MEETING

STATE OF CALIFORNIA

ENVIRONMENTAL PROTECTION AGENCY

OFFICE OF ENVIRONMENTAL HEALTH HAZARD ASSESSMENT

PROPOSITION 65

CARCINOGEN IDENTIFICATION COMMITTEE

ZOOM PLATFORM

CalEPA HEADQUARTERS BUILDING

1001 I STREET

SIERRA HEARING ROOM

SACRAMENTO, CALIFORNIA

THURSDAY, DECEMBER 19, 2024

10:00 A.M.

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

APPEARANCES

COMMITTEE MEMBERS:

Dana Loomis, PhD, Chairperson

Ludmil Alexandrov, PhD

Ahmad Besaratinia, PhD, MPH(Remote)

Jason Bush, PhD

Catherine Crespi, PhD, MS

David A. Eastmond, PhD

Dean Felsher, MD, PhD(Remote)

Joseph Landolph, PhD

Thomas McDonald, PhD, MPH

Mariana Stern, PhD

Sophia Wang, PhD

STAFF:

Dave Edwards, PhD, Acting Director

Isabel Alvarado, PhD, Staff Toxicologist, Cancer Toxicology and Epidemiology Section, Reproductive and Cancer Hazard Assessment Branch

Vanessa Cheng, PhD, Associate Toxicologist, Cancer Toxicology and Epidemiology Section, Reproductive and Cancer Hazard Assessment Branch

Sarah Elmore, PhD, Staff Toxicologist, Cancer Toxicology and Epidemiology Section, Reproductive and Cancer Hazard Assessment Branch

Corey Friedman, Attorney IV, Office of Chief Counsel

APPEARANCES CONTINUED

STAFF:

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

Kannan Krishnan, PhD, Assistant Deputy Director, Division of Scientific Programs

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

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

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

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

Meng Sun, PhD, MS, Chief, Air and Site Assessment and Climate Indicators Branch

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

Kiana Vaghefi, Proposition 65 Implementation Program

ALSO PRESENT:

Wade Barranco, PhD, Lyondell Basell

INDEX

PROCEEDINGS

ACTING DIRECTOR EDWARDS: All right. Well, good morning. Welcome to everyone joining this meeting of the Carcinogen Identification Committee. The meeting is held in person -- being held in person and virtually.

My name is Dr. Dave Edwards. I am Chief Deputy Director and Acting Director of the Office of Environmental Health Hazard Assessment, or OEHHA. Lauren Zeise retired as the OEHHA Director in June of this year.

OEHHA is a department within the California Environmental Protection Agency and is the lead State agency for the assessment of health risks posed by environmental contaminants. As we get started, just a couple of housekeeping items for those attending in the room here in Sacramento. The emergency exits are through the double doors directly in the back where you entered the room and at the front of the room to the left and right under the lighted exit signs. And you can access the restrooms by going out the back double doors and turning left, walking to the end of the hall.

We have two newly appointed members of the Committee and I'll be introducing and swearing them in shortly. Our main agenda item today is for the consideration of vinyl acetate for listing as a carcinogen under Proposition 65. After the vinyl acetate agenda

item, the Committee will take up a consent item on the Section 27000 list of chemicals for which testing has been required, but has been inadequate. This is different from the Proposition 65 list.

For the third and final agenda item, staff will present updates on various Proposition 65 regulatory and other activities.

We will take a 45-minute break for lunch around noon and take a short 15-minute break some time in the afternoon. This meeting is being recorded and transcribed. The transcript will be posted on OEHHA's website.

(Slide presentation).

ACTING DIRECTOR EDWARDS: During this meeting, there will be an opportunity to provide oral public comment on the vinyl acetate item. Individuals who are in person and wish to make an oral comment at today's meeting are asked to fill out a blue comment card and give them to OEHHA staff.

Tina, if you want to raise your hand, that would be great. Thank you.

Blue comment cards are located in the back of the room. When called by the Chair, please approach the microphone. Please state your name, affiliation, and provide your comment. Those who are joining us virtually

and wish to make an oral comment at today's meeting are asked to join the Zoom webinar.

