VIDEOCONFERENCE MEETING

STATE OF CALIFORNIA

ENVIRONMENTAL PROTECTION AGENCY

OFFICE OF ENVIRONMENTAL HEALTH HAZARD ASSESSMENT

PROPOSITION 65

CARCINOGEN IDENTIFICATION COMMITTEE

ZOOM PLATFORM

TUESDAY, JUNE 13, 2023

10:00 A.M.

JAMES F. PETERS, CSR
CERTIFIED SHORTHAND REPORTER
LICENSE NUMBER 10063

APPEARANCES

COMMITTEE MEMBERS:

Dana Loomis, PhD, Chairperson

Ahmad Besaratinia, PhD, MPH

Jason Bush, PhD

David A. Eastmond, PhD

Joseph Landolph, PhD

Thomas McDonald, PhD, MPH

STAFF:

Lauren Zeise, PhD, 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

Jennifer Hsieh, PhD, MS, DABT, 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

APPEARANCES CONTINUED

STAFF:

Kiana Vaghefi, Proposition 65 Implementation Program

SPEAKERS:

Kathryn Guyton, PhD, National Academies of Sciences, Engineering and Medicine

Ivan Rusyn, Texas A&M University

ALSO PRESENT:

Jessica Ryman-Rasmussen, PhD, American Chemistry Council

INDEX

PROCEEDINGS

DIRECTOR ZEISE: Good morning, everyone and welcome to this June 2023 meeting of the Proposition 65 Carcinogen Identification Committee. Welcome to the Committee members, to our invited speakers, to staff, and to the public. This meeting is being held virtually. I'm Lauren Zeise. I'm Director of the Office of Environmental Health Hazard Assessment, or OEHHA. OEHHA is a department within the California Environmental Protection Agency and is the lead agency for the assessment of the health risks posed by environmental chemicals. And OEHHA is also the lead agency for Proposition 65 implementation.

Our first agenda item for today is the key characteristics of carcinogens and their use in hazard identification. OEHHA has been, for several years, using key characteristics approach in our hazard identification work. We're looking forward to the presentations of the invited speakers and to the discussions of the Committee. Today's conversation will help inform future hazard identification work at OEHHA. The second agenda item is on the analysis of tumor data from animal carcinogenicity studies. And staff will present our approach, the analysis of tumor data from animal studies and we are very much looking forward to the Committee discussion. For the third and final agenda item, staff will present updates on

various Proposition 65 regulatory and other activities. So for today, there won't be Proposition 65 listing decisions, no decisions are before the Committee today.

We'll be taking a 45-minute break around lunch time. And then we'll take a brief 15-minute break sometime in the afternoon. This meeting is being reported -- recorded and transcribed, and the transcript will be posted on OEHHA's website.

(Thereupon a slide presentation).

DIRECTOR ZEISE: So now I'll say a few words about how the public can comment during the meeting. So there will be an opportunity to provide public comment after the key characteristics agenda item and the analysis of tumor data item. And individuals who wish to make an oral comment at today's meeting are asked to join the Zoom by webinar. Information on how you can join the Zoom is shown on this slide. You go to the URL and register and you'll receive a link on how to join at the end of the registration process. And if you provided a working email address, you'll also receive an email with a link to join the webinar.

Those of you watching by CalEPA webcast will be able to watch the meeting, but you'll need to join the meeting by Zoom in order to comment. When requested by the Chair, individuals may queue to provide oral comment

by using the raise hand function. When your name is called, please unmute yourself, state your name -- state your name and affiliation if you wish. You're not required to state your name and affiliation, and then you can you provide your comment. And if you'd like to present slides during your public comment and have not already sent them, please email them now to Proposition -- to the address shown on the slide, p65public.comments@oehha.ca.gov. Public comment will be limited to five minutes per commenter.

Okay. So now I'd like to introduce the members of the Carcinogen Identification Committee. First, I just want to note that Drs. Crespi, Stern, and Wang are not able to join us today. But now we will introduce the participating members today. As I introduce you, if you could please turn on your camera, state your name and affiliation. So first, Dr. Ahmad Besaratinia.

COMMITTEE MEMBER BESARATINIA: Good morning. I'm Ahmad Besaratinia. I'm a professor at the Department of Population and Public Health Sciences at the University of Southern California.

Thank you.

DIRECTOR ZEISE: Thanks.

Dr. Jason Bush.

COMMITTEE MEMBER BUSH: Good morning, Lauren and

Panel members. Jason Bush, professor and Chair of the Biology Department at California State University, Fresno.

DIRECTOR ZEISE: Dr. David Eastmond.

COMMITTEE MEMBER EASTMOND: Good morning. Nice to be with you. My name is David Eastmond. And I'm a professor emeritus, University of California, Riverside.

DIRECTOR ZEISE: Dr. Joe Landolph.

COMMITTEE MEMBER LANDOLPH: Hi. I'm Joe Landolph, associate professor within the Departments of Molecular Microbiology and Immunology and Pathology. I'm also a member of the USC Norris Comprehensive Cancer Center at the University of Southern California in Los Angeles, California. And I study chemically-induced morphological and neoplastic transformation of mammalian cells.

DIRECTOR ZEISE: Okay. Dr. Dana Loomis.

Dana, you're -- you'll have to unmute.

CHAIRPERSON LOOMIS: It takes a long time to learn Zoom apparently.

(Laughter).

CHAIRPERSON LOOMIS: Dana Loomis, Director of the Plumas County California Public Health Agency.

DIRECTOR ZEISE: And Dr. Loomis will be serving as our Acting Chair today.

And Dr. Tom McDonald.

COMMITTEE MEMBER McDONALD: Good morning, everyone. Tom McDonald, Associate Research Director at the Clorox Company.

DIRECTOR ZEISE: Okay. Thank you. So welcome Committee members. We really appreciate your taking the time to participate in this meeting.

So now, I'd like to turn to OEHHA staff and introduce the staff. And similarly, I'd like to invite them to turn on their cameras as I do. So Carolyn Nelson Rowan, our Chief Counsel.

CHIEF COUNSEL NELSON ROWAN: Good morning.

DIRECTOR ZEISE: Vince Cog -- Dr. Vince Cogliano, Deputy Director for Scientific Programs.

And then from the Reproductive and Cancer Hazard Assessment Branch, Dr. Martha Sandy, Branch Chief.

DR. SANDY: Good morning.

DIRECTOR ZEISE: Dr. Meng Sun, Section Chief of the Cancer Toxicology and Epidemiology Section.

DR. SUN: Good morning.

DIRECTOR ZEISE: And then staff of the section that the Committee will be hearing from today, Dr. Jennifer Hsieh, staff toxicologist.

DR. HSIEH: Good morning, everyone.

DIRECTOR ZEISE: And Ms. Rose Schmitz, biostatistician.

MS. SCHMITZ: Good morning.

DIRECTOR ZEISE: And then from the Office of External and Legislative Affairs and Prop 65 Implementation Program, Dr. Amy Gilson, Deputy Director for External and Legislative Affairs.

DR. GILSON: Hello.

DIRECTOR ZEISE: Kiana Vaghefi.

MS. VAGHEFI: Yes, hello.

DIRECTOR ZEISE: Good morning. And Esther Barajas-Ochoa --

MS. BARAJAS-OCHOA: Good morning.

DIRECTOR ZEISE: -- analyst Prop 65 Implementation Program.

And I should note Kiana is our new Environmental Scientist in the Proposition 65 Implementation Program and this is her first meeting.

Okay. 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 the virtual meeting of this Committee.

Carolyn.

CHIEF COUNSEL NELSON ROWAN: Good morning. Thanks, Lauren. I just have a few points to make before we get underway today. First, a reminder that the Bagley-Keene Act applies to this meeting. That means that

all deliberations for the group should be conducted during the meeting and not on breaks, or at lunch, or offline. Please feel free to ask me or any OEHHA staff clarifying questions during the meeting. If we don't know the answer, we'll do our best to find out for you and report back.

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 legal questions.

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

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

DIRECTOR ZEISE: Okay. Thanks, Carolyn.

And with that, I'll turn the meeting over to Dr. Loomis the Acting Chair for the meeting today.

CHAIRPERSON LOOMIS: Okay. Thank you very much. Again, I'd like to thank Lauren and Carolyn for their remarks and welcome everybody, Committee members, members of the public who are joining, and the invited speaker -- speakers.

So with that, we're now ready to move on to the first agenda item on key characteristics of carcinogens and their use in cancer hazard identification. So to get

that started, I'd like to turn the floor over to Dr. Cogliano from OEHHA, Deputy Director of Scientific Programs.

(Thereupon a slide presentation).

DR. COGLIANO: Thank you very much, Dana. I'd like to add my welcome to the Committee and to thank you all for attending this morning and also for allowing me to speak about the key carcinogens.

Can people see my screen? I think so.

Yes. Okay.

So let me get the slide show. So the key characteristics, I want to -- the message I want to give you is that the key characteristics of carcinogens are based on a lot of research that's been done over many years.

--o0o--

DR. COGLIANO: In the past, most cancer evaluations depended on studies of cancer in humans and cancer in laboratory animals.

--o0o--

DR. COGLIANO: But one of the issues is that laboratory animal studies are becoming less and less common. This graph shows the number of NTP technical reports by each five-year period. And you can see there's been a steady decline over the last several decades --

--o0o--

DR. COGLIANO: -- and at the same time more types of data becoming available. Human studies now are more often looking at molecular markers, genetic epidemiology. We have genome-wide association studies. Animal studies including other animals like zebrafish, a lot of cell culture studies, and we're getting to be -- getting high through-put screening and robotics to speed up testing of in vitro.

--o0o--

DR. COGLIANO: About 15 years ago, IARC recognized the changing dynamics of -- the changing dynamics of the type of data that we were getting. And we set out to bridge the old and the new to look at the data on humans, and cancer in animals, and try to bridge that with what we knew at the time about mechanisms of carcinogenesis.

--o0o--

DR. COGLIANO: What were the IARC monographs? Many of you know and have been there. But it's a worldwide endeavor that since 1971 has involved over 1,200 scientists from 53 countries. A lot of people have gone into assessing cancer hazards, and writing them up, and getting a good summary of the human, the animal, and the mechanistic data.

--o0o--

DR. COGLIANO: So in the late 2000s, IARC saw vol -- was coming up upon volume 100. And IARC saw this as a milestone, a milestone volume because it was numbered 100, but also it was an opportunity to formulate a very meaningful topic. And so what IARC chose to do was to review all the human carcinogens that have been identified to date, while developing new information that could be pertinent to questions in cancer research and in risk assessment. So volume 100 reevaluated more than 100 human carcinogens that had been identified in volumes 1 through 99. And these include chemical agents, biological agents, physical agents, mixtures, and related occupations. So it was a very rich data set to be looking at the correspondence between human, animal, and mechanistic information.

--o0o--

DR. COGLIANO: The IARC review of human carcinogens in volume 100 addressed some overarching questions. First, what have we learned about tumor sites in humans and animals over many years of doing evaluations and what have we learned about the mechanisms of known human carcinogens?

So to address these questions, volume 100 compiled information that had not been looked at in

previous monographs. Volume 100 identified specific tumor sites that had sufficient evidence in humans or sufficient evidence in animals. And they also asked the experts at the meetings to identify established and likely mechanistic events. The sufficient evidence of tumor sites in humans has already been used a lot in cancer research. When people do case control studies or other studies about a particular cancer site, they often cite now the IARC monographs and saying what are the known agents that do cause that particular kind of cancer? So that was a really good piece of information that you have cancer researchers, but we also tried to answer risk assessment questions.

--o0o--

DR. COGLIANO: So after the volume 100 monographs were completed, scientists at IARC checked all of those monographs and put them into final form. And then in 2012, IARC convened another working group to address some overarching questions. So the findings of volume 100 were built into IARC's Scientific Publication 165, which synthesized the results of volume 100, which in turn built on volumes 1 through 99.

--o0o--

DR. COGLIANO: So the scientific publication on *Tumour Site Concordance and Mechanisms of Carcinogenesis*.

There are two main parts of this scientific publication. One was tumor site concordance, and we were trying to understand the correspondence across animal species, which tumor in animals had a good predictive value for tumors in humans and which ones don't. And we could also look at that to determine whether we have a good animal model for certain kinds of human tumors.

The second part, which is more relevant to the key characteristics today is on mechanisms of human carcinogens. And we tried to understand how carcinogens act. We explored some issues of susceptibility. We identified biomarkers that might be useful for further research or for preventive monitoring. The question we're basically asking though was how can we identify carcinogens without testing for tumors? This was being mindful that the number of animal studies was declining and we don't want to wait 30 years for humans to be exposed to determine -- that detect cancers in epidemiological studies. We would like to be able to detect markers that are predictive of carcinogenesis in humans and we would like to have other test methods, other than waiting for bioassays to determine whether a chemical might cause cancer.

--o0o--

DR. COGLIANO: So in IARC volume 100, the

monographs of the more than 100 human carcinogens, many mechanisms were identified for different agents. And this is a list. You probably recognize a lot of them. Maybe you've even studies these. But what IARC's scientific publication 165 did was grouped these mechanisms into 10 key characteristics that you're probably familiar with. And this is a list of those 10 key characteristics. There are two publications where you can find them. First is IARC Scientific Publication 165 and the other is a publication by Dr. Martyn Smith and many collaborators, in Environmental Health Perspectives.

--o0o--

DR. COGLIANO: So what are key characteristics? Firstly and briefly, they are properties that are shown by carcinogenic agents. They may be considered analogous to the properties of tumors or of cancer cells, which are known as the hallmarks of cancer. But these are not properties of tumors, they are properties of can -- of agents that cause cancer. They're based on the 100 or plus human carcinogens that were known. So we're not putting data into this -- these key characteristics that are on possible animal carcinogens that are maybe suspected. These are really known human carcinogens that have been identified over the years.

The key characteristics can encompass many kinds

of mechanistic endpoints. You saw that large list a couple slides ago. And they're being used by several agencies and -- as an approach to identify, to organize, and to summarize results from mechanistic studies.

We believe they can introduce objectivity to an analysis, because the key characteristics are not limited to looking only at hypotheses by our expert reviews. We look at all the mechanistic data. We classify it into different key characteristics, and then we can look at what key characteristics have information and start to think about, well, what does this mean for how this agent might cause cancer? So in this way, the key characteristics are meant to promote structured evaluations of the strength of mechanistic evidence.

--o0o--

DR. COGLIANO: IARC Scientific Publication 165 also did several analyses of the key characteristics. The method of doing this was to first group similar agents to list 86 distinct agents for analysis. For example, phenacetin, the pharmaceutical is listed as a chemical as causing cancer, but also analgesic mixtures that contain phenacetin are also listed as a Group 1 agent. So those are grouped into one agent for the purpose of this analysis, so we wouldn't be double counting.

Other agents that were grouped were, for example,

the alpha emitters or the beta emitters of ionizing radiation, so that we weren't double counting certain agents that were clearly acting through the same mechanisms.

We mapped the mechanistic endpoints for each of these 86 distinct agents into the 10 key characteristics. And as we did this, we classified the source of the key characteristic data as human in vivo, in vitro, or animal in vivo, or animal in vitro, but we could also look at whether key characteristic data were coming from humans, from animals, how much in vivo and how much in vitro by each key characteristic. The reference you can find for these analyses are again in Scientific Publication 165 and you see the links there, or a group of papers published by Dan Krewski and some collaborators in the Journal of Toxicology and Environmental Health.

--o0o--

DR. COGLIANO: So some of the findings from these analyses. Concordance was also a -- was often observed between human and animal sources. That -- that is we might see a lot of animal data that showed that an agent had a particularly key characteristic. But also, we often did have human data that very -- that matched that. Most carcinogens appear to act through multiple mechanisms as evidenced by the key characteristics that they showed.

And the observed patterns that we may see caveats may not be representative of future analyses.

Several reasons for that were given. One is that carcinogens identified many years ago from the 1970s, 1980s might not be representative of the newly identified carcinogens that are emerging today. The initial carcinogens that were looked at in the first 10 volumes of IARC monographs were a lot of clearly carcinogenic occupations, where there was a lot of cancer observed in the workplace, or some very prominent carcinogens, you know, like benzene, like hexavalent chromium, like asbestos. And they were almost all genotoxic at that time.

And today, we're finding other carcinogens that might not be operating through a genotoxic mechanism. So some of the graphs you're going to see of what we look at with the key characteristics of the first 100 carcinogens may not necessarily be representative of what we see today.

Also, interest in further testing had waned for some of the agents, particularly some of the old chemotherapeutic agents that are no longer heavily used. And also, there was a lot of new toxicity tests that are being -- continuing to be developed. So the types of information we'll have for key characteristics in the

future will continue to evolve as testing methods evolve.

--o0o--

DR. COGLIANO: So one of the things we did for the analysis in Volume 1 -- in IARC's Scientific Publication 165 was to make a database of agents in KC, key characteristics. Now, I don't expect anybody to be able to read all of this, but across all the columns are the 86 agents that were analyzed. And down the rows are the 10 key characteristics. And what you see is a bit of a heat map. The reds are where we have human in vivo and in vitro and animal in vivo and in vitro data for those particular -- each carcinogen and key characteristic. The orange, the yellow, and the green show where we have just three, two, or one of those four sources, and then there's white spaces where we did not have information on the key characteristics defined.

You'll see the red bar across the second key characteristic. That's genotoxicity. That's by far the key characteristic that's been the most studied. And particularly for the early carcinogens, which most likely were genotoxic.

--o0o--

DR. COGLIANO: We looked at the source of key characteristic data. So across the bottom you see the 10 key characteristics. And on the right you see a legend

that you have human data in vivo and in vitro, and animal data in vivo and in vitro. And what you actually see is that for each key characteristic, there is roughly the same amount of data from each of those four sources. A lot more data for key characteristic 2. A lot more agents had data on key characteristic 2, which is genotoxicity. Fewer agents had data on key characteristic 8, receptor binding, or some of the other key characteristics. Sometimes you do see like key characteristic 9 very little human data on immortalization or in vivo data on immortalization. It's mostly in vitro.

But for something like genotoxicity, key characteristic 2, you see roughly the same amount of in vivo and in vitro data, agents with in vivo and in vitro data, and agents with human and with animal data, which means that genotoxicity was really very well covered in these agents, and some of the other agents were -- had data in, you know, generally 25 percent or fewer of the agents.

--o0o--

DR. COGLIANO: We were able to look at a count of agents exhibiting each key characteristic, so you see the key characteristics along the bottom. Eighty-five out of 86 agents, almost 100 percent, did show evidence of genotoxicity. But for the others, it was generally around

50 percent, and some of them were a bit lower than that, fewer agents showing those key characteristics.

--o0o--

DR. COGLIANO: Another one is the count of key characteristics exhibited by an agent. Sometimes you hear people doing -- make a comment that, well, this doesn't hit all of the key characteristics. Well, that's not really necessary. An agent does not have to act through every single one of these key characteristics or every type possible mechanism. This is a way to organize them to see which ones act through each kind of key characteristic or each type of family of mechanisms, and, you know, help with the analysis.

You can see that the agents so far have exhibited from 1 to 9 key characteristics. We haven't seen -- hadn't seen an agent used all -- exhibited all 10 key characteristics.

Now, let's look at the ones that showed only one key characteristic.

