren and thank you for the --from the Committee. It's been a real honor and pleasure to Chair the Committee for 30 years. And I must say I've learned a great deal, not only from my fellow Committee members, but from the regulated community and from the staff. And I guess I should say that I've heard so many plaudits for the document that the staff prepared for this meeting. And I just want to say that it's not unusual. Every single meeting has an incredibly detailed and accurate document that it had to start out with. And it always amazes me how much better the staff is from the average epidemiologic study staff, because one would think that getting a secure job with the State might

make -- might make some concessions to quality. But if anything, it's the other way around. So I want to thank the OEHHA staff for 30 years worth of staff excellence.

And, of course, Joe, for example, has been there for 30 years as well. It's not only me. And I certainly have grown to appreciate the help of Joe, and of David, and of other members of the staff over the years. So thank you very much.

COMMITTEE MEMBER LOOMIS: Thank you, Dr. Mack. I know some other members of the Committee and perhaps of the staff would like to comment. And I'm going to use my seat as Acting Chair to start that off. And I'll just say, first of all, that doing anything for 30 years is a really impressive accomplishment, especially in a political environment like this. Surviving five different governors of both parties is quite a feat. It's been my honor to be Acting Chair for a couple of recent meetings. And I would just say that this public function of running a meeting is really only a small part of what the Chair does. And it has certainly given me an appreciation of the labor that Dr. Mack has devoted to this process for 30 years. I'm grateful for that and honored to have been able to help you.

So I invite other members of the Committee and the staff to --

CHAIRPERSON MACK: Thank you, Dr. Loomis.

COMMITTEE MEMBER LOOMIS: -- speak that wish to do so.

Okay Dr. McDonald, you first.

COMMITTEE MEMBER McDONALD: Yeah. Thank you.

As some of you may know, I started my professional career as a toxicologist at OEHHA in 1994 through 2005. I proudly served in the Cancer Unit working on Prop 65 issues and children's health guidance. I must admit my time at OEHHA seems very long time ago. Yet even then, Dr. Mack was the CIC member and Chair. And so as you write the hazard ID document, sometimes I feel I would view you as my audience for writing them even back then. And so I just recall from that time that you always ran a very good and tight meeting. And I truly find it amazing. You've served so long and so well in this committee. So Dr. Mack, thank you for your long service to the people of California.

COMMITTEE MEMBER LOOMIS: Dr. Landolph, you have your hand up.

CHAIRPERSON MACK: Thank you, Tom.

COMMITTEE MEMBER LANDOLPH: Let's see. Can you hear me? Not yet.

COMMITTEE MEMBER LOOMIS: Yes.

COMMITTEE MEMBER LANDOLPH: Yeah. Can you hear

me?

COMMITTEE MEMBER LOOMIS: Yeah.

COMMITTEE MEMBER LANDOLPH: Yeah. It's been a pleasure serving with you, Tom. We both joined the Committee about the same time and we've both survived five governors. And I'd have to say, you know, Tom is a fantastically, scientifically accomplished person and a superb epidemiologist. He can talk to basic scientists, no problem. He's taught me some significant epidemiology. I hope I've shared some basic science with him. Tom is fantastically honest, polite, fair, and open-minded. He always run the Committee -- he has run it by making sure everybody has a chance to get their say in.

And he taught me very early on, you don't need to know a mechanism of carcinogenesis to put a chemical on the Proposition 65 list. You just need to know that it does cause tumors in animals or in humans. And you can find the other mechanistic data out later. So, Tom, I've always enjoyed your fair and even handed manner of running a committee. Your politeness in letting everybody have their say.

And I think I've only seen you get mad twice in 30 years, and that was mild madness, not the -- you were irked, not really fuming mad, which I would have gotten in those circumstances. So thank you very much. It's been a

great pleasure being a colleague and a member of the Committee with you and it's been a pleasure working with you.

COMMITTEE MEMBER LOOMIS: Thanks. Thanks.

Dave Eastmond, you're next on my screen.

COMMITTEE MEMBER EASTMOND: Well, Tom -- I just want to say --

CHAIRPERSON MACK: Thank you.

COMMITTEE MEMBER EASTMOND: -- thank you very much for your leadership, your collegiality, and your friendship over the years. We'll miss seeing you at these meetings, but we hope you are doing other enjoyable things. Anyway, thanks again.

COMMITTEE MEMBER LOOMIS: Thank you.

On to Dr. Wang, you're next on my screen.

COMMITTEE MEMBER WANG: Well, I just want to say I'm really bummed that is my first and Dr. Mack's last meeting, so -- but I do want to thank you, Dr. Mack. I met you about just over 20 years ago. And through our collective work in lymphoma, I've gotten to know you. But of course, I knew about you before I joined the National Cancer Institute. And, you know, I think for -- speaking for us epidemiologists, I think when you see the name Dr. Mack, you sort of consider that as your Northern Star when it comes to method -- you know, epidemiologic methods.

So I just want to really thank you for the influence you've had in our discipline. And I look -- I hopefully look forward to seeing you in Los Angeles and continuing to do some work on lymphoma. But I want to thank you and really let you know how much, you know, we sincerely respect you as a person. You're just such a nice person, and especially your academic integrity.