Information on how to join via Zoom is shown on the slide. Go to the URL on the slide and register for today's Zoom webinar. You will receive a link to join the webinar at the end of the registration process, and if you provided a working email address, you will also receive an email with a link to join the webinar. Zoom users can also access closed captioning by clicking the "CC" button on the bottom panel of the screen. Those of you watching by CalEPA webcast will be able to watch the meeting, but you need to join the meeting by Zoom to speak. When requested by the Chair, individuals on Zoom may queue to provide oral comment by using the "raise hand" function. When your name is called during -- is called during the opportunity for public comment, you will be prompted to unmute yourself. Please unmute yourself, state your name and affiliation, and provide your comment. If you would like to present slides during your public comment and have not already sent them, please email them now to P65public.comments@OEHHA.ca.gov. Public comment will be limited to five minutes per commenter.

All right. So now I'd like to turn into the swearing in and introducing of the new CIC members. Starting first with Dr. Ludmil Alexandrov. He is an

Associate Professor in the Department of Cellular and Molecular Medicine and the Department of Bioengineering at the University of California, San Diego. Dr. Alexandrov received both his PhD and Master of Philosophy in Computational Biology from the University of Cambridge in the UK and his Bachelor of Science in Computer Science from Neumont University in Utah. He did his post-doctoral training at Los Alamos National Laboratory in Theoretical Biology and Biophysics. Dr. Alexandrov has done extensive work developing knowledge on the ways factors, including environmental and industrial chemicals cause cancer in humans, utilizing the latest tools in doing so. His research is focused on developing novel machine-learning approaches and in leveraging these approaches to elucidate the basic molecular mechanisms underlying cancer development and cancer progression.

Welcome to the Committee, Dr. Alexandrov.

Next, Dr. Dean Felsher, who is attending remotely. Dr. Felsher is a professor of Medicine, Oncology and of Pathology at Stanford University School of Medicine. He serves as Director or co-Director of the Translational Research and Applied Medicine Center and several research and training programs. Dr. Felsher received his BA from the University of Chicago and his MD, PhD from UCLA. Dr. Felsher is interested in how oncogenes

initiate and maintain cancer. Dr. Felsher, along with his laboratory, is studying the basic mechanisms of oncogene addition during which cancer can be briefly reversed by shutting down oncogenes. He is developing novel therapeutics using small molecules, nanoparticles, and proteins/peptides that can be used to target oncogenes and/or restore the immune response against cancer, as well as new diagnostic and imaging methods such as PET, mass spectrometry, and nanoproteomics.

Welcome to the Committee, Dr. Felsher.

All right, I will now lead them in the oath of office. New members, you'll be asked to say "aye" and then state your name. You may choose to solemnly swear or solemnly affirm the oath.

So I guess if both of you could just raise your right hand. All right, this is going to be fun. All right, so we'll just -- for the first line, we'll go ahead and have Dr. Alexandrov say his name first and then Dean we'll go with you. All right, so "I" --

COMMITTEE MEMBER ALEXANDROV: I, Ludmil Alexandrov.

ACTING DIRECTOR EDWARDS: Dean.

COMMITTEE MEMBER FELSHER: I, Dean Felsher.

ACTING DIRECTOR EDWARDS: All right. Now, we're going to try to do the rest in tandem.

(Laughter).

ACTING DIRECTOR EDWARDS: Do solemnly swear --

COMMITTEE MEMBER ALEXANDROV: -- do solemnly swear --

COMMITTEE MEMBER FELSHER: -- do solemnly swear --

ACTING DIRECTOR EDWARDS: -- that I will support and defend the Constitution of the United States --

COMMITTEE MEMBER ALEXANDROV: -- that I'll support and defend the Constitution of the United States --

COMMITTEE MEMBER FELSHER: -- that I will support and defend the Constitution of the United States --

ACTING DIRECTOR EDWARDS: -- and the Constitution of the State of California against all enemies, foreign and domestic --

COMMITTEE MEMBER ALEXANDROV: -- and the Constitution of the State of California against all enemies, foreign and domestic --

COMMITTEE MEMBER FELSHER: -- and the Constitution of California against all domestic enemies, international and domestic --

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

California --

COMMITTEE MEMBER ALEXANDROV: -- that I'll bear true faith and allegiance to the Constitution of the United States and the Constitution of the State of California --

COMMITTEE MEMBER FELSHER: -- and I'll bear true allegiance to the Constitution of the United States and the Constitution of California --

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

COMMITTEE MEMBER ALEXANDROV: -- that I'll take this -- that I'll this -- that I'll take obli -- why don't you let me just -- that I'll take -- that I'll take this obligation freely without any mental reservations or purpose of evasion --

COMMITTEE MEMBER FELSHER: -- that I'll take this obligation freely without any reservations or --

ACTING DIRECTOR EDWARDS: Purpose of evasion.