--o0o--

DR. COGLIANO: There were seven agents. And you see them listed on the left, three of them are pharmaceuticals, three of them are occupational carcinogens, and one is a set of mixtures of mildly and lightly treated mineral oils. Each one of these seven

agents though has sufficient evidence in humans, which means they are really carcinogens. They're not any kind of a weaker carcinogen, because they exhibit only one key characteristic. They have sufficient evidence in humans. They've been classified for a long time as human carcinogens. I guess because people might be curious, the agents on the right with eight or nine key characteristics are DES, trichloroethylene, and diesel engine exhaust. Again, there is sufficient human evidence for all of those as well. So key characteristics can exhibit from one to a large number of key characteristics. Agents can exhibit the large -- from one to a large number of key characteristics. But these are all human carcinogens.

--o0o--

DR. COGLIANO: Key characteristics have been developed for other health outcomes. So the carcinogens were the first. The publication is Dr. Martyn Smith, 2016, in Environmental Health Perspectives. But since then, they've been developed for male and female reproductive toxicants, endocrine disruptors, liver toxicants, cardiovascular toxicants, and immunotoxic agents. And you see the publications for those in various journals.

--o0o--

DR. COGLIANO: So in summary, what I'd like to

leave you with was -- is that the key characteristics for carcinogens have been developed using a lot of data from the last 40 years. First, they started with the first 99 elements of -- 99 volumes of IARC monographs. Those went into volume 100 of the IARC monographs and IARC Scientific Publication 165, which developed the 10 key characteristics that we're familiar with today.

--o0o--

DR. COGLIANO: The key characteristics therefore distill 40 years of scientific knowledge about the mechanisms through which human carcinogens operate. They've been useful in identifying, organizing, and summarizing mechanistic evidence. They've been developed for other health outcomes and they've been accepted and used at IARC, at the NTP, and at OEHHA.

So with that, I'd like to conclude and thank you for your interest and attention.

And I will stop sharing my screen and I will turn the meeting back over to our Chair.

CHAIRPERSON LOOMIS: Thank you, Dr. Cogliano for a very interesting introduction to the topic we'll be discussing this morning. I wanted to see whether there are any questions of clarification from the Committee? If you have a question, Committee members, feel free to just come on camera and speak up.

Okay. It appears there are no questions at this stage. So we'll move on to the next part of the agenda. I'm pleased to introduce our next invited speaker, Dr. Kathryn Guyton. She is currently Senior Program Officer at the National Academies of Science, Engineering, and Medicine. And before joining the National Academies, she was Senior Toxicologist at IARC for seven years during which that time it was my pleasure to work closely with her. While at IARC, she was quite intimately involved in the development and deployment of the concept of key characteristics of carcinogens for IARC monograph evaluations and also participated in implementing the key characteristics into the IARC monographs preamble. She is coauthor of several major publications on the application of the key characteristics.

So at this time, I will turn the floor over to Dr. Guyton.

(Thereupon a slide presentation).

DR. GUYTON: Thank you very much for that very kind introduction. And Dana, it's a great pleasure to see you as well as other colleagues today. And I will -- I will be discussing some of the work that some of you contributed to. So I'll start by thanking everybody and acknowledging the many people who contributed to the topic I'm going to cover today, which is really how the key

characteristics of carcinogens are applied in cancer hazard identification.

So as Dana mentioned, I am a Senior Program Officer at the U.S. National Academies of Sciences, Engineering, and Medicine. I will be discussing work that was done while I was at IARC. Most of it has been published or I will be referencing the IARC monographs preamble. I'm happy to provide further information and references, if you'd like to read more.

--o0o--

DR. GUYTON: I'd like to just begin by saying I have no financial interests related to the subject of my presentation.

--o0o--

DR. GUYTON: So I think Vince gave a very wonderful introduction to the IARC monographs, which he knows very well. But some of you may wonder, well, how does this process occur whereby carcinogens are identified? And really that's all covered in the preamble to the IARC monographs, which was updated in 2019.

--o0o--

DR. GUYTON: And it really comes down to three distinct lines of evidence. Cancer in humans, this is more the domain of people like Dr. Loomis who are epidemiologists. I will only give this a glancing blow

today. We also have cancer in experimental animals, which is the traditional - excuse me - bioassays that are conducted in the lifetime. And then we have carcinogen mechanisms, and that's really where I'm going to focus.

--o0o--

DR. GUYTON: So this table kind of provides the grid of how these decisions and overall evaluations are reached by IARC. I don't want to dwell on it, except to say for the most of the Group 1 carcinogens that Vince referred to, those have been identified based on sufficient evidence of cancer in humans and a smaller set have been identified based on this mechanistic evidence of when it's strong in exposed humans.

--o0o--

DR. GUYTON: And Vince covered some of the agents, but I think this gives you a sense of really over the course of the -- of the history of the program how many of these different agents have been -- have been classified.

--o0o--

DR. GUYTON: And I'm just going to focus on these 126 agents that are in the highest category Group 1, to give you a sense of what causes cancer. What do we know are the causes?

So in this little picture you'll see things that

have a chemical structure. There are chemicals. We also have occupations, fibers, metals, different types of pollutions, and pollutants in air pollution, tobacco in its various forms, radiation, drugs, and viruses. So it's really a very diverse group of agents. And as Vince mentioned, these were all reviewed in the Volume 100. This is a really fantastic resource.

--o0o--

DR. GUYTON: And this is another way. I don't expect you to read all of it, but this is just another way to consider this is by cancer site what do we know about what causes cancer, which is shown in red, and what may prevent it such as quitting smoking in green.

--o0o--

DR. GUYTON: And just to kind of dive into this a little bit more to remind you that what we know is very disparate across cancer types. So for lung cancer, we actually have a number of different agents that have been identified in the environment, but mostly from occupational settings. Now, breast cancer is a totally different story. We have very few known identified causes and I had the pleasure to publish a commentary on this in 2021, with Mary Schubauer-Berigan, who is the head of the monographs program. And we have to recognize that occupational studies tend to be limited for women's

cancers when the endpoint is cancer.

Women tend to come in and out of the workforce and there's different reasons why -- why they're not the subject of these long-term studies. And as a result, the studies are different. They tend to be in dietary settings, medical, pharmaceutical. These are really different database. And I just want to remind you that in 2020, breast cancer became the most common cancer in the world. And it's really about one in 10 of all cancers diagnosed and we have a very poor understanding of the causes that can inform actions to prevent things actually getting worse.

--o0o--

DR. GUYTON: So the reason I highlight that is these -- what's the role of mechanistic data and how can this help with some of these problems that we face when trying to understand what does and also what does not cause cancer. That's another relevant question that's kind of at the opposite end of what I'm talking about.

--o0o--

DR. GUYTON: So coming back to carcinogen mechanisms, a number of years ago -- it might feel like yesterday to Vince, but it was actually in 2009. And we published this paper with many colleagues, some at OEHHA and elsewhere, and what we noted was there's just a huge

gap between what we know in terms of chemicals in commerce and these publicly available reviews. So IARC has done more evaluations as I just showed you. IRIS may be not so many more and we're adding to this -- to this database, but we actually have very, very many unknowns.

--o0o--

DR. GUYTON: And I think Vince showed a different way to think about this in terms of how the data is shifting, but this really raises some key questions and challenges. So first of all, if there is no assessment, does it mean there's no hazard? And how -- amongst these many, many things that have never been evaluated, how would we select and prioritize them? And at the time that we wrote this article, the existing mechanistic approaches, I apologize, were really asking a different question. They were asking is the data relevant to humans and does it support a non-linear dose response? And there were no examples where mechanistic data could answer the question does this substance cause cancer? And that was really -- that's the focus of the IARC monographs program and that was really what we were interested to do.

--o0o--

DR. GUYTON: And through this volume 100 exercise, it was clear that there was no method to search systematically for mechanisms. And that led to a lot of

lack of uniformity across assessments for different agents by different groups of people.

Additionally, it's a huge database and growing in complexity. And how can this be done efficiently? And how -- with all these top three challenges, how do you actually avoid bias? This is one of the main things you want to avoid in any kind of systematic review.

--o0o--

DR. GUYTON: So coming back to our carcinogens I showed you earlier, you know, the essential concept of the key characteristics was could this provide new insights for identifying cancer causes? So this picture, you can think of things as a list, but this is more showing that these things are -- they're interrelated and they're not necessarily prioritized, one way or the other, depending on your carcinogen of interest. And some of these things are sitting near the key characteristic they may have. We have these drugs, which are immunosuppressive. That's a good thing. We need immunosuppressive -- immune suppression at certain times, but it has a dark side and that is that it can cause cancer.

So as you think around this circle, we have a lot of knowledge, and Vince showed this, agents that are genotoxic, those who are easy -- have been easier ones to focus on, but obviously, this has left a lot of gaps. So

that was really the -- some of the concept that I had the pleasure to explore with Martyn Smith and many -- many, many other esteemed colleagues. And just a couple references here if you want to look further.

--o0o--

DR. GUYTON: So one of the things that we thought when I first got to IARC and I heard about these KCs was, well, could we -- you know, being involved in reviews, which are really based around a key question. If you want to go into PubMed and you want to ask give me the data on the thing I'm looking at, you have to phrase this in a way that the -- that the database can answer. And a lot of people use this as a PECO question. That stands for Population, Exposure, Comparator, and Outcome. And really these things are completely amenable to this type of format. You can just simply ask is the agent genotoxic in whatever system you want. You can design some search terms and then you can organize those results across the key characteristics, species, whatever your population of interest is. And this is really just helping to organize your database in a way that helps to structure that expert judgment that goes into these decisions about what causes cancer.

--o0o--

DR. GUYTON: So we published this in 2016 and

really this was a concept that we took forward. And after we had gotten through about eight monograph meetings covering a diversity of different agents, we decided, well, let's kind of sit back and think upon what we've learned so far as a way to inform progress. So this report was really, really, really helpful. And I had the pleasure to author it with the chairs of those particular meetings who really had to face these decisions.

--o0o--

DR. GUYTON: So as a result of that, this led and stimu -- really stimulated -- this experience really stimulated the modification to the preamble. And the preamble modification really brought in a little bit more of a structured approach in terms of these different steps that I'm showing here. Not a surprise to anybody who's ever been involved in systematic review. And that basically the key characteristics could be used as a seed to identify, screen, and organize the information for the first two steps. And then it -- the preamble provides guidance on how to evaluate the studies for quality and for importance.

And importantly, all of the judgments that are done during the synthesis, which considers evidence across the different key characteristics, the preamble already intimating that some key characteristics are more

standalone. As I mentioned, we know about -- a lot about genotoxic carcinogens. And when you see the next one coming down the road, it's not that hard to identify it from a distance, but not possibly as true for other agents where we have less experience.

But importantly, conclusions can be strengthened when there's evidence of multiple key characteristics. Oxidative stress which is KC 5. That one is something that is a really critical type of -- type of key characteristic that applies to many, many different types of toxicities. So how do you kind of make sure that what you're seeing is relevant to carcinogenicity. And I'll show you one example of that through this additional supporting evidence of the preamble, as it did in prior versions, emphasizes when you have that experimental evidence showing suppression of tumor development when key mechanistic processes are suppressed, that can really elevate the strength of the conclusions.

The preamble also introduced new classification categories. Previously, it was strong, moderate, and weak, which were actually not defined. But now, it was possible to align the terms retaining strong, but aligning limited and inadequate more with the other two evidence streams in preparing for that integration step.

So let me just, in the next few slides, kind of

go into a little bit more detail --

--o0o--

DR. GUYTON: -- about some of these steps. And this is where you'll find it in the preamble, if you'd like to open it and read it. It's really quite short and you could probably do that while I'm talking. It might even be more entertaining. But for -- there's different considerations obviously for studies in humans, studies in experimental animals. And I've just listed them here. And these are not -- the kind of obvious things that you would think. You know, we are interested in cancer. We'd love to see those for experimental systems. We'd love to see those chronic studies and some of these other issues that are relevant. If you're a toxicologist like I am, for studies in humans, it's a little bit more about how the study was designed, exposure assessment, and some of these other factors.

--o0o--

DR. GUYTON: So I -- a question that I think comes up a lot, and I think is really key to the application of this concept in decision-making is really how do I tell if I have a limited data set versus a strong. And limited really covers a narrow range of experiments, endpoints, and species. There could be unexplained inconsistencies of -- in studies of similar

design. So one person published some -- one thing. In the same model, somebody else publishes the opposite result and you really -- you really can't explain why those two individuals got different results. And you can also have incoherence. So, you know, different endpoints are showing different answers and the issue is really unresolved.

And strong by contrast means there's really consistent results in several experimental systems. There is an emphasis in the preamble on mammalian systems. So just wanted to highlight that. The coherence of the overall database, having a substantial number of studies. A lot of times, you know, with some of these Group 1 carcinogens, you're talking thousands maybe tens of thousands of studies. So you really have a lot of confidence in coming up with that strong conclusion. Different alleys have been explored. All kind of things have -- rocks have been turned over and you have a confidence that you really know what's happening, and as I mentioned, the suppression of the tumor development.

--o0o--

DR. GUYTON: And I'd like to just come now to two examples of this. So first, epidemiology. Always dangerous when I talk about this, but was Volume 106 and I was a member of the working group. And there are other

members here, so I -- I'm feeling a little confident. But in any case, for this KC 1, which has to do with an agent being electrophilic, that is clearly a property of -- a key property of carcinogens, but other things are electrophilic and also bind. A lot of different things that cause acute inflammation may have this property, et cetera.

So if you wanted to make a decision about this or have influential data, I think this is a good example, where for trichloroethylene, the people -- in epidemiological studies, people who had at least one intact GSTT1, the glutathione transferase, allele had a different risk from those than -- that had two deleted alleles. So you've got two different genetic situations and you're really seeing a different in risk.

In that, it's a different question than what the epidemiologist consider as a whole in their consideration of cause and effect. But for the -- from the mechanistic side, this is really a convincing type of evidence that could support a strong conclusion.

--o0o--

DR. GUYTON: Now, similarly, in the animal studies, you may have studies in a knockout mouse situation. We've seen this with several carcinogens of great interest that have been listed by the State of

California. I just want to highlight pentachlorophenol, where for this KC 5 oxidative stress, which as I said has been a little bit of a conundrum, because it's -- it lacks that specificity for carcinogenicity, but when you have a cancer study in the knockout mice, this can really help to strengthen those conclusions. And I would also emphasize, it's not just any kind of oxidative stress. You're looking for oxidative damage to DNA specifically. And that -- that is a little bit getting -- adding to your specificity, and as well this particular agent had other key characteristics of carcinogens. So altogether, you had a stronger database. So sometimes those examples can really help to illuminate how -- what the intent was in drafting this in this preamble language.

--o0o--

DR. GUYTON: So just coming back to how these decisions are made in the preamble, I just want to emphasize that the strong evidence of the key characteristics can support classifications. And again, for some cancers like breast cancer where we possibly don't and may not have these occupational studies of cancer, we still have that opportunity to go into an occupational cohort, for example, and look at key characteristics of carcinogens in exposed women in the workplace and try to assess is this evidence suggestive,

is it strong, will it support a conclusion that could possibly lead to a classification.

At the same time, you can have strong evidence coming from different types of systems that can complement, let's say, epidemiology studies, if it's in experimental systems, it could be in human cells and tissues to complement sufficient evidence from cancer in experimental animals. This, in another way to phrase it, is about external validity. It's about is your mechanistic evidence supported by another data stream? And usually that's going to come from a totally different system. If it's in humans, it needs to be complemented by the cancer in experimental animals. Likewise, if it's in the animals, it needs to be complemented by the humans. That creates that external validity and that strengthens conclusions.

--o0o--

DR. GUYTON: So the other way that the key characteristics were considered when I was -- when I was -- had the pleasure to be at IARC was when we were looking at all these recommendations that came in for setting priorities for the monographs program, which is done by an external advisory group about every five years. And what happened was there were a number of these that were recommended for evaluation really based on

mechanistic evidence alone or based on mechanistic evidence in combination with the other data streams. So this really is just another way to be -- to provide some specificity and transparency about the basis for recommendations.

--o0o--

DR. GUYTON: And it's also possible, which we did in this -- in -- as part of this advisory group exercise and published key author is Dinesh Kumar Barupal. And essentially he's really more of a database person with his perspective in kind of running these queries based on the KCs in different databases in trying to illustrate across agents, not what the conclusion is going to be, but where is there evidence on these different KCs. And that -- that helps when you're on the staff and you're trying to say, well, which of these -- if we're going to pull in experts who understand epigenetic mechanisms, what are all the agents where that may be a -- that may be a consideration. So it really just helps fill in blanks in the -- in the planning stage. This is a really interesting and it's really all credit to Dinesh this approach.

--o0o--

DR. GUYTON: So this -- I just want to just say some -- share some emerging lessons that once we

implemented this preamble when I was at IARC, what did we find? So I would share similarly as we published in 2019 there's very few human biomarker studies. This is an opportunity I think where we could fill gaps. Most of these have been done on adducts, which are really relevant to that KC 1, which, as I mentioned, better if you have some kind of cause and effect study that would really clarify its role. It is possible to make a classification into Group 2B based on the KCs, again relying on that KC 2, whether it's genotoxic. Not a big leap of faith to do that I don't believe.

And I think this -- you may want to have a look at this later for more details, but what this poster shows: these studies that are shown in this yellow color for KCs 6 through 10, these are all studies that are done in vivo in animals and essentially our working groups were relying on chronic bioassays to make those strong conclusions. So these were effects that were seen in chronically exposed animals. And I think that's -- that's a really interesting point to contemplate as we think about new approach methods and they're coming online and how can we develop and design assays that can really probe some of these things that we're currently relying today in 2023 on in vivo animal studies that are in a chronic setting, very expensive, long term, and other concerns

about them. The high throughput data that we had available had very little impact overall. And again, that could be considered through design issues.

--o0o--

DR. GUYTON: So just in closing, I want to highlight some guidance that's come forth from the U.S. National Academy of Sciences. This very influential report, one of our most popular downloads, really highlighted what's the value of the KC and noted that these key characteristics could be developed for other types of toxic endpoints. And that has already led to a lot of progress, I feel.

--o0o--

DR. GUYTON: Another one that came out more recently gave advice to the IRIS Program that these KCs are useful when you're searching and organizing your mechanistic data. It certainly helps you identify those gaps and also evaluating biological plausibility.

--o0o--

DR. GUYTON: I think there's a lot of recent progress and future prospects for the KCs. I highlighted this invited perspective that really was dealing with -- with breast carcinogens in the gaps and potential opportunities. I think the KCs are very amenable to automation. And we've seen some exciting work in that

area as well. And I think obviously more need to develop best practices for evaluations as more experience is gained and continue to advance KCs for other hazard classes.

--o0o--

DR. GUYTON: So just in closing, I want to thank the different IARC Monograph Working Group members that spent many, many years. It was definitely an exercise where we took advantage of their expertise to refine what was going on, and really, really all -- each and all of them contributed as to the staff who were there, past and present, all the co-authors and the reviewers of the work that I presented, and most of all thank you for listening.

CHAIRPERSON LOOMIS: And thank you, Kate. It's really great to see how the KCs have been applied and evolved in the years since I was at IARC, five years ago now.

Again, we have time for clarifying questions from the Committee. So Committee members, if you have a comment or a question, please feel free to speak up.