So thank you.

COMMITTEE MEMBER LOOMIS: Dr. Bush.

CHAIRPERSON MACK: Thank you, Sophia.

COMMITTEE MEMBER BUSH: Yeah. Thank you, Tom, for your leadership over the last 10 years that I've been on the Committee. It's been a pleasure serving with you. My only regret is that we can't be in person doing this, so I can shake your hand and give you a hug. Thank you for your service.

COMMITTEE MEMBER LOOMIS: Dr. Stern.

COMMITTEE MEMBER STERN: Yes, I want to thank, Tom, for your years of service and Chair with the -- with the group that not only has been -- he started the Cancer Registry at USC, and he's been there for 30 years or more too, but he also is one of the founding members of our department, the department where I am, so it's an immense honor for me to be able to serve in this Committee together with you, Tom. I have learned a lot from your

comments here. And I just hope that moving forward, now that I'm the only epidemiologist from USC left in the Committee, that I can represent us well.

COMMITTEE MEMBER LOOMIS: Dr. Besaratinia.

COMMITTEE MEMBER BESARATINIA: Yeah, I would like to echo what Dr. --

CHAIRPERSON MACK: Thank you, Mariana. And I hope Argentina does well in the next couple days.

(Laughter).

COMMITTEE MEMBER STERN: I hope so too.

(Laughter).

COMMITTEE MEMBER BESARATINIA: Yeah. As I was just saying, I'd like to echo what Dr. Stern just said. I haven't had the pleasure of working with Tom on this Committee, but I am privileged to work at USC, the same department where Dr. Mack is. I haven't directly collaborated with him, but I have been working with his trainees who are pioneers in the field, which just tells you what a trailblazer he has been. And all they say about Tom is the greatest of the great thing. And I would appreciate his contribution and work, not only to this Committee, but also the work that he has done and continues to do at USC.

Thank you, Tom.

COMMITTEE MEMBER LOOMIS: And Dr. La Merrill.

COMMITTEE MEMBER LA MERRILL: Tom, I feel like I've had a great pleasure in joining this Committee under your leadership and really got to understand what it means to be a good leader, such an important endeavor, and also how the process works through your role here. And I'm really honored that we had time to overlap. And I wish you all the best in what you do next. So thank you very much.

COMMITTEE MEMBER LOOMIS: Okay. Vincent.

DR. COGLIANO: Thank you, Dana. I'd like to highlight the contribution Dr. Mack makes to this committee of experts by virtue of his international stature and reputation. A quarter century ago, while working at the other side of the country at the U.S. EPA, I became acquainted with Dr. Mack as a national expert on a variety of topics. We interacted on PCBs, at a saccharin workshop, and on other topics.

So I'd like say, Dr. Mack, your grand stature has enhanced the credibility and the reputation of the Proposition 65 program. And you have guided it in the compilation of the most comprehensive list of known and suspected chemical carcinogens. And this is an important scientific research for the State and the entire nation.

Thank you, Dr. Mack.

COMMITTEE MEMBER LOOMIS: Thanks, Vincent.

And Martha.

DR. SANDY: Yes. So as -- similar to Tom, I started in 1994 and that's when I met Dr. Mack as Chair of the CIC. It's been a pleasure. I want to thank you, Dr. Mack, for your many years of service to the People of California as a member of the Committee. And I also wish to thank you for your steady leadership over the years in your role as Chair of the Committee.

Dr. Mack has a no nonsense style. And he's always kept the Committee on track and focused on the issues related to hazard identification at each of their meetings. He also runs those meetings very efficiently making sure that we got through all the agenda items, even if, as it did happen occasionally, we had to delay, or shorten, or even sometimes even skip taking lunch.

So to sum up, I really -- I want to recognize Dr. Mack's significant scientific expertise and experience, particularly in the area of cancer hazard identification, which has been invaluable to the scientific work of the Committee.

Thank you, Dr. Mack.

COMMITTEE MEMBER LOOMIS: Thanks, Martha. Are there any other members of staff who'd like to comment before we close?

All right. I don't see any.

Are there any other issues we should talk about before adjourning the meeting? Lauren or members of the Committee anything?

DIRECTOR ZEISE: No, just underscoring, it's just been such a pleasure working with Dr. Mack over all these years, and we really wish him the best.

CHAIRPERSON MACK: You know, let me just say thank to everybody who commented. I don't know if I'm worthy of all those nice remarks, but it's certainly nice to hear them for the time being.

Bye-bye.

DIRECTOR ZEISE: Bye, yes.

COMMITTEE MEMBER LOOMIS: Thank you for your years of service. Really appreciate it.

Hearing nothing else, I think we can adjourn the meeting. Thank you all for a really thoughtful discussion today on a particularly challenging topic.

Great work.

(Thereupon the Carcinogen Identification Committee adjourned at 4:47 p.m.)

CERTIFICATE OF REPORTER

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

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

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

IN WITNESS WHEREOF, I have hereunto set my hand this 29th day of December, 2022.

JAMES F. PETERS, CSR
Certified Shorthand Reporter
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