COMMITTEE MEMBER FELSHER: -- Purpose of evasions.

ACTING DIRECTOR EDWARDS: All right. And that I will well and faithfully discharge the duties upon which I am about to enter.

COMMITTEE MEMBER ALEXANDROV: -- and that I will

well and faithfully discharge the duties upon which I am about to enter.

COMMITTEE MEMBER FELSHER: -- and I will well and faithfully discharge the duties about which I'm about to enter.

ACTING DIRECTOR EDWARDS: All right, congratulations.

(Applause)

ACTING DIRECTOR EDWARDS: We are honored to welcome you to the CIC Committee. Your deep understanding of carcinogens and contributions in your fields will add to this esteemed body, which makes the State of California a leader in identifying carcinogens and protecting people in the state from them.

All right, so now I will introduce the CIC members -- the rest of the Committee. So as I introduce you, please state your name and affiliation.

Jason.

COMMITTEE MEMBER BUSH: Good morning, everyone. Jason Bush, Associate Dean, College of Science and Mathematics, Professor of Cancer Biology, California State University, Fresno, and adjunct faculty, UCSF Fresno.

ACTING DIRECTOR EDWARDS: Thanks

Catherine.

COMMITTEE MEMBER CRESPI: Yeah. Catherine

Crespi. UCLA School of Public Health and Jonsson Comprehensive Cancer Center. I'm a Professor of biostatistics.

ACTING DIRECTOR EDWARDS: Thank you.

David.

COMMITTEE MEMBER EASTMOND: Dave Eastmond. I'm a Professor Emeritus from the University of California at Riverside.

ACTING DIRECTOR EDWARDS: Joe.

COMMITTEE MEMBER LANDOLPH: Hi. My name is Joe Landolph and I'm Associate Professor of Molecular Microbiology and Immunology, Pathology, and Molecular Pharmacology and Toxicology, and a member of the Cancer Center of the University of California -- University of Southern California in Los Angeles, California.

ACTING DIRECTOR EDWARDS: Thank you.

Dana.

CHAIR LOOMIS: Good morning. Dana Loomis. I'm Chair.

It's on. At least the green light is on.

See if this works better. Yeah. Dana Loomis. Recently retired from the Plumas County Public Health Agency and the Desert Research Institute.

ACTING DIRECTOR EDWARDS: Tom.

COMMITTEE MEMBER McDONALD: Hi. Thomas McDonald.

I'm Associate Research Director. I serve as the lead of Product Safety for Research and Development of all of the Clorox Company.

ACTING DIRECTOR EDWARDS: Mariana.

COMMITTEE MEMBER STERN: Good morning, everyone. I'm Mariana Stern. I'm a Professor of Population and Public Health Sciences at the University of Southern California, and the Keck School of Medicine, and Associate Director of Population Science at the USC Norris Comprehensive Cancer Center.

ACTING DIRECTOR EDWARDS: Sophia.

COMMITTEE MEMBER WANG: Good morning. My name is Sophia Wang. I'm a Professor in the Beckman Research Institute at the City of Hope and a member of the City of Hope Comprehensive Cancer Center in Duarte, California.

ACTING DIRECTOR EDWARDS: All right. And now, Ahmad, who's attending remotely.

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 in Los Angeles.

ACTING DIRECTOR EDWARDS: Welcome, everyone. Great to see the majority of us here in person today. We do appreciate you taking the time to provide your advice and judgment at this meeting.

All right. Next, I'd like to introduce OEHHA staff. For those in the room, I invite them to raise their hand. And for those joining via Zoom webinar, I invite them to turn on their cameras.

So we'll start with Dr. Kannan Krishnan. He is the Acting Director for Scientific Programs. And if I ever need to step out, Dr. Krishnan will take my place. I'm not expecting that today. And from the Reproductive and Cancer Hazard Assessments Branch, we have Martha Sandy, who is the Branch Chief. Dr. Meng Sun, she is currently Branch Chief of the Air and Site Assessment and Climate Indicators Branch. And right, I guess, leading up to December, before that, she was the Section Chief of the Cancer Toxicology and Epidemiology Section.