COMMITTEE MEMBER McDONALD: Yeah. Dr. Guyton, this is -- this is Tom McDonald. Thank you. It's a super interesting presentation. Very much appreciated that. I wanted to explore, I saw on your criteria slides that you always, it seemed, to have either animal or human evidence

along with mechanistic. But then in your examples, you had some where IARC was considering just mechanistic -- or just key characteristics. Has IARC approached a chemical without animal or human-sufficient data and -- or for towards a listing?

DR. GUYTON: Yeah. That is a great question. And perhaps I could have been more clear in how I presented it. So let me say it this way. If you only have mechanistic data, you have strong evidence of KCs, and it's appropriate, you could make a classification on that basis alone. But as you go higher into the classifications, if you want to get into Group 2A or up to Group 1, then you really need that complementary evidence showing, what I called, external valid -- a stronger sense of external validity, so that you're really seeing supporting evidence from different lines of evidence, if that -- if that makes sense.

COMMITTEE MEMBER McDONALD: Yeah, that does. Thank you.

DR. GUYTON: Yeah. But at the same time, you can't use animal mechanistic evidence to complement animal bioassay evidence. Those are actually the same. Those are kind of viewed at the same level. You would have to have that mechanistic evidence coming from a human system. That's kind of the IARC thinking there. But it's a place

dominated by epidemiologists, I would say, over time, so there's always a lot of weight given to studies of cancer in humans, I think, more so than many classification systems. But again, that is one of its -- one of its great strengths. And certainly, the Group 1 agents based on -- based on those studies, it -- you know, it creates a very solid evidence base from there. And if you don't have that evidence, you certainly have options for lower level classifications, so...

COMMITTEE MEMBER McDONALD: Great. Thank you.

CHAIRPERSON LOOMIS: Are there any other questions or comments from the Committee?

It looks like there is one. Go ahead, please

COMMITTEE MEMBER BESARATINIA: Yeah. Hi. Wonderful talk. Really enjoyed it. Well, I believe you touched upon this issue that I'm going to speak about in one of your last slides. As you we all know, we are living in the age artificial intelligence and the use of AI is becoming increasingly popular in research. I'm sure you know better than anyone else how laborious and time-consuming KC evaluation of potential carcinogens is.

My question is does IARC have any future plan on the potential use of AI and incorporating machine learning methods and computational modeling into evaluation of KCs for future monographs?

DR. GUYTON: Oh, Ahmad, that is -- that's a fantastic question, very thought provoking. I will say that IARC is convening a workshop in July looking at issues related to the KCs and I do expect this issue of AI machine learning will come up. I would say to date some of the work I showed you that Dinesh Barupal really spearheaded has really been about gathering the evidence together and not making -- and not making the judgment, if you will.

But some of the work from Ruud Ter Meulen, that paper that I cited, and I'm happy to get back to that or I'll put it in the chat, was really trying to say could you -- could you really base on -- could your machine learning get to where your expert working group did, based on, you know, this method, which is actually -- it's a reproducible method, right? We have the search terms. We have the criteria. Could you build a system? I think some of the work that we published was really more on the side of you could do those kinds of things as a way to prioritize, but not really replace the human element in this judgment, because it is so complex.

And I think those are -- that's a strength of systematic review approaches, they make those judgments transparent, but they don't replace them. It takes -- it takes some balancing of strengths and weaknesses of your

evidence based on reaching your conclusion and understanding limitations.

COMMITTEE MEMBER BESARATINIA: Thank you.

CHAIRPERSON LOOMIS: So it looks like Dr. Eastmond has a question. Please go ahead.

COMMITTEE MEMBER EASTMOND: Hi, Kate. Nice presentation. I just had a follow-up question. You had mentioned that some of the key characteristics, oxidative stress can be sort of nonspecific. And could you comment a little bit more about how one might make decisions when that's the primary effect that's being seen and what other -- you know, how you would evaluate this. You mentioned that oxidative damage to DNA would be one consideration, but have you thought about if that's how that would be considered in a sort of hazard identification decision-making process, when that's the primarily or sole characteristics that's being involved?

DR. GUYTON: Yeah, Dave, great question. And I think many of us, especially those who are toxicologists, you know, we love oxidative stress and we really think it's super important, but I would say according to the preamble, it's not a standalone KC. You really would need some other evidence that would really strengthen your conclusion, even if you had -- if you only had oxidative damage to DNA and you'd explored it under multiple systems

and you really just had that, I still think it would be a little bit of a leap, because what if -- you know, is this really -- you know, that can happen and it can -- it can maybe not go to the next step of truly causing mutations, right? This is what these lesions would do in theory, right?

COMMITTEE MEMBER EASTMOND: Sure.

DR. GUYTON: Or would you actually get -- could you suppress it and see more such lesions through antioxidants or through genetic manipulation? Some of those types of experimental approaches might strengthen, but, you know, ultimately, if you think, well, in your mind, this would cause a mutation. Well, then why didn't I see that mutation? Did nobody study it or did it -- was it not found?

So that might be where you might go to limit it, because you think there's still some aspects of the database that need to be explored. Does that make sense?

COMMITTEE MEMBER EASTMOND: Yeah. No, I think. I just wanted your thoughts. Thanks.

DR. GUYTON: But others might disagree. I mean, we haven't seen every data set. So there could be one that would push you over the edge.

CHAIRPERSON LOOMIS: Other questions or comments?

Well, I don't see any raised hands yet, so I'm

going to take advantage of the Chair's seat here, since we have a little bit of time and make a comment and, Kate, see how you would like to react to it.

So you and Vincent both gave a bit of historical perspective on the IARC monographs mentioning in particular that -- and we've found a lot of the -- many of the carcinogens that were identified in the first 40 years of that program through epidemiologic studies, particularly occupational studies, and that also historically important have been rodent cancer bioassays, of which there are fewer and fewer. And I would also point out that there are actually fewer epidemiologic studies of the kind that we used to do. Just imagine if you looked back at the early monographs from IARC, some of the epidemiologic studies that discovered, if we can use that word, some of the known carcinogens are actually really crude, bad studies that we would never do now.

And, in fact, there are studies that couldn't even be done, because the kind of workplaces where those occupational studies in particular were done hardly exist any more around the world. You know, that's partly due to different economics. It's due to automation efforts to clean up exposures. Those old studies were done in situations of, you know, really gross exposures to highly toxic agents. And those things still occur in the world,

but not so much. And the work forces aren't nearly as big as they were. And as the speakers pointed out, you know, modern work forces are also different from the ones that got studied back in the seventies.

So I would argue that we probably can't expect to use epidemiologic studies in the same way going forward that we did for the pre-Volume 100 history of the IARC monographs say. So we really need a different toolkit in order to make progress now with different kinds of agents, different exposure situations, and different data streams.

Any thoughts about that?

DR. GUYTON: Well, Dana, I agree with everything that you -- that you're saying. And we've certainly seen that, I think. I think some of the challenges that you experienced when we were -- when we were both at IARC and people have urgent questions does -- you know, does this agent cause cancer? I'm seeing an uptick of -- uptick of this cancer in my country and I want an answer. Well, even if you launched your cancer epidemiology study today, it -- by the time you get the answer that the urgency of it may be gone and the opportunity for intervention may be gone.

So I think, you know, every -- every type of study has a different, you know, fit -- we could call it fit for purpose. We could call it a domain of

applicability. They answer different questions. I think the beauty of the KCs is, first of all, you could do these studies with a KC-relevant endpoint, and you could do that in an occupational setting. You could do that in your dietary exposure study or you could do it in your pharmaceutical study, if you wanted to do -- to try to get a more human relevant type of scenario with the epidemiology context in mind and designing a high quality epidemiology study. But your answer may come in a much more timely way and it may provide different insights, right? It's not just what type of cancer, but it may give you an insight into, well, how is this -- how is this agent acting and what might be susceptibilities that could be different between men and women, between older and younger populations, or with different types of co-exposures.

So, yeah, I think -- I think we have to really be thinking ahead. And it may not be that long on the horizon, especially if you're watching regulations in Europe and in the United States where we're not going to be having these long-term bioassays in animals even, to the extent that we did. And that's been a great tool. We've made many, many decisions on those types of data and how can we make those same decisions with new data streams.

And we have to start building that confidence to get there. But I think it's -- for epidemiology, I would say it's more same -- you know, it's using the same tool and all those lessons, but perhaps with a different outcome that may still be just as informative. That's what we actually need, right, to answer this yes -- it can be no answer. That's fine, but we need -- you know, we need these answers timely.

CHAIRPERSON LOOMIS: Yeah. Well, those are really good points. Thanks.

Let's see if the Committee has any other questions or comments before we close.

Dr. Landolph is raising his hand there. So go ahead.

You're muted. Can't hear you.

COMMITTEE MEMBER LANDOLPH: Yeah. How about now? Can you hear me? Yeah.

Kate, that was a great talk. I enjoyed it. I just wanted to point up that a lot of these hunts for carcinogens, they're not only screening exercises. We've been working on nickel for a long time just trying to look for the molecular mechanisms of nickel carcinogenesis. And, of course, they had epi and they had animal studies a long time ago. But, you know, we want to know how does it work? And it turns out now with the new whole genome

sequencing, we find deletions and amplifications of chromosomes, as well as the regular chromosome breakage. We found ROS and Max Costa's lab has found a lot of epigenetic effects by nickel.

So a lot of these compounds that you're looking for to find out whether they're carcinogens or not, they're really research projects, you know, if you want to get a clear, clean, and crisp, and comprehensive answer. So it's going to take a lot of work, but it's coming.

DR. GUYTON: Yeah. Yeah. Totally appreciate that. I'm -- what I heard you say was Key Characteristic 2 and 5, which, you know, that can get you -- that can get you at least to first base in the IARC terminology. So I think it's also, you know, more on the evaluation end of data, rather than doing those studies or funding those studies. But this conversation between what's influential to assessors and what -- you know, what researchers can do, I also feel that's extremely valuable.

So I really appreciate all the good work you've done. I think nickel is one that continues to be -- to be of concern. So appreciate your thoughts.

COMMITTEE MEMBER LANDOLPH: Yeah. It's also interesting that a lot of these carcinogens have mixed mechanisms. They're not simple mechanisms. They're multiple mechanisms. Nickel is one of those which does

genotoxic and epigenetic effects. So it's -- you have to look really hard to get to the actual ultimate mechanisms of -- by which they act.

DR. GUYTON: Yeah. That's a really, really good point. And I think with the KCs, you know, we looked at benzene as an example. And that one had eight of these KCs. You know, it's really ticking so many -- so many different boxes, but in part that's because it's really well studied, so we understand. For many others, we just don't have the data and it's difficult to say. So that's where I say when people look at a data set and they say aha it's strong, well, you know, there may be -- there may yet be a number of blind alleys you haven't ex -- you know, checked out to make sure, you know, you aren't misled. You know, it's not -- it's not really a one study leads to -- leads to a strong conclusion type of paradigm. It's actually much, much different than that. So -- well, I appreciated the chance to address all of you. This is really a great pleasure for me.

CHAIRPERSON LOOMIS: Well, thank you very much. It's great to have you with us.

Well, we will now move on to the next part of the agenda. And so it's my great pleasure to induce our next invited speaker, Dr. Ivan Rusyn. He is a professor in the Department of Veterinary Integrated Biosciences in the

College of Veterinary Medicine and Biomedical Sciences at Texas A&M University, which is in Texas, U.S.A. He's also Chair of the Interdisciplinary Faculty of Toxicology and Director of an NIEHS T32 training program in regulatory science and environmental health and toxicology, and Director of the university's Superfund Research Center.

Dr. Rusyn has also served on several IARC monograph working groups, including as Chair of the Working Group for Volume 125 where the concept of key carcin -- key characteristics was applied. And he's authored several of the publications, including some we've reviewed today, on application of the KCs. So, Dr. Rusyn, the floor is yours.

(Thereupon a slide presentation).

DR. RUSYN: Dr. Loomis, thank you so much and I really appreciate the Committee members all the hard work that you are doing, and some of you have been doing for decades. So thank you.

And thank you for agency staff to also inviting me to give you maybe again more of a retrospectic -- retrospective view on the last 10 years of key characteristics since they have been put in place. And I really would like to thank also Vince and Kate for providing excellent foundation for what I will be discussing today.

I have had a lot of help from a colleague of mine, Fred Wright at North Carolina State University with some of the statistical analysis that I'll be presenting today. And the types of analyses and the visualizations that I'll show you have been kind of bounced off, you know, a number of my colleagues as well that -- whose names you've already seen a couple of times today, Dr. Wei-Hsueh Chu here at Texas A&M, Dr. Guyton, and also Dr. Zeise as well.

As it is important for us in this public forum to acknowledge all of the possible conflicts, I want to share with you that my laboratory right now is funded exclusively by NIH and U.S. EPA. But in the past year -- 10 years, we received funding from American Chemistry Council and from some of the trade associations in Europe for some of the work with petroleum substances.

I engage in a number of venues, advisory committees, and other things with IARC, with U.S. EPA, with American Chemistry Council, California EPA and other State and local partners. American Chemistry Council funds part of my lab's research right now, together with seven other members of the consortium the tests tissue chip application. So these funds are pooled together and our funders have no role in directing the research and publications. Albeit, it's a very interesting interaction

with a number of them. We'll have a speaker later today from American Chemistry Council. Dr. Ryman-Rasmussen has been very kind to come and teach at Texas A&M to our students in toxicology and our Practice Risk Assessment course. So again, we've been engaged with a broad swath of different stakeholders.

And a final disclaimer is that Texas A&M, on behalf of myself and Dr. Chu, and CalEPA are in the process of somewhere -- I'm not sure really where that is. It's so far above my pay grade -- negotiating a support contract for work that is again unrelated to key characteristics at some of the agency advice on pharmacokinetics and inhalation exposures. But I'm not sure whether that contract will or will not be successful.

--o0o--

DR. RUSYN: So but today, what I really wanted to talk about is the last 10 years. So if one looks at the work that has been put in place since 2015 and the reality it's really, you know, 2014, so almost 10 years, IARC has gone and at least the monographs have been published, which means that they can be examined in full text, rather than just the summaries for 73 of those agents. So Volumes 112 through 130 included 67 chemicals for dietary life factors to occupations. And Dr. Guyton, if you paid attention, showed a table including up to Monograph 133.

So volume 131 came out recently. My analysis did not include that, but, you know, more substances are added three times per year. So this is a growing database. And what I'm showing there are the years. The first meeting, the Volume 112, happened in 2015, the monograph was published in 2017. And the last one that I evaluated, 130, both the meeting and the monograph came out in 2022.

But IARC is not the only organization that uses key characteristics. It was already mentioned that U.S. EPA IRIS Program includes them and their cancer hazard evaluations. What you see there in yellow is the link to their handbook. And the handbook does mention key characteristics and how to use them. But IRIS program has already been using them in a number of assessments. As you can see, these are in process, but they have links to documents or scoping reviews. So if you kind of add up all of these things, that's another dozen or so. And the National Toxicology Program Report on Carcinogens part of it also has public guidance and search strings on key characteristics. And this is the link to this document.

And they also included key characteristics already in a couple of updates to report on carcinogens. It came out in 2018. And they're working on a number as well that will be included in the next update to the Report on Carcinogens.

So when you add all of these things up, there is a hundred or so agents that have used key characteristics. And this really is a robust database that has been put together by a variety of individuals. And I only looked at the IARC monographs. But even if you count all of the individuals who participated in these working groups, this is well probably over 115 individuals that come from countries, different occupations, and different parts of science. And they all have, you know, experienced the advice that is provided in the preamble. And before 2019 revision, it was provided in the instructions for authors. But they all had to kind of, you know, learn this, and apply this, and use it. And now we can take a look as to what actually has transpired.

--o0o--

DR. RUSYN: So as already was mentioned by Dr. Cogliano, there is, you know a lot that a number of risk assessors embrace about the concept. This is information about agents that are known to cause cancer in humans. They are inclusive of mechanisms that operate at the different doses and across different tissues and organs, as is really, you know, was -- key characteristic is something that really enables systematic review to come to mechanistic and other evidence evaluation, which is very voluminous and is prone to bias, because toxicologists

study a particular mechanism. They really think that's the mechanism, the most important one. And they frown upon others who, you know, go to a church of a different mechanism.

This is really a finite set of -- you know, a short list of things to search for. You know, unlike some of the other mechanistic constructs, which can be endless, this really is providing a very robust start and finish. And as Dr. Guyton already mentioned, this means that the search terms can be defined, so you can really apply PECO criteria and PECO statements across different groups of people and different agents.

This still is just a start of the weight of evidence approach. As again, Dr. Guyton has shown, the key characteristics is just the data and assembling data, and, you know, looking at where it fits. And then experts get together and then really look at those, you know, strong, limited or inadequate characterizations. So there's still a weight of evidence approach. And it really gives assessors peace of mind.

So we are looking at known mechanisms and really, you know, some of the unknowns, you know, we're learning about mechanisms every day. But in reality, you know, if we look at whether that's truly a new mechanism or whether that's just a vignette of something that already has been

defined, really we're dealing with known knowns. But we may or may not have data for each one of those, but at least we can then use ToxCast and other data to understand where maybe we are missing research or funding from a particular mechanism. So there's a lot of positives.

But, you know, we all need to acknowledge that there has been a lot of criticism and the criticism has come from, you know, a few individuals and organizations. And that's -- you know, it doesn't make that advice any less valid. And that advice or criticism has evolved in the last five or six years. So some of the early criticisms were that this is really -- you know, there was no guidance how to do this. Well, in reality, there is very detailed guidance in the instructions for authors and also IARC staff was there to really, you know, guide all the working group members on the principles and then let them apply those principles.

The early criticism was that these are not predictive of cancer. And these key characteristics were never actually meant to be predictive of cancer. They were meant to be a data organization tool that then will be used in the weight of evidence approach.

You know, again, the oxidative stress criticism some even question whether it's a plausible human cancer mechanism. I think we can have a good discussion and

robust discussion about that and I'll have a last slide on that on how these key characteristics cut across different icities.

--o0o--

DR. RUSYN: But some of the more recent criticisms have been that really this has been some sort of a conclave of experts who are not regulators. I think if one does really take time to look at those who are listed as authors on key characteristics publications, they'll see that it's really an incredibly diverse, both internationally and kind of, you know, stakeholder type collaborative of individuals. And then this whole overlap, you know, that cannot be discriminating that we already had a little bit of that discussion and I hope that we can have that after my presentation as well.

So all of these, you know, positives and criticisms need to be taken into account. And I wanted to be, you know, incredibly transparent with you, not to say that this is something that everybody just, you know, thinks is, you know, better than sliced bread.

--o0o--

DR. RUSYN: So what actually was done?

So these 19 monographs, they're voluminous, you know, they're hundreds of pages. You know, Chapter 4 where mechanistic data is described, you know, is -- you

know, some of these monographs are longer than others. But basically, you know, I took a lot of time to go through each one of these books and, you know, I've tried to look my expert judgment to supplement some of the decisions that were really made by the working groups themselves.

So there is a, you know, spreadsheet that has 19 tabs for each of the monographs. And each tab has all the agents that were evaluated in that particular monograph. So I'm just showing pretty much a random screenshot of one of those. I don't even remember which monograph this is. But here is an agent. Here's final classification. Human, animal, and mechanistic evidence strength as described by the working group in Chapter 5 of the monograph. And then you already have seen from Dr. Cogliano's presentation that -- and especially it's in the current preamble, IARC working groups have been really trying to be diligent in separating model system evidence, exposed humans, and human cells, and mammalian. And really it's rodent studies, in vivo rodent studies, in vitro. And then other in vivo. Sometimes there is, you know, fish and other organisms, other in vitro, a lot of data. It would be bacterial studies and genotoxicity and other types of studies.

The ToxCast data has really come to fore since

about 2015, 2016. Some of the monographs also looked at ToxRefDB as EPA was querying all of their 90 day and two-year cancer bioassays and putting that into the database. There are a couple of monographs that actually looked into ToxRef database. And then this overall strength, this is -- again, in the Chapter 5, the working groups have drawn conclusions on each of the key characteristics. And the terminology evolved a little bit pre- the last revision of the preamble versus post, but it's really not that different.

What is expert judgment is this stuff in the middle, as you can see these no, yes, equivocal, or empties. This is me using my best 20 years of not only toxicological knowledge, but also, you know, dozens of IARC monographs and National Academy working groups looking at risk assessments in trying to read, evaluate -- and evaluate the data. And when it's empty, meaning that there was no data on that particular key characteristic from that particular model system, when it says no, the working group enlisting all of the evidence evaluated pretty much was saying that there was really no evidence from mammalian in vivo, for example, for is it electrophilic or it can be metabolically activated.

It's not simply there was no evidence. No. That there is evidence and there is no evidence for that

particular agent, you know, acting through this key characteristic. Now, when I put a yes, preponderance of evidence was positive. When I put equivocal, it meant that there were some studies that were showing that it could be involved, some studies meant -- showing that it wasn't involved. So it's -- you know, it can go either way and I coded it as such.

And so I used that, you know, same idea going through all of these. And really because I, you know, haven't done research on most of these chemicals, I was just taking the information at the face value using my best expert judgment. And then some of the statistical analysis was done on this evidence pivoted in a slightly different way. So it's the same data, but this other table assembled the mechanistic conclusions, so at least agent lists the final classification.

And then I'm focusing on the mechanistic data role, as you can see here, mechanistic strong, mechanistic limited. Sometimes it says it's supportive. Sometimes it says it was not used. Sometimes it was used to upgrade the classification. And then for each of the key characteristics, I'm listing the strong, moderate, or weak. And this basically is -- you know, here it says suggestive. And again, it's a different way of three different names for largely the same thing. So to deal

with slight evolution of terminology, I re-coded everything as strong, moderate, and weak. And I think this is pretty much in spirit of what both the preamble and the previous evaluations have done.

And then there are really two types of analysis. One is descriptive statistics, kind of similar to what was published in Krewski et al. And I'm a co-author of that paper of the kind of retrospective evaluation, putting the key characteristic mindset and looking back at all of the known human carcinogens.

And now here we're actually looking forward with working group members specifically instructed to actually use this terminology. And we looked at by chemical, by cancer hazard classification, kind of, you know, how key characteristics were used for classification, and then which of type of evidence was used. And then, together with Dr. Fred Wright, we looked at some of the patterns, because I think a lot anxiety in the outside world is that, you know, when there is oxidative stress, then kind of everything -- the whole, you know, hell breaks loose and this ends up being a Group 1 carcinogen. So to look at this using information retroactively for 19 different monographs, I think that can give us some idea as to how different groups of experts were actually calling things and to see whether there was some patterns or not.

--o0o--

DR. RUSYN: So first let me kind of look -- walk you through some of the descriptive statistics. So first question really is how often were key characteristics used? Dr. Cogliano showed you that for known human carcinogens, there was a lot of use of key characteristics. Well, in reality, for these last 19 monographs, out of those 73 agents, only nine were classified as Group 1. So there were lots of agents Classified as 2A, 2B, and then Group 3. So that really is a more representative look at how things are.

And what's remarkable, and again this wasn't something that I had a preconceived notion of, as -- you know, when I embarked on this, was that the experts in these IARC monograph working groups are extremely cautious in calling key characteristics, you know, strong or moderate, because only 25 percent of all possible chemical key characteristic combinations, so 73 agents times 10 key characteristics, only 25 percent of the time it was either strong or moderate.

And as you can see is, you know, on average, you know, it was 1.3 key characteristics that were called strong for agent. And on the opposite what is important is that the working groups have actually said that it was either weak or no evidence whatsoever. So the

preponderance of evidence in this database actually shows that actually, you know, most of the key characteristics for most of the agents, there was no data for them.

And then if you look at the individual ones, then you also are seeing some interesting patterns. So here, these are 10 key characteristics and the colors represent them being called strong, moderate, weak, or no conclusion. And what you can see is, you know, these seven ones are the classical mechanisms of carcinogenesis.

You know, this is, you know, straight from the lectures that I teach our students in the first year on the kind of basic mechanisms of, you know, toxic effects of chemicals. And we all agree that these are very important and they can and known to participate in cancer mechanisms. The question becomes is whether it's one or many of them working together. But here nonetheless, you can see that it is genotoxic, because really it has the most data across all different agents, not just known human carcinogens. But among these 73 and the X axis here is the number of substances, and you can see that almost all of them had some evidence on genotoxicity. The second one most populous is really cell proliferation. The third one is oxidative stress. But metabolic activation, and immune-mediated effects and receptor-mediated events are also pretty well covered.

What is also interesting is that three key characteristics really have little data. It's DNA repair, epigenetics, and immortalization. And, you know, you'll see that pattern as I go through the data for you.

--o0o--

DR. RUSYN: So the second question is really how many key characteristics were available for Group 1 or 2A, 2B agents. And here, you know, as you can see from the data, Group 1 carcinogens have more key characteristics than were deemed to be strong moderate as opposed to Groups 2A and 2B. And this is really again a new type of analysis, because what Dr. Cogliano showed from Krewski et al. paper, we were only looking for Group 1 carcinogens. So here this is a comparison between something that goes to Group 1. And again, you know, there's not a lot of these, you know, only five, and then Group 2A, 23, Group 2B, 41, and the other ones. You know, if you subtract those from 73 were Group 3.

So, you know, you see that strong is significantly more in Group 1 and Group 2A compared to group 2B. But this is pretty much where the patterns actually end, because for 2A and 2B classifications, there's really too wide of a range from any key characteristics were deemed strong, moderate, or weak. So again, this fear that at the moment you have a key

characteristic that is strong, you immediately zip up to Group 1 is really not supported by the historical data. And again, this is, you know, dozens and dozens of experts looking at, you know, different types of data sets, different types of agents. This really is just not true.

And among the KCs that were deemed strong, there's clear trend for an average number of KCs depending on cancer hazard class. So here, you can see Group 1, 2A, 2B, and 3. And as you kind of move left to right, you see that the color intensity diminishes. So most of the strong ones are in Group 1. And this is a fraction. So again, it's somewhat misleading, because, you know, for this particular one, a hundred percent is five agents, and for this one a hundred percent is 23 agents. So one should not really, you know, delve too much into the length of these bars, but not of the last patterns are pretty clear. You go left to right, you have less or fewer strong key characteristic calls and you have more moderate, weak, or no calls at all.

So again, I think this is highly informative, but also what you see is that there is a -- you know, this strength of evidence is across different key characteristics. And some of them have more strongs for Group 1, but other ones you again still see genotoxicity as a strong key characteristic for both agents in 2A and

2B. So again, you know, fearing that an oxidative stress or genotoxicity strong will automatically elevate this, really you require other types of evidence to really be in Group 1 and Group 2A.

Now, this comes to mechanistic upgrades. This was already a question that Dr. McDonald asked, you know, can you classify an agent using mechanistic data alone. And as Dr. Guyton mentioned, according to the new preamble, you can do that into Group 2B. But again, you know, let's look at where in the individual monograph working groups were.

When a mechanistic upgrade was exercised, and this was done nine out of 73 times, and so not every time it went to actually Group 1. Most of the time, it went, you know, from 3 to 2B or from 2B to 2A. Strong evidence for several key characteristics was in place. And, you know, a lot more were supportive when working group had enough evidence from human and animal in vivo studies, but they looked at the mechanistic study, and they said, yeah, mechanistic data is supportive of this classification as well. So I think that's also fair to look at.

For the upgrades, you really, you know, need to have a lot of strong key characteristics, but the number varies from seven to one. And if you look at the upgrade versus supportive versus non-used, you see clear

statistical, you know, significant difference. And again, as you kind of, you know, go down into these supportive, or moderate, or not used, it's really a wide range of different individual numbers.

Among the key characteristics that were used to exercise mechanistic upgrade and the most impactful were strong calls for genotoxicity, cell proliferation, and metabolic activation. So you can see is genotoxic, you know, a hundred percent of those nine compounds were upgraded, but also, you see that cell proliferation, cell death, and metabolic activation, and it's really not oxidative stress, right?

So oxidative stress is an important key characteristic, but working groups were really not automatically upgrading using oxidative stress key characteristics. So again, I think this data is quite informative and should alleviate some of the concerns that have been expressed repeatedly by the critics of key characteristics.

--o0o--

DR. RUSYN: Now, I'm kind of, you know, going to show you two slides looking at this in a slightly different way. Now, I'm asking a question what data -- you know, from which model system, from humans, from rodents, from in -- you know, other types of models, in

vitro versus in vitro really went into each key characteristic?

And so here, this is where again, these are my expert judgments. You know, until now, I was showing you all working group conclusions. So here again, yes, I have looked at what the monograph says and what it lists as individual studies. And it was concordant studies for that particular key characteristic from that particular model system. Equivocal meant that again there were some positive, some negative studies, none is self-explanatory. There is no studies. And this one is basically the worst data to show that that key characteristic was not involved for that particular agent.

And here again, there's a number of conclusions we can draw. You know, one is that it is quite -- you know, unfortunate, is that data from exposed humans is really scarce, which means that we -- as going forward, we cannot really rely on data from exposed humans, because we'll have less and less of it, unless biomonitoring efforts really go forward.

Now, for the Key Characteristic 2 is genotoxic, the most informative data were human and rodent in vitro studies, not bacterial mutagenicity assays. So as you can see here these green ones, that's actually when you have these studies in mammalian cells, not in bacteria, because

in bacteria, there was a lot of studies that go, you know, positive. They go negative. They are, you know, with S9, without S9. There's usually a lot of data. And, you know, when there's a lot of data. There's more equivocal information than positive or negative information.

And rodent in vivo studies were really the most informative for the cell death proliferation. That's again something that Dr. Guyton already mentioned. You really need to have a 90-day study or a two-year cancer bioassay. And cell proliferation and cell death is evaluated in those. And that's really when most of the information was actually impactful. As you can see, more than 50 percent of -- or actually almost 75 percent of times when this key characteristic 10 was called as a yes, this was data coming from in vivo animal studies.

And what's already also was mentioned by Dr. Guyton, ToxCast data, really was this peace of mind data. It largely was used to say that key characteristic, you know, probably not involved for this particular agent. So is it useless? Absolutely not. It's incredibly useful, because it also tells you that there's probably very little out there that is unknown to us. So it's useful data, but it's not useful date to classify with respect to cancer hazard. It's actually to ensure that that particular mechanism or key characteristic are actually

not involved.

Now, it's the same information, but looked at in a different way. Now, I'm actually looking at each key characteristic and trying to look at where the information is coming from. And here again, I think, when you look at this way, there's a lot of conclusions that can be drawn. Most data rich key characteristic is genotoxic. But most impactful of this, you know, is human and animal in vivo and in vitro. Again, this bacterial assay is a lot of equivocal data, and most of the agents had rodent or human in vivo or in vitro information.

Now, for this particular, you know, key characteristic, a lot of data is equivocal, much larger proportion than for anything else. And again that pretty tells us that there's a lot of different assays, there's a lot of different endpoints that can be studied from adducts to, you know, higher order damage. And when you have a lot of information, you're likelier to actually see inconsistent studies. And data from exposed humans actually did contribute to seven of the 10 key characteristics. So however little there was, it was actually highly impactful and was highly impactful across the spectrum of key characteristics.

And finally, again, I cannot support more what Dr. Guyton was saying that rodent in vivo mechanistic data

was by far the greatest contributor to most key characteristics. So for those of -- you know, those of regulators or scientists out there who are trying to -- you know, to eliminate this evidence stream completely, I think they have to, you know, think long and hard about what we will be missing, and whether or not we can actually make health protective decisions without this particular data stream.

--o0o--

DR. RUSYN: So last one -- type of analysis I want to show you before I conclude with a comparison across different KCs is this kind of more statistical approach. So really we're looking at patterns here, associations. And we've done this in four different ways. And you can think of this as -- again, if I see one, is it likely for me to see the other? And this means it could be yes and yes or it could be no and no. So again, this does not preclude that the evidence always has to be of one type.

So the first type of analysis, Dr. Wright and I looked at was really for this overall strength call. And this is a call by the key -- by the monograph working group. When you have this overall strength strong for one, does it mean that the other key characteristic will be strong as well. And essentially, this is all pairwise

comparisons.

Now, ToxCast data was really the most filled in data set, because, well, we have mapped ToxCast assays to seven out of the 10 key characteristics, which means that, you know, there's hundreds of assays and there are usually dozens or maybe at least, you know, six or seven ToxCast assays that could be mapped to a key characteristic, and there's a lot of information. So I think it's instructive as well to see when one is yes is the other yes as well, and when one is no is the other no?

Now, Comparison C is really kind of, you know, going vertically. If I have a certain type of evidence, am I more likely to call it a strong, a limited, or something else? So again, is it -- is there bias for us or, you know, when we see human evidence, are we more likely to call it strong or not. And then finally, this upgrade, when the overall strength in a particular key characteristic is strong, is it likely or not that this will be a mechanistic upgrade, again not necessarily to Class 1 to Group 1, but it could be from to 3 to 2B, to from 2B to 2A, or from 2A to 1.

So there are four types of analysis and I'm going to, you know, quickly go over them.

--o0o--

DR. RUSYN: This biggest surprise I had was

actually how little association have we actually discovered. So for this association of the overall strength, really there are only three most kind of, you know, known things that every student should know that come togther -- appear to actually go together using these data. When an agent is electrophilic or can be metabolically activated, it's also likely to be genotoxic. When it's metabolically activated or electrophilic, it's also likely to cause cell death and compensatory cell proliferation. And then genotoxicity and oxidative stress also were co-occurring.

But what's important is that 42 other pairwise comparisons were actually not significantly, you know, associated with each other. And this was done, you know, using, you know, again a particular type of analysis and multiple testing correction to really have statistical rigor in this comparison.

Now, when you look at just ToxCast data, you see a few more patterns. Again, three of these key characteristics had no data, so they were excluded from the analysis. And again, it's, you know, not surprising there is a lot more ToxCast data actually being concordant.

--o0o--

DR. RUSYN: And I wanted to show you in a

different way, that it's not actually when one is yes, the other one is yes as well. It's actually for seven out of the -- for four out of those seven significant pairwise comparisons, most of the information was actually driven by not genotoxic, not epigenetic. And as you can see very few of them were yes and yes positive. But for some of them -- for some of these interactions between receptor-mediated events, between cell proliferation, and between oxidative stress, these were actually more balanced. When one was no, the other one was no. And when one was yes, the other one was yes. Again, these are highly significant associations and I think they are worthy of us thinking as to whether we may need to actually run this many assays, while maybe some of the assays actually are redundant, if we're thinking about screening more compounds in the future.

--o0o--

DR. RUSYN: Now, this model system, you know, when we have human data or rodent data, in vivo or in vitro, are we more likely to call something strong, or moderate, or weak? And really there are four different types of comparisons we tried. So one is say when I'm calling something strong versus something else, is the particular type of data important? And the answer is no.

When you look at strong or moderate versus weak,

really there's only one significant result, you know, it's more likely that there will be concordance or when -- is genotoxic will be called a particular way, depending on the mammalian and in this particular case again, it's mostly rodent in vitro data. So I think it's an interesting observation.

And in looking just strong and weak on the opposites, it's the same trend as just genotoxicity in mammalian in vitro. And then these moderate versus weak again, there's really no significant result. So again, what this tells me is that weight of evidence and expert judgment is really, really important. And I don't think AI can really kind of, you know, learn these trends and then immediately start calling things. I think working groups really spend a lot of time discussing and making sure that they carefully call these things and they're not just simply, you know, looking at patterns necessarily. So again, these pairwise correlations being so weak tells us that each agent is different, each data set is different, and you really need to have expert judgment.

--o0o--

DR. RUSYN: So finally, it's the -- you know, the question that I think worries most is whether the overall strength, something being strong, moderate, or weak is actually going to drive a mechanistic upgrade. And again,

of all of these pairwise correlations, only one is significant. When something is genotoxic and the strength of that evidence in a genotoxic key characteristic will or is significantly determining the mechanistic upgrade. When it's strong, you know, it is going to be upgraded, but not always. As you can see, there is, you know, many more were called strong and then these data were not used. But when it's weak, then again it's highly likely they will not be used.

So again, genotoxic is, as Kate called it, no brainer key characteristic, but it still has to be applied with a lot of caution, because a strong call in genotoxic does not always, and actually less than half of the times, leads to a mechanistic upgrade.

--o0o--

DR. RUSYN: So last slide that I have is I wanted to again address this persistent comment that the -- those who critique key characteristics have brought up, is that these key characteristics lack specificity. And Dr. Eastmond already asked this question as well. So myself, and Dr. Chu, and a couple of our students recently put together kind of, you know, these key characteristics across seven different -icities that have been called, so these were, that Dr. Cogliano showed already, from carcinogens to cardio toxicants and others.

And then what you can see if again it's expert judgment putting key characteristic and linearizing them, because they're kind of the same at cell proliferation or cell death. You can see that six out of seven -icities for them this is a very important mechanism. Now, oxidative stress and receptor-mediated events are occurring in five out of seven. So again, this is common -- you know, these are common types of mechanisms. When you look at epigenetics and chronic inflammation, you can see that this is across four different -icities than, you know, genotoxicity and electrophilic activation and hormone receptors really are occurring, you know, fewer and far between. Even genotoxicity is not unique to cancer. It also was -- it also was identified as a key characteristic of both male and female reproductive toxicants.

So again, you know, specificity is one issue. How it is being used and interpreted is a completely different one. Now, as you can see, there's, you know, a few more that occur maybe in two. And then there's some that are truly specific or selective. But again, they're pretty narrowly focused. Most are for immunotoxicants. These are very, you know, small things in immune cell, you know, propagation and, you know, maturation.

The second one is for cardiotoxicity, this, you

know, receptor-mediated events and also the excitability and, you know, ion channels. And then, you know, some others have unique ones. But it's not surprising that these key characteristics actually co-occur in different -icities. What I think guarantees specificity for everything except for human cancer is which cell types that have -- they have been studied in. When you study something in a hepatocyte and in a Kupffer cell, you know you can pretty much actually attribute that to liver. But for carcinogenicity, you have to look holistically. And to add to Dr. Guyton's answer, I think that working groups that I've participated on have always looked for target tissues in animals and in humans and then looked for key characteristics in cells from those particular target tissues.

And then altogether, that actually provided some additional specificity, but I don't think we can say that oxidative stress is not a cancer mechanism. And the fact that it's a mechanism of different -icities does not diminish the information that we can actually get from mechanistic studies. So with that, thank you very much for your attention. I'll be happy to answer any questions.

CHAIRPERSON LOOMIS: Thank you very much, Dr. Rusyn. Let's go to the Committee and see if there are

again any questions of clarification or comments?