And then we have staff of the Cancer Toxicology and Epidemiology Section that are joining us today: Drs. Isabel Alvarado, Vanessa Cheng, Sarah Elmore, Neela Guha, Kate Li, Gwendolyn Osborne, Karin Ricker, and Feng Tsai. We also have members from our Office of External and Legislative Affairs, our Proposition 65 implementation team. We have Tina Cox, who's a Senior Environmental Scientist, Section Chief of the Proposition 65 Implementation Program. Tina is also acting for Amy Gilson, OEHHA's Deputy Director for External and Legislative Affairs, Kiana Vaghefi, an Environmental

Scientists in the Proposition 65 Implementation Program, and Julia Dollof, a Senior Environmental Scientist and our new Proposition 65 Ombudsperson. And then from OEHHA legal, we have Corey Friedman, Senior Staff Counsel.

All right, so I think that's all of the introductions. So now I'll ask Corey Friedman for some introductory remarks about Bagley-Keene and other legal issues related to participation in today's virtual meeting. Corey.

COREY FRIEDMAN: Good morning.

How is that?

Good morning.

No. Okay.

Better?

Okay. Good morning, everyone. Nice to see you. For those I haven't met before, nice to meet you. I'm Corey Friedman, as Dave said. I have just a few things to remind you of before we get started with the substance of the meeting.

Feel free to ask me questions at any time during the meeting. I'll be here the whole time. If, for any reason, I have to step out, my colleague Kristi Morioka is here as well. So there will be a lawyer present the whole meeting. First, a quick reminder that Bagley-Keene Open Meetings Act applies to this meeting, the basic idea of

which is that the public's business should be done in public. So for the Committee members, please remember that all discussions and deliberations about agenda items need to be conducted during the open meeting, so not during breaks, lunch or with individual members on or offline, including phone, email, chat, text, any other methods.

For those who are participating remotely, you need to appear on camera during the meeting, unless you have a loss of internet connectivity or something else that makes it technologically impractical for you to keep your video on. So if something like that does happen, please announce the reason before you turn off your video.

Remote committee members also need to disclose if there is anyone 18 or older present in the room with you and your relationship to those persons. So I will pause now to see if anyone needs to make that disclosure. Seeing no nodding heads, so I will continue.

Next, all the experts serving on this Committee have participated in mandatory ethics training and have disclosed any actual or potential conflicts of interest, including any relevant ex parte communications about the subject matter.

Finally, I'd like to remind you that the listing criteria that's been adopted by this Committee is in your

binders under "Criteria". These criteria were adopted by the Committee to help you make decisions about potential listing of chemicals. Your decision should be based on those criteria, not on the consideration of any possible future impacts of a listing, such as whether or not warnings would be required for any particular exposure. In other words, the members of this Committee were appointed by the Governor because of your scientific expertise and are considered the State's qualified experts on the carcinogenicity of chemicals, but there is no need to go outside that charge.

I think we have a slide here.

(Slide presentation).

COREY FRIEDMAN: This is just as a reminder. There are four separate and independent listing mechanisms, i.e. ways in which a chemical can be listed under Proposition 65, in addition to the State's qualified experts method, whereby the CIC or the DARTIC, which is the equivalent to the CIC, but for reproductive toxicants. In addition to that method of listing, there are the other ones on that slide. It can be listed as formally required by an authoritative body or under the California Labor Code. However, the criteria for those other methods are not relevant to your determination today, so you should not consider them. It does not matter whether or not the

requirements for the other methods of listing have been met.

During the course of the meeting, if you feel like you have insufficient information or you need time to think about the issues in front of the Committee, there's no requirement that you make a decision today. You can defer your decision to another meeting and give staff suggestions on the information you need. We would be happy to get that information and present it at a future meeting. But, of course, staff are here today, so if there's any questions that you can ask that can be answered today, everyone will make the utmost effort to do so.

Your charge today is to determine -- or actually your charge at every meeting is to determine whether the chemicals presented are clearly shown through scientifically valid testing, according to generally accepted principles, to cause cancer. The standard is a scientific judgment call. It's not a legal standard of proof. This Committee can decide to list a chemical based exclusively on animal evidence. The chemical need not have been shown to be a carcinogen in human studies.

As stated in the guidance criteria adopted by this Committee, the CIC will normally identify a chemical for listing if the weight of scientific evidence clearly

shows either that a certain chemical causes invasive cancer in humans or that it causes invasive cancer in animals, unless the mechanism of action has been shown not to be relevant in humans.