Well, I'm not seeing any immediately, so I'll offer a comment and a question. So you mentioned that there seems to be a preference for making the calls of strong evidence based on data from exposed humans or animals in vivo, mammals in vivo. And I think you referred to it as a bias. I would say that's actually not a bias, it's a desirable feature, you know, since it should be getting us as close as possible to, you know, the right test system.

DR. RUSYN: What I said it was out -- through this analysis, we examined whether this was a bias or not. For example, if we have human data, do we more likely to call something as strong evidence for key characteristic. And I think it's not really having those data, but actually having the strength of the database and other evidence as well. And so what my analysis shows that there is actually very little bias in these evaluations. So I am sorry if I was not clear in that.

CHAIRPERSON LOOMIS: Well, thanks. It looks like Dr. Landolph has his hand up, so please ask your question.

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

COMMITTEE MEMBER LANDOLPH: Sorry. Yeah. Ivan, very nice talk. What is -- what are the largest number of key characteristics you've ever found in a carcinogen?

DR. RUSYN: So I'm going to the data, and I want to say that for Group 1 carcinogens, that were evaluated in that batch, again, 19 monographs, 73 different agents, five agents went to Group 1. And two of those agents had five key characteristics, two of the agents had two key characteristics, and one of those agents had no key characteristics. But again, it was, you know, the type of dietary exposure that really is impossible to study mechanistically. So again, you have to interpret all this with obviously caution and appreciating the diversity of things that IARC monographs are looking at.

COMMITTEE MEMBER LANDOLPH: All right. Thank you.

DR. RUSYN: If you recall, from Vincent's presentation, there were a couple three agents that had eight or nine. But those were again known human carcinogens that have been studied to death for the last 50 years, right? So -- and some of the things that the IARC monographs have looked at more recently do not enjoy as extensive of a database as some of the historical calls by IARC.

COMMITTEE MEMBER LANDOLPH: And I'm guessing, you know, for aflatoxin, which sticks in my mind, because it's so disproportionately mutagenic once it's activated by orders of magnitude over some of the carcinogens, I'm

guessing it's primarily activation and DNA adducts, and mutation coming out of that, and you don't really need all the other things. It's just so damn strong and genotoxicity.

DR. RUSYN: But people do study things. And IARC monograph working groups are looking at the entire evidence base. So one would think that we will close the book on some of the agents and stop studying them, but that unfortunately is yet to happen, so...

COMMITTEE MEMBER LANDOLPH: Yeah, I agree completely. Thank you very much.

CHAIRPERSON LOOMIS: Okay. I think Dr. Bush also has a question.

COMMITTEE MEMBER BUSH: More of a comment than anything. I just -- thank you Dr. Rusyn. This really helps with our framework. I think, you know, our challenge is trying to, you know, map these discrepancies. You know, we have to make a black or white call on, you know, a gray area. And, you know, I think this does help very much in that deliberation, at least in my opinion. So thank you for the presentation. It's very helpful.

CHAIRPERSON LOOMIS: Are there any other comments or questions from the Committee?

Okay. Dr. Landolph, your hand is still up. I don't know if you wanted to say something else or just

forget to put it down.

COMMITTEE MEMBER LANDOLPH: Thank you. I can't get this thing to go down. Sorry.

CHAIRPERSON LOOMIS: Let's see. Dr. McDonald, it looks like you just came on camera. Did you want to comment or --

COMMITTEE MEMBER McDONALD: Yeah, I did want to explore the topic a little bit further, Dr. Rusyn. You know, there's the criticism of counting key characteristics and doing limited versus strong. I just want to get your perspective about -- I'm glad that you brought in professional judgment and how -- I'm curious how the IARC committees were viewing a lot of this where do they view it in terms of a mechanistic story or an adverse outcome pathway that leads to a specific tissue type? I mean, are the upgrades to the observed tumor types -- can you go into a little bit more about how different groups have approached that?

DR. RUSYN: Yeah. So I cannot speak on behalf of all of the groups, but since key characteristics were put in place, I think I participated in three or four monographs, and before that, and a handful as well, so -- and I chaired a mechanistic subgroup and chaired overall monograph once, again in that period from 112 to 130. So Dr. Guyton can kind of comment more from the staff

perspective, because staff's role is really to enforce the rules and to make sure that the working groups are sticking to the preamble, and not veering into these endless mechanistic conversations.

So working groups really are instructed to, first, collate the evidence using the systematic literature search approach and then kind of look through each of the key characteristics and the papers that have been identified as relevant and containing data, and then start making calls on strong, moderate, or weak, or again, you know, whatever the strong, limited, and inadequate terminology they were using.

So working groups would take these data in isolation and look at each key characteristic and then, you know, reach conclusion through the debate of the strength of evidence, the internal/external validity considerations, and other things.

And then altogether, then they would put this information, and then they would look as to, you know, what types of evidence you would have, and whether or not this type of evidence would lead to a classification into 2B. As you've seen from the preamble, each of the sections proposes its own classification using data within their domain. So first, you kind of do the classifications in your subgroup and then when you get

into plenary, you are actually comparing classifications and you're saying, oh, we all came up with 2B. Great. So there's, you know, human and animal data say this and mechanistic data is supportive or human and animal data is inadequate or limited, but mechanistic subgroup feels that there's strong evidence for a number of key characteristics, and they all come together. And with whatever little data we have in animals, it's actually highly concordant.

So then the discussion would be had to propose a mechanistic upgrade. And there has to be a vote from the -- you know, from the entire working group. And sometimes you would have a minority opinion or, you know, someone who's a dissenting vote, and that is written up in the monograph. And it's an incredibly structured but open and kind of logical process where you make decisions internally, and then you actually, you know, compare your decisions to other strength -- streams of evidence, and then collectively you ultimately arrive at the final classifications.

So I hope that describes it. And Dr. Guyton, would you like to weigh in.? If my memories of last in-person pre-COVID meeting are correct.

DR. GUYTON: Yeah. So, Dr. Rusyn, I think you described it perfectly. I think the only thing I would

say to complement is that depending on the type of evidence being considered, let's say it's a mechanistic study in exposed workers and it's really an epidemiology study. Well, then you may be able to pull in some expertise who have that field experience to weigh in. What's the quality of this study? Well, how does this relate to other types of studies?

At the same time, I think both Dr. Rusyn and I emphasized with so many of the -- for so many of the KCs evidence coming from these chronic be it 90-day or the longer term bioassay, you may want to get your veterinary pathologist to go ahead and help review that information before you -- as you're trying to judge, as I said, intern -- it's the internal validity, how good is that study, how strong is that evidence stand alone, and how does it fit with the rest of what you're trying to wrestle with?

And I think that's one of the great strengths of the monographs is really this interdisciplinary opportunities where you have different experts from the field who are able to say, hey, I know you don't really know anything about maybe mechanistic information, but you've done a lot of epi studies and I'm looking at this epi study and, you know, what should I look for -- when -- you know, is this a really strong study or maybe it's not. Maybe it's totally uninformative and I should just set it

aside. So I think those -- some of those, in addition to all the points that Dr. Rusyn made, are part of this expert judgment process.

DR. RUSYN: And, Dr. McDonald, again just to add to your comment whether this is a really box checking exercise, and we're counting cards, and then there's a magic number. That is a very common concern of those who really have not participated in the process either as a participant or an observer. And I invite again those on the kind of members of the general public who are, you know, interested in how the -- these things happen as to, again, you know, participate, you know, to submit their name to the working group observer and then go and actually have access to all of the deliberations and all of the drafts. It's an incredibly open process for those who have not experienced it.

But retrospective analysis that I've presented, over 19 monographs and 73 different agents is really, you know, looking in the past and asking a question, you know, would we be able to check the boxes and call Group 2B, 2A, or 1 just based on the type of evidence that we have as kind of Dr. Besaratinia said, can we train AI to do this? The answer, in my opinion is no. It's always context dependent. It's always an expert judgment. It's always a group decision, and you can have zero to five key

characteristics, and you can have five key characteristics that are strong and still end up in 2A or 2B. So it's really not a -- you know, a box check -- checking exercise and hopefully again this analysis going retrospectively over, you know, more than decade will, you know, appease some of the criticisms and concerns that have been levied on this particular process.

COMMITTEE MEMBER McDONALD: Thank you for those perspectives. Appreciate it.

CHAIRPERSON LOOMIS: You know, as former IARC staff, I might also comment on this notion of counting KCs. You know, we have the same problem with epidemiologic studies, right? There's a simplistic tendency to say, well, we have this many positive and that many negative, you know, and count the votes that way.

I don't think that's at all what happens with the KCs. Just like with epidemiologic studies, the evaluation of study quality is extremely important and we really need to pay attention to that. Rather, I think this retrospective analysis shows that the greater challenge is that it's really difficult to get to strong unless you have a lot of studies. And that also is probably a necessary feature. You know, it makes sense logically that you feel more confident in making a call when you have more information, and that information is higher in

quality.

But I think that's one of the messages I took away from looking at Dr. Rusyn's analysis that more data is better, and, you know, that the more we have the more likely we are to feel confident to make a call of strong evidence.

DR. RUSYN: But we can also -- with more data, we can actually lead to no relevance of that KC or more data can lead to equivocal conclusions. So more data does not mean a certain classification, I wanted to point that out as well.

CHAIRPERSON LOOMIS: No, absolutely. And I think that's, you know, the other side of the challenge, that it's hard to say no effect when you don't have enough data to demonstrate that. In fact, it's probably harder to do that than to say, well, there is an effect or there might be an effect.

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

COMMITTEE MEMBER BESARATINIA: Yeah. Dr. Rusyn, great talk. Really enjoyed it. My question is, as you know, there are numerous assays to evaluate each of these KCs, and each of these assays have their own strength and limitations. I'm wondering if there is any explicit guidance on what methodological strengths and limitation

to consider when evaluating a potential agent -- an agent for potential carcinogenicity? Does IARC provide such guidance to its panel or working group?

DR. RUSYN: Excellent question. And I will invite Dr. Guyton to weigh in on this as well, because she actually has done some of the analysis that she showed in those posters along those lines. Let me just start by saying there's really two types of mechanistic evidence that the working groups have looked at since key characteristics were put in place. One is just kind of your regular as you go publications. People do, you know, whatever they are funded to do or they're please to do.

They use assays and methods that they think are most appropriate and that's largely unstructured, you know, data set. But it's -- you know, it's organic data set. It's incredibly rich and informative. And then on the other hand, you have ToxCast data that is standard package that most of the compounds have been run through. And when we map those ToxCast assays to key characteristics, as I already said, only seven out of 10 could be met. And in reality, if you really press a mechanistic toxicologist, like are those assays really relevant? Probably, there's three or four key characteristics, and the coverage of that particular key characteristic is still limited.

So it's a great data set. It's standardized. You have hundreds of chemicals run through it, which means that you can put your chemical on the ranked scale with other known carcinogens, you know, oxidative stressors, or receptor activators, and really say, well, yeah, it activates receptors, but it's in the bottom 80 percentile and I probably should not really pay too much attention to it.

So those two different things are what working groups are looking at. What you're asking is is number three, is this perfect list of assays that if we would only arrive at it then, and run every chemical, then we truly can make an informed decision. And that's largely unattainable. However, what the AOP universe is trying to do, so adverse outcome pathways, they're trying to really, you know, put these boxes together in sequence for a particular, you know, exposure to the outcome, and then to see which of the in vitro assays really match those boxes. So kind of can you reconstruct an entire process with in vitro assays and maybe some in vivo assays?

And this is an incredibly painstakingly and long and hard process. And in the last 10 plus years that AOP concept has been around, there are only really two adverse outcomes for which that exists to a degree where regulators are now comfortable using it. One is a skin

sensitization, the other one is very recent and it's not an official OECD guidance yet to my knowledge, but should be published this year on developmental neurotoxicity.

So groups of experts got together and said, we agree that this how is happens and then we agree that we have assays to probe each step. The question is now can we do the same for cancer? And as a mechanistic toxicologist I think maybe, but we are not there yet. So hopefully, that answers your question to a degree. And Dr. Guyton, would you like to maybe weigh in on the analysis you've done with Dr. Smith?

DR. GUYTON: Yeah. So first of all, great question and second of all, great answer from Dr. Rusyn. I might complement it by just saying, you know, for some -- for some of these KCs we do, we as a community have standardized assays. Dr. Eastmond is much more of an expert in this area when it comes to these -- for example, like the genotoxicity battery. So this is a kind of standardized test and you do have -- like you have in ToxCast, you have so many chemicals that have been screened through that, and it's a little perhaps easier to judge for any individual chemical based on this wealth of experience, what's quality assay and how to interpret the results.

But even there, there was a publication recently

that just said, you know, there's still a lot of chemicals that may be on the bubble. Nobody can really decide. They get screened and re-screened. Sometimes they're positive, sometimes they're negative. And those -- for those more questionable cases, it's always going to be hard to make the call when there's -- when there's gray area.

Having listened to many, many working groups, I would say, you know, if you're in a gray area, strong is not a gray area. Strong is an area where you have colored things in in a bold and you're ready to say if more research were done -- were done, it would not change my conclusion. I feel like this has been adequately studied and explored, and I'm ready to kind of call it a day. And it doesn't mean that more things will be found -- won't be found later, but at least we're able to kind of put a marker on where we are, you know, bearing in mind assessments are snapshots in time, right, so --

DR. RUSYN: Just sort of to add, I believe as Dr. Bush who said that, you know, the CIC needs to make a kind of -- you know, a clear cut decision and so do working group -- working groups at IARC, and so does IRIS Program, or Division of the National Toxicology Program. And what they -- those organizations have found, is that key characteristics really helps them with making those

decisions, because you're making decisions in a smaller universe. You're not looking at the entire mode of action analysis, where things can go left, right, and sideways. You're actually looking at each key characteristic. You're zeroing in on relevant evidence. And even if it's voluminous evidence, you're still looking at internal/external validity, the strength of evidence, the -- you know a Bradford Hill criteria, whatever you want to name it. Strong decisions are reserved for cases where everyone agrees that this is it. And as I've showed you, again only one-eighth of the time working group having had an agent and a set of key characteristics had concluded it as strong, and 67 percent of the time, it actually made no conclusion at all.

So I think this is highly informative and it shows how difficult, and how high the bar is, and how diligent the experts are. These are, you know, not bunch of cowboys, you know, myself excluded who are riding in and, you know, blazing saddles, and just shooting at everything that goes there. So, you know, hopefully you see this from the data rather than just from the experts who have participated.

COMMITTEE MEMBER BESARATINIA: Thank very much. It was very helpful, both Ivan and Kathryn. I appreciate it.

CHAIRPERSON LOOMIS: Well, thank you, everybody. Thanks, Dr. Rusyn and Committee members. We are approaching our designated lunch time. So unless there are any other burning questions from the Committee, I'm going to call a close to this questions and answer sessions. I'm not seeing any hands, so at this point then, I will turn it over to Chief Counsel Carolyn Rowan to give the warning about the State of California Open Meetings law.

CHIEF COUNSEL NELSON ROWAN: Thank you. I just want to remind the members quickly that during breaks, like the lunch break, you shouldn't talk amongst yourselves about the subject matter of the meeting, and that includes phone calls, texts, and chat.

My recommendation would be that you also don't talk to third parties about the items being discussed on the break. And if you do, you should -- you should disclose the fact that you had a discussion with someone on the break and give the general content of that discussion, so it's part of the public record. It's just best to chat about something else over lunch.

And that's it for me for now.

CHAIRPERSON LOOMIS: Okay. There you have it.

So I will propose that we adjourn now for lunch. The agenda gives us 45 minutes. So it's almost 12:20 and

that brings us back at 1:05. So if that's agreeable to everyone, let's come back at 1:05 and we'll resume the meeting at that time.

DR. RUSYN: Dr. Loomis, a quick question, if I may?

CHAIRPERSON LOOMIS: Sure.

DR. RUSYN: Do invited speakers need to be present after lunch as well, because the agenda, you know, involves some of the other topics. So I just was wondering if and when you'll be releasing us?

CHAIRPERSON LOOMIS: Well, I didn't know that was up to me.

DR. RUSYN: All right. Well, then can we ask the lawyers?

CHAIRPERSON LOOMIS: Let's let Lauren comment on that.

DIRECTOR ZEISE: Yeah. Hi, you know, we are going to have an opportunity for public comment after lunch and it would be great if you and Kate would be able to join the discussion. So if you're able to join after lunch, that would be wonderful

DR. RUSYN: Great. Okay. That's answers my questions, so we'll reconnect in 45 minutes. Thank you

DIRECTOR ZEISE: Thank you so much.

CHAIRPERSON LOOMIS: There you have it. Thank

you.

(Off record: 12:20 p.m.)

(Thereupon a lunch break was taken.)

AFTERNOON SESSION

(On record: 1:05 p.m.)

CHAIRPERSON LOOMIS: Well, good afternoon again. It's the appointed time for the meeting to reconvene. So I'm going to ask the Committee members who are present to come on camera for just a minute, so we can take stock of who's here.

All right. It looks like we may be missing one or two. So we'll wait for just a minute before we reconvene.

All right. Well, I think that's long enough to wait. Hopefully, the remaining member or members will rejoin momentarily. It's now time for the opportunity for public comment. So let's turn to Amy with the slide with instructions on providing public comment. And I'll briefly review that.

Okay. So in order to make a comment, you must be in the Zoom meeting. So the instructions are shown here and you may have received them already through the OEHHA webpage. If you want to make a comment, you can click on the raise hand icon to indicate that you'd like to speak. And then when your name is called, you'll be prompted to unmute yourself and identify yourself with your name, and affiliation, and give your comment. Comments will be limited to five minutes.

So let's go ahead and see whether there are any commenters waiting to speak.

MS. VAGHEFI: There is one raised hand by Jessica Ryman-Rasmussen. I am going to give you permission to unmute yourself and then you will have five minutes.

DR. RYMAN-RASMUSSEN: Okay. Thank you. Hello, everyone. I'm Jessica Ryman-Rasmussen. I work for the American Chemistry Council, ACC. ACC is a trade association that represents the leading trading -- that represents the leading businesses or companies engaged in the multi-billion dollar of chemistry. And I am -- I am commenting on behalf of ACC today.

So we've been discussing today the key characteristics of carcinogens. But unlike the specificity of silicosis from silica dust, not all of the KCCs are specific to the endpoint of carcinogenesis. Induces chronic inflammation could be said to be a key characteristics for acne vulgaris, while induces oxidative stress and alters cell proliferation, cell death, or nutrient supply could be said to be key characteristics of exercise and wound repair respectively.

Therefore, it's not clear that the KCCs should be used for regulatory decisions. Seven years ago, the KCCs were proposed as a basis for organizing mechanistic data. However, since that time, key characteristics for other

endpoints have been proposed and use of the key characteristics has expanded, in some cases, to directly informing hazard identification.

Becker et al. in 2017, which was a study funded by ACC, and ACC -- and Rick Becker is one of my colleagues here at ACC evaluated whether key characteristics of carcinogens could distinguish carcinogens from non-carcinogens in a study entitled *How Well Can Carcinogenicity be Predicted By High Throughput "Characteristics of Carcinogens" Mechanistic Data?* This study used U.S. EPA's ToxCast data of effects of chemicals in mechanistic assays - so this is bioactivity data - and mapped these assays and data to seven of the 10 KCCs. They compared the results to U.S. EPA's previously derived cancer classification for the same chemicals, conducted extensive statistical analyses, and used machine-learning algorithms to evaluate the predictiveness of KCCs to distinguish or predict EPA designated carcinogens from EPA designated non-carcinogens.

The results clearly showed that bioactivity corresponding to the so-called key characteristics of carcinogens was no better than chance in predicting cancer classifications. Since that time, studies by Bus in 2017, and Goodman and Lynch in 2017 have raised concern with using the KCCs as a tool for assessing cancer hazards. In

Smith et al. in 2021, recently affirmed that the KCCs are too broad and nonspecific for evaluating the potential cancer hazards of chemicals. These findings raise legitimate questions about the value of the KCCs. The KCCs have no value in hazard identification, as evidenced by the 2017 study by Becker et al. showing they predict cancer classification no better that a toin coss -- coin toss.

The KCCs also have no value for just organizing information because of the potential risk of anchoring errors. The Merck manual describes anchoring errors as quote, "When clinicians steadfastly cling to an initial impression, even as conflicting and contradictory data accumulate," end quote. Here the name itself, "Key Characteristics of Carcinogens," instead of, for example, "Key Characteristics of Potential Carcinogens," contains a conclusion, even though some of the KCCs are not specific to carcinogenicity.

Interestingly some of the KCCs, such as oxidative stress, sustained or receptor activation, which is a type of modulate receptor-mediated effects and cell proliferation have been proposed as key events and modes of action, or MOAs, published before the KCCs.

However, because --

MS. VAGHEFI: One minute.

DR. RYMAN-RASMUSSEN: -- because some in the scientific community regard KCCs as new and different, the use of KCCs is not necessarily subject to the formal causality criteria of the IPCS mode of action framework for carcinogens or the OECD AOP guidance which were developed for regulatory use. These concerns raise questions about how KCCs should be used, if at all. Meek and Wikoff in 2023 proposed good practice that assimilates KCCs into an integrated M -- AOP and MOA pathway construct, essentially using KCCs as a means to identify key events.

This is consistent with earlier conclusions in Becker et al. In 2017 for incorporating mechanistic data into cancer hazard evaluations, we specifically recommend adoption of the AOP or MOA framework that articulates toxicity pathways, comprised of sequences of key events starting with an initial molecular event followed by a series of key events linked to one another ultimately resulting in a specific adverse outcome.

MS. VAGHEFI: Thirty seconds.

DR. RYMAN-RASMUSSEN: In closing, we encourage the CIC to conduct its own risk assessment benefit of the regulatory use, give the concerns we've noted. We appreciate the opportunity to comment.

MS. VAGHEFI: All right. Thank you. I don't see

any more hands raised.

DIRECTOR ZEISE: Okay. Is Dana on?

And if not, I wonder if any of the speakers have anything they would like to say in -- considering the public comment or -- and then maybe the Committee?

DR. RUSYN: You know, I appreciate Dr. Ryman-Rasmussen's comments. I think I already provided very similar points without seeing actually her written comments. All of the papers that she mentioned were already included in my presentation. I did not have a specific point-by-point response. I just wanted to add one thing which is I agree that ToxCast data by themselves cannot be used to predict anything. But this is again not how key characteristics are being used. They are used to organize all of the evidence available, including ToxCast. And as I have showed you in my analysis, ToxCast data are useful to show that the key characteristic is actually not involved.

So for completeness sake, they are incredibly useful. But I am not aware of a IARC monograph working group reaching a conclusion about strong key characteristic using ToxCast data alone. Again, I was just recalling reading through these 19 monographs and all of the things, I don't believe I have encountered such a case. So it's a very useful analysis, but it's an

analysis that is really, you know, irrelevant to the information that I present.

DIRECTOR ZEISE: Thank you, Dr. Rusyn. And I also see that Dr. Guyton's hand is up, so if you'd like to comment.

DR. GUYTON: Yes. Thank you for that opportunity and I've really appreciated these comments and perspective. I would echo what Professor Rusyn has said the Becker et al. publication, which we have read with great interest, really concern that ToxCast data. And as I mentioned and Dr. Rusyn mentioned, that hasn't actually been informative for IARC monograph evaluations. It doesn't mean that it's not useful at all. The monographs are really into this question, does the substance cause cancer? And this particular database is not designed to answer that question, so it's not really surprising that this analysis produced those results.

I do think it highlights some opportunity that several of us highlighted for future progress to develop assays that are much more aligned with the KCs and really begin to explore how they can be exploited in different types of experimental systems, including in epidemiology studies. As I mentioned, I think occupational cohorts are a great opportunity and perhaps not as tapped as they might be given all of the concerns Dr. Loomis raised about

the changing landscape of what those exposures are and the types and the natures of the studies. You know, we have the opportunity to be much more sophisticated now. And I think we want -- all want to be prepared to evaluate that evidence when it -- when it is available and to use it to make these very critical judgments.

So -- and again, with respect to the mode of action framework, I think this is -- this is asking mainly a different question than the KCCs as I framed it. The KCCs kind of give you a different PECO question, which is does -- is the agent genotoxic? That's really -- it's a much simpler question than what is the flow diagram, if you will, from exposure to outcome? That is a much more complicated question. And the KCCs intend to kind of break that down.

I think as Ivan highlighted, this can really help when you're making an expert judgment, because like anything, if you break it down, it's easier to see -- to get some clarity on what actually you're deciding on. So those are my perspectives. I'm happy to continue the dialogue, either separately or in any format to clarify any misunderstandings.

DIRECTOR ZEISE: Thank you, Dr. Guyton.

I see that Dr. Cogliano's hand is up. And you need to unmute.

DR. COGLIANO: I'm sorry about that. I'd first like to make the point that we did not call them the key characteristics of potential carcinogens because they were developed with the database only of 100 known human carcinogens. We didn't want the key characteristics to be possibly tainted with agents that their -- the carcinogenicity was in doubt. These are all carcinogens that everybody recognized, so they are the key characteristics of known carcinogens.

I'd like to take the opportunity to say I was really impressed with some of the analysis that Dr. Rusyn presented and how they match with the initial analyses that Dr. Krewski and colleagues have done on the original hundred carcinogens.

The -- I think we had about five or six on average of the known human carcinogens, five or six key characteristics were positive. And I think Dr. Rusyn showed that a smaller amount is -- has been found in the more emerging carcinogens in the last 20 or so IARC monographs. So that one shows that working groups are not running wild with a few key characteristics and classifying carcinogens. There's still animal and human data involved there. But also, I think it shows that the more you study an agent like DES, like trichloroethylene, like diesel engine exhaust which had eight or nine key

characteristics, you're going to find more things and people want to find out more about how they're operating once they know that they are and they're likely to be carcinogenic.

So I think that there's a good correspondence there that -- between the initial carcinogens that were identified from -- form primary occupational studies and well known mutagens in the 1970s to have more key characteristics than the emerging carcinogens now. And also in Dr. Guyton's presentation, I think that they do show a real caution or care in applying key characteristics to questions. And I think that's the thing we've got to do.

We have to recognize the key characteristics do come from known carcinogens from analysis partic -- where there are a lot of experts participating. And it's how we apply it that's going to be the issue in the future.

So thank you.

DIRECTOR ZEISE: Thanks, Dr. Cogliano.

I see that -- I see Dana's connecting to audio, so -- sorry, Dr. Loomis is connecting to audio. So hopefully, he will join us shortly. Maybe if we could just take a little pause for a minute or two and try to get him online.

Welcome back, Dr. Loomis. So, yes, we've just

had a discussion following public comment. And thank you for joining on. And I'll turn it over to you. I see that Ivan Rusyn's hand is up.

CHAIRPERSON LOOMIS: Okay. Very good. Yeah, my apologies. We're having some thunderstorm activity here and my computer shut down unexpectedly. And so it took a while to get back on, but I am here now.

So we can continue. So Dr. Rusyn, I see your hand is up again, so please go ahead.

DR. RUSYN: Yes. Thank you. I just wanted to cover one more topic that Dr. Ryman-Rasmussen has brought up. And this has again been something that has endured quite a bit of conversation is key characteristics, adverse outcome pathways, MOA framework. And I think this is really interestingly described in the 2023 Meek and Wikoff commentary in Toxicological Sciences that they put together based on a 2022 symposium that happened at the SOT meeting a year ago -- year and a half ago almost now.

The point of all of these and which one is better is really, in my opinion, irrelevant. I think what is important is what is the question, and what is the database, and what is the process. And U.S. EPA IRIS Program, NTP report on carcinogens, IARC Monograph Working Program have included key characteristics as part of their process. And they're using them in accordance with the

process that has been described.

The key difference between adverse outcome pathway and the key characteristics is that adverse outcome path -- well, there's several and I'll just try to, you know, stick to two. One is AOP is really a crowdsourcing type of activity where anyone can start an AOP, go to AOP if they key -- propose a key event and the adverse, you know, event, and then try to link them. And these really are typically chemical agnostic. They're just describing like, you know, something like skin sensitization or developmental neurotoxicity where it's a process.

So in reality, carcinogenesis is a process. So there are some adverse outcome pathways that have been proposed for certain types of, you know, cancers. The challenge with AOPs is that again they have not been really used to make a decision on a particular chemical. They have been used so far, as I mentioned, to organize new approach methods or in vitro, in silico and maybe short-term animal assays into a battery of assays to address a certain icity. And these -icities have been very specifically, so skin sensitization, developmental neurotox are very narrow in scope where again it took more than a decade for, you know, OECD, working groups to get together and to really map assays to, you know, parts of

the adverse outcome pathway.

And this perhaps can happen for cancer overall, or for organ-specific cancers, or for cell-specific cancers of different organs. So, for example, in breast cancer the luminal to basal, the, you know HER2 positive and negative and ER positive and negative. And for those perhaps adverse outcome pathways can be built, but the question is do we sit and wait for this to happen or do we actually move forward in trying to break a complicated process such as carcinogenesis into a finite number of key characteristics and then evaluate evidence within each, come to conclusions of strength, and then to try to reassemble all of that together?

And as I've showed you, this process has been applied to more than hundred agents in the last 10 years. And to my knowledge, AOPs really have not been used in any particular decision. And we all know that mode of action framework, you know, can be used, you know, according to the -- in eye of the beholder really it's -- you know, it's not a very stringent or process that will replicate itself if you put a different group of experts together with the same question.

The strength of IARC experience is that there has been 73 and now more and counting agents evaluated by different experts, using the same framework. And the

analysis that we presented really shows the patterns. And in my opinion, those patterns are not concerning to me from a point of a view of some sort of a bias or something like that. So hopefully that's what the CIC will take away from it rather than to look for, you know, a -- you know, a better way to do things.

Unfortunately, there is not a better way. There are different ways, but those other ways really have not been applied as much as key characteristics in trying to do systematic review type analysis.

CHAIRPERSON LOOMIS: Thank you for that response. Let's see if any members of the Committee would like to comment on what we've just heard.

Dr. Guyton.

DR. GUYTON: Yes. And I would certainly defer to any Committee members. But, you know, I think perhaps maybe either from Dr. Loomis or Dr. Cogliano in your experience at the monographs, these classifications that emerge are not linked always to a specific cancer type. So we know that there are many, many different types of cancer. I talked about breast cancer now being the leading cause, and it is not one disease. It's many, many, many different diseases and we see that.

But if we compared that to let's say an epithelial tumor, like a colon tumor, it is really going

to have a different type of classification. And I think the case -- the K -- the key characteristics are kind of endpoint free, if you will. So you're able to make a classification from animals that is not necessarily going to say this agent causes or might cause lung cancer, or this cancer, or that cancer. We do not have that ability today. And generally, that -- that's coming more from the epidemiologists, so I don't know Dana if you wanted to comment on that.

CHAIRPERSON LOOMIS: Well, the whole notion of specificity in causation is pretty interesting actually. And, you know, I think perhaps it's -- there's a philosophical desire to achieve specificity in causation, but we don't often see that except in infectious disease, which is a special case, because the whole nomenclature and taxonomy of those diseases was completely redefined after the development of microbiology.

So our understanding of causation of those diseases can be specific, because that's the way we defined them to be. But I think -- you know, we don't even see that with great clarity in terms of cancer epidemiology. I think one of the comments that was made earlier, which I would echo is that most of the carcinogens discovered in the first 40 years of the IARC monographs turned out to be lung carcinogens. I don't

think that's necessarily because, you know, that's a unique causal pathway. I think it has more to do with the properties of lung cancer and the nature of exposure in the places that the studies that identified those carcinogens were being conducted.

So I don't think we should make too much out of the search for specificity, either in the type of outcome that's associated with a certain exposure or in the association of cancer with particular key characteristics. That doesn't seem to me to be a weakness that the key characteristics are not specific.

Any other comments? Vincent, did you want to add to that or any other Committee members?

DR. COGLIANO: Well, I don't think I have anything to add to that. I think those are very good points you made, particularly with the older carcinogens from IARC. They are a very different subset than the carcinogens that are emerging today.

CHAIRPERSON LOOMIS: Yeah. All right. Let's just see whether other members of the Committee would like to speak to any part of the discussion that we just had before we close the public comment section.

Okay. My understanding is that there are no other public comments, is that correct?

MS. VAGHEFI: There are no other raised hands for

public comments.

CHAIRPERSON LOOMIS: Very good. So at this point, we will close the public comment opportunity and move on to the next agenda item.

But the agenda indicates a break at this time. It seems like we just had a break, so I'd like to take the opinion of the Committee and the staff members about whether we should proceed for a little bit and then take a break later.

DIRECTOR ZEISE: Yes, I think it's fine to take a break later. And I would just, you know, ask if there are any additional questions or discussion with our speakers. And if not, I think we can thank them, unless they would like to stay for the discussion of the -- excuse me -- analysis of cancer data, but --

DR. RUSYN: Well, I appreciate the opportunity, but again, if there are any follow-up questions, please do feel free to ask and by email or any other means. So thank you.

CHAIRPERSON LOOMIS: Thank you.

DR. GUYTON: Likewise. And I appreciate the opportunity to visit with you all today. It's been a pleasure.

DIRECTOR ZEISE: Yes. And on behalf of OEHHA, I'd like to thank you for joining the discussion, and your

presentations, and the great discussion. So thank you.

COMMITTEE MEMBER EASTMOND: Thanks, Kate and Ivan.

CHAIRPERSON LOOMIS: Thanks. Thanks to both of you. Enjoy the rest of the day.

Very good. So let's move on to the next agenda item, Analysis of Tumor Data from Animal Carcinogenicity Studies. I will turn the floor back to Dr. Cogliano for this one.

(Thereupon a slide presentation).

DR. COGLIANO: Thank you very much, Dr. Loomis. So we're going to be discussing in the next hour or so a few topics pertinent to the analysis of animal tumor data.

At OEHHA, we evaluate a large number of chemicals and we wish to be able to compare data sets, to compare tumor types within a chemical, to compare different sexes, strains, and species, and even to facilitate on comparing across chemicals for California EPA regulatory offices, which sometimes have the mandate to choose the safest chemical for a particular application.

So to facilitate these comparisons, we strive to have standardized methods. Now, for consistency and transparency these methods are described in OEHHA guidelines, which were developed with knowledge of what was also happening at the U.S. EPA, at the NTP, and IARC

and in other places -- authoritative places that do these assessments. These guidelines design -- describe a framework for data analysis that tries to make good use of all available data.

They describe general methods that can be applied to the generally available data set, but also that allow for a series of reasonable contingencies to be used, when data are less than ideal, so that the analysis can proceed in the face of less than perfect data.

So the next you're going to hear examples of some of these contingencies, for example, what happens if we have less than ideal information on the number of animals at risk and an experiment where we have less than ideal information on the appropriate comparison group.

So I'd like to first -- introduce our first speaker. Rose Schmitz from OEHHA to talk about some of the issues in animal tumor analysis.

Rose.

MS. SCHMITZ: Thank you Vince. Good afternoon, everybody.

--o0o--

MS. SCHMITZ: Today, Dr. Hsieh and I will present a few topics related to animal cancer bioassay data as they pertain to OEHHA's hazard identification documents. I'll begin by covering some of the scientific principles

we consider when we analyze animal cancer bioassay data. I'll then discuss a few of these principles in more detail, specifically how tumor incidences are presented, including the use of effective number in the denominator and the statistical tests used to determine significant increases in tumors.

I'll also touch on the concept of multiple comparisons before breaking for clarifying questions. Dr. Hsieh will conclude this portion of today's presentation by discussing considerations about controls in assessing treatment related effects, including the assessment of rare tumors before breaking for clarifying questions again.

--o0o--

MS. SCHMITZ: When we valuated and analyze animal cancer bioassays for hazard identification purposes, we strive for consistency by taking a systematic and scientifically-supported approach. We do not simply report authors' analyses and conclusions. Rather, we take into consideration aspects of study design, such as study length, dosing regimen, number of animals placed in each group, and more, and we conduct our own analysis in accordance with standard practices of critical analysis.

We always review any reported increased tumor incidences. However when additional histopathology data

are available, we also look for other tumor sites where there are apparent increases. Where appropriate, we perform standard, widely-accepted statistical tests to evaluate the significance of increases, namely the Fisher's exact test for pairwise comparisons and the exact trend test to assess trends.

When reduced survival occurs -- can you all hear me? Okay. I heard an echo.

When reduced survival occurs in a study, we'll examine the cause if the information is reported. Often reduced survival can result from treatment-related tumors, but there are other causes as well, such as competing toxicity, viral outbreaks, and more.

Another important consideration is the timing of tumor occurrence. We want to understand whether most animals survived until the first occurrence of tumor at a particular site. For example, in the survival curves pictured on the right-hand side of the slide, there is significantly reduced survival in the high dose group compared to the control and the other treated groups. We can see that the curve corresponding to the control -- oh, sorry, corresponding to the high dose group, represented by the open squares, diverges from the other groups early in the study and appears to decline at a faster rate. The control group is represented by the filled squares, the

low-dose group is represented by the open circles, and the mid-dose group is represented by the open triangles.

Suppose one of the tumor types of interest in this study first appeared in week 76, the dark red dotted rectangle highlights that while over 90 percent of the animals in the control, low-, and mid-dose groups were alive and at risk of developing a tumor of that type at week 75, fewer than 70 percent of the animals in the high-dose group were alive at that point in time. If the original number of animals in each group was 50, this means that around 15 animals in the high-dose group did not survive long enough to develop the tumor, and using the original group size as the incidence denominator would not correctly reflect the number of animals at risk.

Whenever individual animal data detailing the day or week of death for each animal is available, we use that information to adjust the incidence denominator and present the effective number of animals at risk of developing a particular tumor. This is a more precise representation of the fraction of animals at risk than simply using the original group size for the incidence denominator.

--o0o--

MS. SCHMITZ: As I just mentioned, whenever possible, 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.

One of the key factors that effects how we're able to present data and hazard identification documents is the level of detail of the data we have access to. For example, NTP through the chemical effects and biological systems database makes available individual animal data. However, we often don't have access to such detailed data from studies reported in the literature. When information on time of occurrence of tumors or time of death is not reported, OEHHA may report denominators, which reflect the number of animals examined at the site, if that's provided by the study authors. Other times, the number of animals in the treatment group is used as the denominator.

OEHHA will always provide a table footnote clarifying the type of incidences presented. And the definition of effective number is consistent with the IARC preamble.