In addition, whether on not there are human exposures to the chemical or whether or not current human exposures are sufficiently high enough to cause cancer is not relevant to the listing decision. The CIC only considers hazard. Dose response assessment occurs at a later stage outside the purview of this particular meeting. Whenever OEHHA proposes a, "No Significant Risk Level" for a listed chemical, the members of this Committee are given the opportunity to comment.

As I've said before, feel free to ask clarifying questions of the OEHHA staff during the meeting. And if we don't know the answer to your question right away, we'll try to find it, as fast as we can and report it back to you. Also, if after this meeting at any point you have any questions about Bagley-Keene, feel free to get in touch with me and I'm happy to answer them.

And that is it for me for now. So I will turn it back over to Dave Edwards.

ACTING DIRECTOR EDWARDS: Thanks, Corey.

All right. Well, now, I'll turn it over to Dr. Loomis, the Committee Chair for the meeting today.

Dana.

CHAIR LOOMIS: Thank you, Dave. I'd like to begin by reading all of their -- continuing members of the Committee, it's great to see all of you again and also express my pleasure in meeting the new members joining us today for the first time. I want to thank Committee staff for their work to get us prepared for this meeting and members of the public who have chosen to attend today, whether in person or online.

So, with that said, we'll go ahead with the first agenda item, which is consideration of vinyl acetate as known to the State to cause cancer. We'll begin with a presentation by the staff. I think Dr. Sun will kick that off for us.

(Slide presentation).

DR. MENG SUN: Thank you, Dr. Loomis and good morning everyone. Welcome, CIC members. I'm speaking to you today on behalf of all staff scientists of the Cancer Toxicology and Epidemiology Section. Let me first provide some background on the process by which vinyl acetate was brought to you today. Vinyl acetate was brought to the CIC for consultation and prioritization in 2016. And the CIC recommended that vinyl acetate be placed in the medium priority group for future listing consideration. OEHHA selected vinyl acetate for consideration for listing, and

in August 2023, OEHHA solicited from the public information relevant to the assessment of evidence on its carcinogenicity. Information received at that time was reviewed and considered by OEHHA in the course of preparing the October 2024 hazard identification document, or HID. This document, as well as the references cited, and the public comments received on the document have all been provided to you for your consideration.

The HID and the presentation you will be hearing and seeing today are the work products of all staff scientists of the section and not just those who are speaking to you today. OEHHA scientists are at the meeting and will be able to answer any clarifying questions.

So now I will turn it over to Dr. Osborne to start the presentation.

DR. GWENDOLYN OSBORNE: Can you hear me?

Okay. Good morning. Today, we're going to present a summary of the evidence on the carcinogenicity of vinyl acetate.

[SLIDE CHANGE]

DR. GWENDOLYN OSBORNE: There we go.

Okay. All right. I'm going to start with an introduction, then present the carcinogenicity data starting with epidemiological studies, then Dr. Li will

present the animal studies, Dr. Ricker will present the pharmacokinetics and metabolism of vinyl acetate, and Dr. Cheng will present data related to the key characteristics of carcinogens and similarities between vinyl acetate and its key metabolite acetaldehyde.

[SLIDE CHANGE]

DR. GWENDOLYN OSBORNE: Okay. Vinyl acetate is a monocarboxylic unsaturated aliphatic ester as shown on the top of the slide, and is volatile and soluble in water and organic solvents. It is a high production volume man-made chemical used in many applications.

Vinyl acetate is mainly used as a monomer to produce polymers and copolymers, such as polyvinyl acetate and ethylene-vinyl acetate copolymers. There are many industrial or commercial applications of these vinyl acetate-based polymers, such as adhesives, paints and coatings. In addition, vinyl acetate is approved by the FDA as a food additive as vinyl acetate monomer and vinyl acetate-based polymers.

Vinyl acetate has been detected in the environment and various consumer products due to its wide use. Occupational exposure is likely via inhalation or dermal contact. The general population may be exposed to low levels of vinyl acetate via inhalation of contaminated air, ingestion of contaminated water or food, or dermal

contact with products containing residual vinyl acetate monomer. However, no biomonitoring data were available.