--o0o--

MS. SCHMITZ: 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, and 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.

--o0o--

MS. SCHMITZ: The concern of multiple comparisons in statistical testing has been raised in the past as it applies to the pairwise and trend tests performed by OEHHA. I want to start by clarifying that it's not OEHHA's practice to perform statistical tests on an

exhaustive list of species, sexes, dose groups, and sites. For example, in analyzing a typical NTP report, roughly 480 tests could be performed, however, OEHHA does not conduct anywhere near that amount. We perform tests for sites where an increase is apparent, which is typically a handful of tumor sites if any at all.

That being said, when we analyze animal cancer bioassay data, oftentimes we are conducting significance tests in multiple treatment groups, multiple tumor sites and types, and sometimes for multiple points in time. Any time we make simultaneous inferences about a data set, the Type I error rate increases, meaning the chance of observing a false positive result increases. There are different techniques that can be used to control the Type I error rate, however, these are not commonly employed with animal cancer bioassay data.

In a 1983 paper, Haseman pointed out that most tumor types have low -- have a low spontaneous frequency and thus for these tumor types, false positives are unlikely to occur. Even regarding tumors with higher background rates, which may be more prone to false positive results, significance of pairwise comparisons of tumor incidences and significance of dose-response trends are not the only considerations when assessing a compound's carcinogenicity. Some of the other

considerations Haseman mentioned are biological relevance, genetic toxicology, and more.

Furthermore, Rusyn, Chiu, and Wright highlighted in their 2020 letter to the editor of Toxicological Sciences that it has not been demonstrated that the current, widely accepted methods of unadjusted multiple testing lead to a substantial false positive problem in analysis of animal bioassay data for carcinogenicity.

Acknowledging these considerations regarding multiple comparisons, OEHHA has long performed unadjusted testing of animal cancer bioassay data in its hazard identification documents, and in doing so, takes the same approach as many other organizations that assess chemical carcinogenicity. OEHHA's hazard identification documents summarize the available data pertinent to a compound's carcinogenicity in a standard and widely accepted method. The Committee members, as experts in carcinogen identification, are able to make their own determinations as to how much weight to place on the significance of the tumor findings.

--o0o--

MS. SCHMITZ: Now, I'll take a break for any clarifying questions.

COMMITTEE MEMBER EASTMOND: May I go forward?

So, Rose, thanks. That was actually helpful

and --

MS. SCHMITZ: Absolutely.

COMMITTEE MEMBER EASTMOND: -- puts a lot of things in perspective. I did have a couple of questions. So when I read the NTP bioassays, the older ones certainly do trend tests for every tissue. Then they do pairwise comparisons on those tissues. They used to do life table analysis for each tissue as well. So that's five tests for each tissue. And then when you start with the combining like hepatocellular adenoma results with hepatocellular carcinoma results, and now we have hepatoblastoma results and these are all pooled together, that in itself brings many, many different analyses that are pooled together and then looking for a significant increase in any one of those. And is that the way? Do you do that as well? I think you're doing the same approach.

MS. SCHMITZ: No. We're actually -- thanks for bringing this up. What we're doing is looking at the raw data and looking for, you know, where an increase is apparent and then conducting tests there. So if we're seeing -- a lot of times, there are many, many tissues and tumor types where it's clear that there is, you know, no increase. And so we're not conducting tests on any of those tissues.

COMMITTEE MEMBER EASTMOND: But wouldn't we -- technical that --

MS. SCHMITZ: It's only a handful of sites where we end up doing tests.

COMMITTEE MEMBER EASTMOND: But essentially that means you're doing a post-hoc analysis, right, from a statistical point of view, because you've already scanned through it and only picked to follow up on ones that you think will be positive.

MS. SCHMITZ: I guess you could -- you could classify it that way. I think there's different ways defining post hoc, but if we're -- you know, yes, the experiment has been done, especially -- you know, we're not part of conducting the experiment, so we don't design the statistical, you know, analysis ahead of time for these, but we're looking at the data. We're looking at the tumor incidences that are presented, whether it's, you know, from NTP or a study reported in the literature. And, you know, especially, you know, my colleagues with decades of experience of looking at these types of tumor data can say, okay, you know, I think we're seeing an increase here. Like, let's see what -- you know, if there's a significant result in a pairwise test, or trend, or so on.

COMMITTEE MEMBER EASTMOND: But so for example

with NTP bioassay, they've already done those analyses. They've analyzed everyone -- everything, and then they flag the ones that are positive. You clearly pick those to follow up as well. So you're relying upon their analyses, which have previously been done.

MS. SCHMITZ: Not necessarily because they tend to conduct their tests on poly-3 adjusted incidences. And so they're going to have possibly slightly different results. And that's, you know -- earlier, I talked about how we use effective numbers. And, you know, there are many different ways to account for intercurrent mortality. And their approach is to use the poly-3 adjusted values. We use effective number generally. And so we're -- you know, we're cognizant of conclusions that they may have made, but we always are doing our own -- our own tests on tumor sites that we think there is an apparent increase, and we use the effective number, if we can.

COMMITTEE MEMBER EASTMOND: Okay. Are there other of these authoritative bodies that use the same approach that you do or this is pretty unique to OEHHA?

MS. SCHMITZ: I believe IARC, and anyone who's served on an IARC panel can jump in here, but I don't believe that they present p-values that are corrected or, you know, they're basically just conducting the tests for tumor sites where there are apparent increases.

COMMITTEE MEMBER EASTMOND: I mean, I'm thinking more like EPA, or NTP, or FDA, or Health Canada, or EFSA, or OECD, Japan, et cetera.

MS. SCHMITZ: Well, if I'm thinking about --

COMMITTEE MEMBER EASTMOND: So it's like your comparable agencies.

MS. SCHMITZ: Okay. As I'm thinking about, you know, for example OEHHA's authoritative bodies, you know, we have IARC who does this in a similar way and then U.S. EPA, again they're -- so they have a different way of adjusting for intercurrent mortality. A lot of times they will remove any animals that didn't survive for the first year of the study. And so once again, you know, if you're tweaking the denominators slightly, that can affect your test results, but they will, you know, perform the tests in a similar way that I do.

It looks like Martha wants to chime in.

COMMITTEE MEMBER EASTMOND: Sure.

DR. SANDY: Yes. Hi, Dr. Eastmond. Yeah, just another example of the U.S. EPA, many of their programs, they will analyze data that's submitted to them and they will do something similar, if not using effective number by picking a certain time, animals that survive to 52 weeks, for example, will be the denominator. It depends on the study and the way it's carried out. But the

analyses I think there are done by EPA and other authoritative bodies are similar to our approach in being concerned when they have the information to take into account intercurrent mortality.

CHAIRPERSON LOOMIS: Let's see, Vincent.

DR. COGLIANO: I think I'd just like to add that similar to the work U.S. EPA for close to 20 years, we do things similar to the way Rose suggested. We don't -- we did our own statistical analysis and not just -- not just accepted what was in the published paper. We did have different ways of adjusting for animals that were at risk. And sometimes we did if the animals were alive at the time of first tumor. If we didn't have that reported, we did animals alive at 52 weeks. We did what we could. It's basically the idea of reasonable contingencies when you don't have perfect data to allow the analysis to proceed.

But I think that even though we might have had slightly different ways of adjusting for animals at risk, the basic approach is the same. We -- U.S. EPA did look at -- do their own statistics in evaluating that.

And your first point, Dr. Eastmond, about, yeah, we do kind of look at U.S. EPA at the studies at the tumors that had been flagged by NTP or by an author in a journal as a positive and then subjected them to statistical tests.

I think that's really almost more of -- can be considered building upon an a priori hypothesis that these are positive results and we wanted to verify that they really are positive about the way we would be doing the statistics. And then in journal articles, you often don't see any of the negative data at all.

That's all I wanted to say.

CHAIRPERSON LOOMIS: Thank you for that.

Do any other Committee members have questions or comments on this piece of the presentation?

COMMITTEE MEMBER EASTMOND: I have another quick question. So do you make adjustments when the survival is better in the treated than in the controls?

MS. SCHMITZ: No. We gen -- we just -- we calculate effective numbers. So -- and we're -- when we are looking, for example, at, you know, liver adenomas -- oh, does Martha -- do you want to answer this instead? I see you're raising your hand there.

DR. SANDY: I'll just jump in this just to speak specifically to the question are we doing some adjustment for when treated live longer than controls. By the effective number approach, you know, it's agnostic as to what the treatment group is. You're looking across the experiment. And in, you know, a single species and sex, when was the first occurrence of the tumor that you're

looking at, let's say? It's a liver tumor and it's a carcinoma. Then you apply that day -- that day the first liver carcinoma was observed in any of the groups, the controls or the treated groups, in that experiment to determine what the denominators are for each group.

COMMITTEE MEMBER EASTMOND: Okay.

DR. SANDY: And, Rose, if you want to add something, please go ahead.

MS. SCHMITZ: No. That's what I was just going to say. Basically, we're looking at all of the groups together. And we -- you know, with the control, and the treated groups, and taking that, you know, first occurrence, and applying that number to all of the groups. So as you said, it's sort of an agnostic approach.

COMMITTEE MEMBER EASTMOND: But, I mean, one of the -- this is -- I can't remember the chemical this came up with -- came from, but the idea is that cancer is a disease of old age, if the treated live longer and live more healthy than the controls, that's basically going to give you a -- essentially, they're going to have a higher likelihood of developing tumors in the treatment than in the controls. And that's why I asked this. It's not a real common occurrence, but I remember it coming up once or twice in the past.

DR. SANDY: I'll --

CHAIRPERSON LOOMIS: Hands up. Let's see, Martha, you're trying to speak. Go ahead.

DR. SANDY: Yes. So if there's a true clear difference, and for some reason the controls are living much longer, and it is a tumor associated mostly with old age, yes, there are some specific ways that we can analyze that. It happens very infrequently, but if it does occur, that can be taken into account. I'm thinking all the way back to 1998 right now on a particular chemical, but...

COMMITTEE MEMBER EASTMOND: Very good, yeah.

CHAIRPERSON LOOMIS: All right. Let's see if there are other questions from the rest of the Committee. Dr. Landolph, I think you had your hand up first.

COMMITTEE MEMBER LANDOLPH: Thank you. Yeah, I wonder if you'd comment on something that I've seen for many years, and that's that, you know, we rarely get repeat experiments within the same lab, let alone between labs. So often, we're forced to make decisions on data that, you know, it's statistically significant, looks like a linear dose response curve, but there's not a repeat and that's always kind of bothered me, but I know these experiments are so time-consuming, and expensive, and they last such a long time. You know, by the time you send out the histopathology, you're talking about a five-year shot and over $10 million. So it's really precious data, but

it's difficult to get repeats sometimes. They -- you just don't see them very frequently.

MS. SCHMITZ: Oh, yeah, you're absolutely right. I'm trying to think back at my time at OEHHA here. You know, we -- I'm not sure I can think of one where we've had, you know, an experiment that was, you know, replicated. But, you know, it's another reason why we're saying, you know, we're -- that the animal cancer bioassay data is just one part of the picture that we're presenting to you all in the hazard identification document. And so, you know, we kind of -- it's almost like a -- you know, that is a limitation. It would be great if we had unlimited time and resources to really conduct, you know, repeated experiments, especially times when there's problems like, you know, if the MTD was exceeded or something like that. You had a lot of early deaths, but we just -- we do the best with the data that we have and, you know, hope that you all factor that in when you're, you know, analyzing the whole of the -- you know, of the data that we're presenting.

COMMITTEE MEMBER LANDOLPH: Yeah. That's what the same thing we do is do the best we can with the data that we have. The problem is as the money gets tighter and tighter, it's liable to get -- to become a worse situation rather than a better one.

Thank you.

MS. SCHMITZ: Um-hmm.

CHAIRPERSON LOOMIS: Dr. Besaratinia, your hand is up. Go ahead.

COMMITTEE MEMBER BESARATINIA: Yeah. Thank you, Rose. It was a very helpful presentation. In one of your latter slides, when you were showing how to calculate incidents in your studies, I believe the denominator said that the number of animal alive at first occurrence and examined at the site, is it the number of animal alive at the beginning of the experiment or at the time of first occurrence of tumors, which one of them?

MS. SCHMITZ: The time of the first occurrence of that particular tumor. And so we would use a different -- you know, for example, if the first liver carcinoma appeared on day, you know, 322, but we're also looking at kidney tumors and the first kidney tumor occurred on day, you know, 567. We use different cutoffs for the different tumor sites, so we're specific for that particular site. Does that make sense?

COMMITTEE MEMBER BESARATINIA: Yeah, but you would not take into account animals who died in between for example from other causes, not particularly tumors. How would you account for those?

MS. SCHMITZ: Yeah. If an animal did not survive

up until, you know, the time of first occurrence, whether it's, you know, because they -- well, yes, generally they're dying from something else. Although I say would be part of -- part of the tumor count. So those are removed from the denominator. They're considered not at risk.

COMMITTEE MEMBER BESARATINIA: But they -- I'm just thinking with regard to the classic definition of incidence, because the follow-up times should be taken into account when you are calculating the incidence rate. And the denominator, as I recall from my epidemiology courses, would always refer to the number of animal that are alive and at the beginning of the follow-up period.

CHAIRPERSON LOOMIS: Well, I would just -- that's one way of calculating incidence, but it's what epidemiologists know as the incidence proportion. So the way it's being described here has a parallel with human epidemiology, and that is you take account of the population at risk at the time of each informative event. So that's precisely what's being done here, with bit of approximation. But this is the classical approach to incidence estimation in humans and in experimental animals.

MS. SCHMITZ: Does that answer your question?

COMMITTEE MEMBER BESARATINIA: Yeah. I'm going

to double check my notes and go back and refresh my memories about this, because that is quite different from what I recall from my training, but thank you for the explanation.

DR. SANDY: I would just suggest that Rose might show that survival curve again to help illustrate.

MS. SCHMITZ: Sure.

DR. SANDY: We want to focus on the animals at risk of getting a tumor if they die before we think the tumor would have been observed in any of the animals. They weren't -- they didn't survive long enough to be at risk to see that tumor occurrence.

CHAIRPERSON LOOMIS: So that area in the red box is what's known as the risk set. And in this particular instance, the risk set is defined at the time of the first tumor occurrence. We could actually define a risk set for every tumor and then repeat those calculations, and the entire incidence estimation would be based on all of those risks sets.

MS. SCHMITZ: Precisely.

CHAIRPERSON LOOMIS: All right, Dr. Bush, let's go to you.

COMMITTEE MEMBER BUSH: Just a minor comment and kind of following up on this. So what we often see in the HID that you produced is combining different tumor types

of the same organ. And when you're doing that, you are -- your denominator becomes, or if you've got two different -- and adeno -- and adenoma versus an adenocarcinoma, you are choosing the denominator between those two that is still the first appearance of tumor, is that correct?

MS. SCHMITZ: Yes.

COMMITTEE MEMBER BUSH: Regardless of what that was.

MS. SCHMITZ: Yes, that's right. We take whichever the first occurrence was. And I actually have a -- I don't know if it would helpful. I have a slide showing like a table that shows our calculations for such an instance.

COMMITTEE MEMBER BUSH: Thank you.

MS. SCHMITZ: Just let me locate it.

COMMITTEE MEMBER BUSH: I hope I'm not hijacking the conversation.

MS. SCHMITZ: I don't think so. We created this slide just for -- whoops. Sorry. Oh, dear. Here we go. And hopefully it will show. Here we go. Let me make this a little bit larger

So here, we can see if we're looking at lung tumors. This was from our coumarin HID. We had adenomas that were first observed on day 558 and then carcinomas

that were first observed on day 716. And then if we're looking at the combined incidence, then we take the first first occurrence, if that makes sense. And you can see there's not -- you know, as you guys probably are aware, we don't take a straight sum. There's clearly an animal here who had an adenoma and carcinoma. We don't double count.

COMMITTEE MEMBER BUSH: Thank you. That's exactly what I was saying. So appreciate it.

MS. SCHMITZ: Yeah, no problem.

Okay. Any other questions on this portion before we move on for -- oh, you're muted, Dr. Eastmond.

CHAIRPERSON LOOMIS: You have your hand up again, Dr. Eastmond. I don't know if it's again a new question or --

COMMITTEE MEMBER EASTMOND: No, it is a new question. Sorry. And my mute was on.

I was just going back, kind of -- I still tend to be concerned about the issue of multiple comparisons. So on that example there in that one table, there are basically one, two, three and then times four statistical tests, so there's 12 statistical tests on that one table, correct? And -- you know, and that's replicated by whatever tissues one looks at. So it strikes me as -- I understand you're doing what you're doing and I think it

makes sense, but I also -- for me, in the back of my mind, I'm always looking at this from a point of view is we are making multiple comparisons and we need to be cautious because of that. And that's -- are there any things you do specifically to protect against multiple comparisons?

MS. SCHMITZ: We don't. I appreciate actually your comment just now that you're always keeping that in the back of your mind, because ultimately that's kind of what we're relying on is that you all, in your expertise, are keeping -- you know, are considering the fact that we're conducting multiple tests and that the animal cancer bioassay data is a portion of the data that we're presenting to you all. And so you can make your own determination about how important you think it is in terms of all the pieces of the puzzle.

I think, you know, there are a number of ways to correct for multiple comparisons that have been proposed over the years. I would say that the carcinogen risk assessment community is not wholly in agreement that the issue of multiple comparisons is one that needs to be solved nor are they in a agreement about which approach for solving it is the most appropriate. And so OEHHA presents the data to you all in a -- you know, a systematic manner that's fairly straightforward and relies on you to do just as you said, you know, keep that in your

mind that, you know, there are multiple tests being conducted and so you can, you know, determine how important you think the evidence is.

COMMITTEE MEMBER EASTMOND: Okay. Thanks.

CHAIRPERSON LOOMIS: Dr. Landolph, is your hand up from before or do you have a new comment?

COMMITTEE MEMBER LANDOLPH: New comment and question. Yeah. So I -- Rose, I just was thinking about that curve you showed where the survival is perturbed where you have the control. And then the -- yeah, that one. That's it exactly. And then you have the low dose, the survival, going down, and the mid-dose, it's going up. And then the high-dose it's going down again. So that will really screw your dose response curve up. So looking at these tables, you know, and trying to make decisions, how do you account for that type of a thing, when we were looking at the tables? Do you put any footnotes in there for us to help us out? What do you do or is there nothing you can do?

MS. SCHMITZ: I will actually -- I will pass this question to either Meng or Martha as to how differences in survival are discussed in the HIDs. Thank you so much.

COMMITTEE MEMBER LANDOLPH: And the reason I bring this up is because, you know, of course replicate experiments are fantastic. We like to have that and we

love to have dose response if we've got it, you know, as a further serious criterion and at the age it is causing the effect. But when a dose response gets screwed up, then it starts to draw some questions in your mind as to what the heck is going on.

DR. SUN: Yeah, I can try to answer this and maybe Dr. Sandy can add more. Just because the low-dose and mid-dose have a different survival from the control, doesn't mean the dose response curve is being altered. As you can remember, we are using week 75 as the cutoff for the effective numbers.

COMMITTEE MEMBER LANDOLPH: Um-hmm.

DR. SUN: And the animals survived to after week 75 are considered at risk. And they were examined at this particular site. So they would be considered in the denominator. And the dying a week early or later after week 75 does not necessarily mean they will change the dose response curve in the final incidence. And also, they may have died with tumors, so that would be one denominator and one numerator contribution for the animal.

But as long as they survive to the first occurrence of this tumor, they are being considered. They are not being censored. So that would not affect the dose response curve. In the HID, we do note survival differences. We layout how significant the differences

are. We give you the body weight change and food consumption like obvious signs of toxicity.

COMMITTEE MEMBER LANDOLPH: So in cases where the dose response curve does look unusual, you know, it may go up a little for the low dose, it may go down for the median dose, and then it may go up again, is that just statistical fluctuation and inability to get enough animals to measure the endpoint accurately or what would cause that?

DR. SUN: There may be a number of reasons that cause the altered dose response, if it would be reflected in the trend test p-values. And if we can find the obvious reason -- apparent reason to report, we would try the present it in the document, but there could be a number of factors that cause this. For example, the altered animal body weight can often affect the tumor -- spontaneous tumor rate.

Dr. Eastmond.

COMMITTEE MEMBER LANDOLPH: So if the -- if the dose response is a little bit aberrant, as long as the trend test is pretty good, then you would accept that as evidence of causation, is that correct?

DR. SANDY: You know, I think I'll jump in if I can. So Dr. Landolph, what we -- we try to -- you know, we review critically the bioassays, the studies, whether

they're published in the literature or they're in reports and we try to summarize them in a helpful way for the Committee in -- in our hazard identification documents, we also provide you with the references, the studies themselves, if we have them.

And so we do -- as Meng just said, we do give general comments about the study. It -- where there differences in survival between the treated and controls? Were there differences in body weight, or in drinking water consumption, or diet, or things like that? Were there other toxicities that were obviously -- were reported? You know, what are the known limitations reported for these studies, if there are any? We try to give you that information that may have -- that we think might have a impacted tumor response and that you should be able to take into consideration.

But we cannot tell you -- we often do not know how to explain a dose response that's seen, you know. And that's really -- that's up to you as the scientific experts to evaluate the data as they exist. And we are just trying to give you that information in as standardized and robust a way as possible.

COMMITTEE MEMBER LANDOLPH: Okay. Thank you for your efforts. I appreciate it.

CHAIRPERSON LOOMIS: All right, we've had a very

good and robust discussion on this piece of the presentation, but I think we have another part. And so I'd like to move on and hear that part from Jennifer and then we will have opportunity for more discussion of both parts of the presentation before we take a break.

DR. HSIEH: Okay. All right, can you guys hear me?

COMMITTEE MEMBER LANDOLPH: Yes.

DR. HSIEH: Good afternoon. Thank you for coming.

Now, we will consider or discuss the consideration about controls when assessing animal carcinogenicity study findings. In an animal cancer bioassay, the primary goal is to test whether a particular treatment, such as exposure to a chemical, results in an increase in tumors in the treated animal compared to animal that were not treated with the chemical. It's important that the study include a concurrent control group, where animals are maintained and treated under the same conditions, except for the chemical of interest.

It's a generally accepted principle that the concurrent control group in an animal cancer bioassay is generally the most appropriate comparison group for statistical analysis and assessment of treatment-related tumors. This statement is supported by the IARC preamble

and other agencies, such as U.S. EPA, FDA, and NTP agree with IARC on this matter.

Next slide, please.

--o0o--

DR. HSIEH: Consideration of historical control data may also be useful in certain situations. Historical control data refers to the tumor incidence observed in untreated control animals of a given species, strain, and sex in previous studies. For example, NTP compiles and maintains historical control databases specifically for the studies NTP has conducted, organized by animal species, strain, and sex. Other laboratories, animal suppliers, and organizations can also be source of historical control tumor incidence data.

Historical control data are useful to determine tumor types that are rare in untreated animals. This application has been mentioned in the IARC preamble and the U.S. EPA Carcinogen Risk Assessment guidelines, and U.S. NTP's report on carcinogens handbook, and in FDA guidance.

Rare tumors are defined as tumors that occur infrequently in untreated animals, usually with incidence rates of less than one percent. This commonly accepted definition dates back to at least the 1970s and has been consistently utilized by authoritative bodies, including

NTP, U.S. EPA, IARC, and FDA.

Historical control data help to provide additional context when assessing the biological significance of rare tumor observed in treatment group in a particular study. For example, while observation of a rare tumor is recognized as alarming by the study pathologist, a finding of one animal with such a tumor out of 20 animal in a treatment group in a specific study may not be fully appreciated by non-pathologist. However, if the historical control incidence is given and shows that such tumor only occurred in one out of 1,000 untreated animal, then the non-pathologists can better appreciate the biological significance of this finding.

Next slide, please.

--o0o--

DR. HSIEH: Now, let's discuss what constitute appropriate historical control data. When selecting such data, it's crucial to ensure that the historical control closely resemble the concurrent control in terms of factors, such as animal model, animal care, and environment, and the time period of the experiment, among other relevant considerations. These factors are important because any differences between the historical control animals and the conditions at testing laboratory with those of the concurrent control group can introduce

bias and impact the interpretation of the results. This is especially when strain or substrain differences in spontaneous tumor incidence exist.

The IARC preamble states that, "Historical controls should be selected to resemble the concurrent controls as closely as possible with respect to species, sex, and strain, as well as other factors, such as basal diet and general laboratory environment."

And the U.S. EPA Carcinogen Risk Assessment guidelines note that when utilizing historical control data, the most relevant data come from the same laboratory and the same supplier, and are gathered within two or three years, one way or the other, of the study under review. This approach helps to avoid issues such as genetic drift, which can occur over time within animal strain or colony, and discrepancy in pathology examination at different times and in different laboratory.

Other considerations include ensuring comparability in terms of the route of administration and the length of the experiment. The NTP historical control database take these factor into account in presenting and organizing the data. And overall, historical control data should be used with caution due to potential impact of differences in laboratory procedure, animal management, and environmental condition over time, which can

significantly affect the occurrence of tumor in control animals.

OEHHA adhere to the best practice for employing historical control data and utilize rigorous and appropriate criteria to select the historical control data in evaluating finding from cancer bioassay.

Next slide, please.

--o0o--

DR. HSIEH: So now let me provide you an example where historical control data were proved useful in determining the rare tumor and treatment-related tumor site.

As shown here, in OEHHA's nitrapyrin HID released in 2015, we presented three forestomach squamous cell carcinomas in male mice in the high-dose treated group from the study by Stebbins and Cosse, 1997. Since there was no laboratory historical control data available from the testing laboratory, OEHHA relies on historical control data from NTP studies conducted between 1990 and 1996, as reported in Haseman et al., 1998. The historical control data were chosen based on the same species, strain, sex, length of experiment, route of administration, comparable basal diet, comparable general laboratory environment, and the study being conducted close to the time period of the Stebbins and Cosse study.

As a result, forestomach squamous cell carcinoma was considered rare and treatment-related in male B6C3F1 mice, with a historical incidence of one out of 1,355, or 0.1 percent. In this analysis, the best available historical control data were utilized to identify rare and treatment-related tumor in accordance with the guideline document mentioned previously.

OEHHA employs rigorous and appropriate criteria to select historical control data. The Committee members, as experts in carcinogen identification, are able to make their own determinations regarding the weight to be placed on the significance of the tumor finding.

With that note, we conclude today's staff presentation. And thank you for your attention. And now, I will hand it back to our Chair, Dr. Loomis, for a brief Q&A session. And thank you.

CHAIRPERSON LOOMIS: Thanks, Jennifer. Yeah, let's see if there are brief questions from the Committee on this part of the presentation.

Dr. Eastmond, you're back.

COMMITTEE MEMBER EASTMOND: I'm back. Thanks for that explanation. I just had a follow-up question. Do you ever flag or make accommodation when you're concurrent control is unusually low when compared with historical control values, because that will drive trend tests quite

frequently.

DR. HSIEH: Yeah. Martha, do you remember early in the previous --

DR. SANDY: Yes. Yes. So we do often provide you in the HIDs, we'll often make -- add information on the range of historical control data, not just for rare tumors, but when there's an occasional tumor type that there's variance. We have mentioned that.

I don't know if Meng wants to add anything.

DR. SUN: Yeah, I can just add that the concurrent control is always considered most appropriate control. So if the tumor incidence in the concurrent control is extremely low, that means you should expect a spontaneous tumor rate in the treated group to be extremely low as well. So I don't think that would affect the consideration of tumor findings in this group of animals, but we do provide historical data just as reference for your consideration.

CHAIRPERSON LOOMIS: Are there other questions or comments from the Committee?

I'm not seeing any at this time, so we can open it up again for further discussion of both presentations if there is any inclination to do that. Let's take a quick look.

Okay. It appears there are no other hand raised.

So we've had a far-reaching and very thoughtful discussion of these two presentations. Given that we didn't take our break earlier, I would propose that we do that now, returning in 15 minutes at 2:45.

And do we need to have the Bagley-Keene warning again before taking a break?

CHIEF COUNSEL NELSON ROWAN: Hi. Sure. One more warning wouldn't hurt, so --

DIRECTOR ZEISE: Okay. Carolyn is frozen on my screen. Is she on yours?

CHAIRPERSON LOOMIS: Yes.

DIRECTOR ZEISE: Okay. So I don't know if Kristi is here as backup. Kristi Morioka. Is Kristi -- if not --

SENIOR ATTORNEY MORIOKA: I am.

CHAIRPERSON LOOMIS: Okay. Great. Do you want to give advisement.

SENIOR ATTORNEY MORIOKA: Yeah. Just so everybody remembers not to discuss the contents of the meeting while you're on break with any of the Committee members. That include via email, text message, phone calls, anything that can be construed as a serial meeting.

Thanks so much.

CHAIRPERSON LOOMIS: All right. Thank you. And back at 2:45.

(Off record: 2:29 p.m.)

(Thereupon a recess was taken.)

(On record: 2:45 p.m.)

CHAIRPERSON LOOMIS: Welcome back. I hope everyone had a pleasant break. Next agenda item is another opportunity for public comment on the second agenda item. And so I'll ask Amy to put the slide back up and we'll review the parameters for public comments.

So as it says here, members of the public who are logged into the meeting have an opportunity to comment on this agenda item. If you'd like to comment and you're in the meeting, you can raise your hand, at which point you'll be recognized and given an opportunity to unmute. When you are unmuted, please give your affiliation and your name, and then your comment, which would be limited to five minutes. Further instructions about how to comment are on the slide in front of us and available on the OEHHA website.

So at this point, I'll ask if there are any raised hands from the public?

MS. VAGHEFI: As of now, I don't see any raised hands from the public.

CHAIRPERSON LOOMIS: Okay. Well, we'll give people a chance to raise their hands if they haven't done so yet, since we just came off break. And then if there

are none, we can move on to the next item.

Well, it appears there are no public comments on this agenda item. And so if everyone is agreeable, I propose we move onto the last agenda item, staff updates. So at this point, the staff will update the Committee on Proposition 65 activities, including listings, regulations, and litigation that have taken place since the last meeting.

So Kiana, I might ask you now to present the new listings on safe harbor levels that have been established

(Thereupon a slide presentation).

MS. VAGHEFI: All right, thank you, Dr. Loomis. I will be providing you with an update on important Proposition 65 developments since the last CIC meeting. I'll start by going over the chemicals or endpoints added to the Proposition 65 list, as well as chemicals considered but not listed. Then I will review 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.

--o0o--

MS. VAGHEFI: All right. Since the Committee's last meeting, five chemicals have been added to the Proposition 65 list, 1-bromo-3-chloropropane, 1-butyl

glycidyl ether, glycidyl methacrylate, 1,1,1-trichloroethane, and leucomalachite green have all been added as carcinogens.

--o0o--

MS. VAGHEFI: Antimony (trivalent compounds) were considered for listing as causing cancer under the Labor Code mechanism based on information from the Lancet oncology article summarizing the IARC working group's evaluations. However, after careful review of the recently published IARC monograph on antimony (trivalent compounds) this group of chemicals was found not to meet the criteria for listing. And for this reason, we will not proceed at this time with the listing process.

--o0o--

MS. VAGHEFI: All right, and since the Committee's last meeting, we proposed an update to the no significant risk level for exposure to ethylene oxide from two micrograms per day to 0.058 micrograms per day. We also proposed a no significant risk level for antimony trioxide and are reviewing comments received on the proposal.

And now, I will turn things over to Carolyn.

--o0o--

CHIEF COUNSEL NELSON ROWAN: Thank you, Kiana. And hello again. I have some updates on Proposition 65

regulations and litigation. Since the Committee last met, OEHHA has adopted a 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 65 if the manufacturer reduced the levels of acrylamide to the lowest level currently feasible, as defined in the propose -- or in the regulation. It also sets forth concentration levels in foods that are deemed to comply. The regulation was approved by OAL last December and became effective on April 1st, 2023.

I also have a few litigation updates for you.

--o0o--

CHIEF COUNSEL NELSON ROWAN: Thank you.

We have a -- there's been a new lawsuit filed. It's the Personal Care Products Council versus Bonta case. In May, the Personal Care Products Council filed a lawsuit in federal district court alleging that Proposition 65 warnings for cosmetic and personal care products that contain titanium dioxide, airborne unbound particles of respirable size, violate the first amendment. And the complaint alleges that such warnings are unconstitutional, because exposures have not been shown to cause cancer in humans. Therefore, any warning would be false, misleading, and highly controversial. The complaint for

declaratory and injunctive relief was filed against Attorney General Bonta.

Other updates on the Physicians Committee for Responsible Medicine, or PCRM, versus Newsom case. This is a challenge to OEHHA's decision not to list processed meats. And we are currently in the discovery stage. There were recently some discovery motions and a hearing. We're waiting for the court's decision on that.

There's the National Association of Wheat Growers versus Bonta case, which is another First Amendment challenge. This one is to the glyphosate warning requirement and we've talked about this previously. The most recent update is that the Ninth Circuit heard oral argument on April 19th, 2023 and we are now waiting a decision -- for a decision from that court. In CalChamber versus Bonta, that's the case that involves another First Amendment challenge to the safe harbor warning for acrylamide. The district court has that case again after the Ninth Circuit affirmed a grant of a preliminary injunction, and so the case is proceeding there.

And finally, I think I updated you previously on the Council for Education and Research on Toxics versus Starbucks case. The Third District Court of Appeal issued a decision affirming the trial court's decision, which had upheld OEHHA's coffee regulation. And CERT filed a

petition for review by the California Supreme court and that was denied by the California Supreme Court. So that means the Court of Appeals decision is now final and the coffee regulation remains valid.

Does anyone have any questions on those litigation updates?

Dr. Landolph.

Oh, you're on mute.

COMMITTEE MEMBER LANDOLPH: Yes. That one on the CERT versus Starbucks, that was the one where they ask some of us on the CIC to write about that for the judge. And basically it was a situation where -- a very interesting situation where the carcinogenicity of the coffee constituents was outweighed by the immunosuppressive effects on cancer. Is that the basis that it was ruled on in court?

CHIEF COUNSEL NELSON ROWAN: In court -- so -- and I should add that the -- those proceedings that I think you're describing were before my time. But yes, the -- so the coffee regulation was used as a defense in that case. It was a third-party enforcement lawsuit and the trial court found that the regulation was supported by the evidence, so...

COMMITTEE MEMBER LANDOLPH: Okay.

CHIEF COUNSEL NELSON ROWAN: Yeah.

COMMITTEE MEMBER LANDOLPH: That was good. And the other one on the acrylamide, I think that started out, if I remember right, when Joan Denton was the head of OEHHA. And basically, we had -- you know, we were asked what we thought about acrylamide in food. And after that it went secret. So I guess is that where that all started?

CHIEF COUNSEL NELSON ROWAN: You mean, when you say where it all started, just in that time period, do you mean?

COMMITTEE MEMBER LANDOLPH: Yeah, the regulations about acrylamide in food.

CHIEF COUNSEL NELSON ROWAN: Oh, the new regulations. Those again began before my time, so I'm not sure exactly when that process of adopting the new regulation began. It was -- it was ongoing when I came into the picture.

COMMITTEE MEMBER LANDOLPH: Okay. Yeah, I think that's where it started.

DIRECTOR ZEISE: Yeah, maybe I can --

CHIEF COUNSEL NELSON ROWAN: Yeah, thank you.

DIRECTOR ZEISE: -- inject here a little bit in that we did come to the Panel for advice on a package of four different regulations on acrylamide, which at the time did not proceed. So I think what you're thinking of,

Dr. Landolph, is sort of a historical note. This is something that came later.

COMMITTEE MEMBER LANDOLPH: Okay. Thank you.

CHIEF COUNSEL NELSON ROWAN: Thank you, Lauren.

Any other questions?

It looks like Dr. Eastmond has a question.

COMMITTEE MEMBER EASTMOND: Yeah, I have a question. This is just a general one I make at most meetings is, you know, over time we've been told to hang on to our copies of materials related to some chemicals under concern for litigation. We never seem to be told when we can get rid of them. If there are things that we no longer need to keep, or if you could let us know what we need to hang on to, that would be helpful, because, I mean, these are binders that we have sitting around. It would be helpful to know. Thanks.

CHIEF COUNSEL NELSON ROWAN: Sure. Yes, definitely. Appreciate you being careful about that in matters that might be under a litigation hold. So we can provide maybe an update on the current -- the litigation hold list for you.

COMMITTEE MEMBER EASTMOND: Thank you.

CHIEF COUNSEL NELSON ROWAN: Thank you.

Any other questions?

I don't -- I can only see a few people at the top

of my screen.

Okay. Thank you.

CHAIRPERSON LOOMIS: Thank you, Carolyn.

Well, at this point in the meeting, I would normally ask Lauren to summarize the Committee actions. But since there were no decisions to be made at this meeting, I'll turn it over to her for final comments.

DIRECTOR ZEISE: Okay. Well, thank you very much. I guess I'll summarize just that there was a rich and informative discussion on the key characteristics of carcinogens. It was interspersed and followed also from presentations that we heard from our Deputy Director, Vince Cogliano, and from Drs. Ivan Rusyn and Kate Guyton who were guest speakers. So really appreciate the engagement, and the discussion, and thoughtful comments, and questions by the Committee on that.

And then we also had a good discussion on approaches that OEHHA takes to adjust for intercurrent mortality in our hazard identification documents in animal bioassays. So again, appreciate the discussion there and also the discussion on the use of controlled data. So really appreciate the engagement on these topics. And then, of course, we heard the updates just now on our regulatory actions, listings, and litigation in progress.

So with that, I guess I would like to turn to the

Committee and thank you for participating and for the active engagement at this meeting and thank Dr. Loomis for chairing the meeting, thank the public for their participation. I saw a number of attendees in the meeting and appreciate the comments. And would like to also thank our staff at our RCHAB for their presentations to the Committee from implementation and legal as well for preparing the materials for the meeting and for running the meeting, and again thank again the public for their engagement and our speakers. So I hope everyone has a wonderful summer. And with that, I will close my remarks and turn it back to you, Dr. Loomis.

CHAIRPERSON LOOMIS: Thank you, Lauren. Well, let me thank you and echo the appreciation to the Committee for thoughtful discussion, the invited speakers, and for -- to the staff for everything they did to make this meeting happen, as well as their presentations during it. And with that, it's my pleasure to adjourn the meeting.

Have a good summer.

(Thereupon the Carcinogen Identification Committee adjourned at 3:02 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 20th day of June, 2023.

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