[SLIDE CHANGE]

DR. GWENDOLYN OSBORNE: Vinyl acetate has been reviewed by two other health agencies, IARC, or the International Agency for Research on Cancer, is one of the authoritative bodies for Proposition 65. And they classified vinyl acetate as a Group 2B carcinogen in 1995 with inadequate evidence in humans and limited evidence in experimental animals. In making the evaluation, the working group took into account these three considerations:

Vinyl acetate is rapidly transformed into acetaldehyde in the body.

Second, there is sufficient animal evidence for the carcinogenicity of acetaldehyde which is listed as a carcinogen under Proposition 65. Both vinyl acetate and acetaldehyde induce nasal cancer in rats.

And third, both vinyl acetate and acetaldehyde are genotoxic.

The note that vinyl acetate was not listed by Proposition 65 via the Labor Code mechanism, because this mechanism requires a classification of Group 1, 2A or 2B with sufficient evidence in humans or animals, which vinyl acetate did not have at the time of IARC's review in 1995.

Additional studies have since been published, which will be described later in the presentation.

In 2011, the European Chemicals Agency classified vinyl acetate as a Category 2 carcinogen, suspected of causing cancer. The CIC placed vinyl acetate in the medium priority group for future listing consideration when we prioritized chemicals in 2016. This is why we prepared the hazard identification document and are presenting it for your evaluation today.

[SLIDE CHANGE]

DR. GWENDOLYN OSBORNE: Now, we'll go through the evidence relating to the carcinogenicity of vinyl acetate starting with the epidemiological studies.

Are you clicking?

Okay. The literature search identified less then 10 relevant epidemiologic studies reporting on vinyl acetate exposure and cancer.

There was only one study population per cancer outcome with some overlapping publications. Each included study was evaluated thoroughly for potential biases using general guidance from the NTP Report on Carcinogens Handbook and the IARC Monographs Program Preamble. All studies, except one, were conducted in workers who were co-exposed to many known and suspected carcinogens. Some examples of these are shown on the slide, such as vinyl

chloride, 1,3-butadiene and styrene.

Overall, there were some elevated risk estimates, but these studies all had issues with quality and quality, and chance, bias and confounding could not be ruled out.

[SLIDE CHANGE]

DR. GWENDOLYN OSBORNE: One study was not in an occupational setting, which we'll now take a closer look and that study was Heck at al. This was a study of air toxics conducted within the Multi-Ethnic cohort. The analysis included more than 48,000 women in the greater Los Angeles area. This map shows the exposure concentrations of vinyl acetate in Los Angeles. Residential addresses were geocoded according to the year 2000 census tracts and linked to National Air Toxics Assessment, an ongoing review published by the U.S. EPA.

Several U.S. studies of time activity patterns provide evidence that home measurements of air toxics are a good proxy for overall exposure to these chemicals. The participants were then followed up for incident invasive breast cancer between 2003 and 2013 through linkage to the California Cancer Registry.

[SLIDE CHANGE]

DR. GWENDOLYN OSBORNE: These are the vinyl acetate results for the Heck et al. study with the risk estimate of one shown by the dotted vertical line on the

left. In all women combined, a more than fivefold increased breast cancer risk was reported with one interquartile range increase in ambient residential vinyl acetate levels in the overall analysis after adjustment for several potential confounders. The authors were able to conduct several sensitivity analyses, since the large sample size provided adequate statistical power. The risk estimates remained consistently elevated in these sensitivity analyses, including in non-smokers, stratification by hormonal receptor cancer subtype, by race/ethnicity, and in women who never moved from their residence throughout the study period.

The highest adjusted risk estimates were observed in women with hormone receptor-negative tumors and in African American women. Vinyl acetate levels varied across neighborhoods and racial -- and between racial/ethnic groups. The authors noted that African American participants lived primarily within the area bordered by several freeways with high levels of traffic-related and specific agents compared to white participants.

[SLIDE CHANGE]

DR. GWENDOLYN OSBORNE: There were several strengths of this study, including a large sample size, prospective cohort, multi-ethnic population, detailed

questionnaire that collected data on multiple covariates, and detailed residential histories available for residents who lived in California during the study period.

There were also a few limitations. Precision may have been hampered by using air pollution models that give exposure estimates at the census tract level, not for individuals. A non-exhaustive list of chemicals was assessed, some of which could be correlated with other unmeasured chemical exposures. And finally, important earlier life exposures could be missing since the exposures were estimated only during the study period, so that concludes the presentation of the epidemiologic studies. And now, Dr. Li will present the evidence in animals.

[SLIDE CHANGE]

DR. KATE LI: Can you hear me?

Thank you, Dr. Osborne.

Thank you, Dr. Osborne.

Now, I will present vinyl acetate carcinogenesis studies in animals. A total of 24 long-term studies has been conducted in rats and mice by laboratories across the U.S., Japan, and Europe. In rats, there were 16 studies conducted in five strains with two using the inhalation route and 14 via drinking water. For mice, there were eight studies in three strains, including two inhalation

studies, and six drinking water studies.

[SLIDE CHANGE]

DR. KATE LI: This overview slide displays all animal studies. We group studies by species, route of exposure, strain and sex, and administered doses. All reported studies are long-term bioassays. In rats, 10 studies highlighted in red font has examined postnatal exposure to vinyl acetate starting at six weeks of age or later with exposure duration of 100 or 104 weeks, as noted in M for male, F for female rats and in parental or F0 rats in the two generation studies. For example, there are two inhalation studies in rats. One in males and the second in females. Additionally, six studies were focused on early life exposure starting preconception and/or in utero, continuing after birth to the offspring or F1 animals until 104 weeks of age.

[SLIDE CHANGE]

DR. KATE LI: In mice, the studies in red color show six postnatal exposures with treatment durations of 78 or 104 weeks and two studies were early life exposures in F1 animals starting in utero and continuing after birth until 78 weeks of age. The bright blue represents studies with treatment related or positive tumor findings, specifically positive findings were reported in 13 rat studies and five mouse studies.

[SLIDE CHANGE]

DR. KATE LI: Now I will show studies conducted before and after the IARC 1995 monograph. Studies outlined in blue boxes are the ones IARC relied on as the basis for the classification of vinyl acetate. There were four inhalation studies in rats and mice and four drinking water studies in rats available at the time.

Now -- oh, yeah. In the HID, OEHHA incorporate additional studies published after the IARC classification, showing in the red boxes. There are 16 drinking water studies, including 10 rat studies and six mouse studies. Among the positive studies added after 1995, many tumor sites identified are distant from the site of entry. In the following slides, I will take you through the findings from the rat and mouse studies.

[SLIDE CHANGE]

DR. KATE LI: We have many tumor incidence tables to present. In the following slides, each tumor incidence table is organized by tumor site and type, administered concentrations, and exact trend test values.

Tumor incidence with asterisk mark in the treated group indicates that there is a statistically significant increase compared to the control group by pairwise comparison. I will refer to these findings as significant increase and I will refer to a statistically significant

dose-related trend when p-value is less than 0.05 as a dose-related trend. In addition, rare tumors are illustrated with "r" in all slides.

[SLIDE CHANGE]

DR. KATE LI: Now, I will present you tumor findings from rat studies.

[SLIDE CHANGE]

DR. KATE LI: In the 104-week inhalation studies of Sprague-Dawley or SD-derived, Crl:CD(SD)BR rats, animals were exposed to vinyl acetate by inhalation starting at six weeks of age for 104 weeks. In male rats, nasal tumors including nasal squamous cell papilloma, squamous cell carcinomas, and carcinoma in situ were observed. Total nasal tumors were significantly increased in the high dose group with a dose-related trend. Exact trend tests valuse are presented in the last column on the right. Spontaneous occurrence of nasal tumors is rare in male rats, so each type is labeled with "r".

[SLIDE CHANGE]

DR. KATE LI: In the corresponding inhalation study conducted in female rats, rare squamous cell carcinomas of the nasal cavity were observed in the high-dose group, but not in the control animals.

[SLIDE CHANGE]

DR. KATE LI: This table is the Fischer 344 rat

studies. Animals were treated with vinyl acetate starting at seven to eight weeks of age in drinking water for 100 weeks and observed up to additional 30 weeks.

In females, as shown here, incidences of liver hepatocellular adenomas, uterine endometrial stromal polyps, and thyroid C-cell adenomas were significantly increased in the high-dose group. Dose-related trends were observed for uterine, thyroid, and pituitary tumors.

In the corresponding study conducted in males, no treatment-related tumor findings were observed.

[SLIDE CHANGE]

DR. KATE LI: In the studies of Fischer 344/DuCrj rats, animals were administered vinyl acetate in drinking water starting at six weeks of age for 104 weeks. In male rats, tumors were observed in the oral cavity and testes. In the oral cavity and lip mucosa, squamous cell carcinomas and squamous cell papilloma and carcinoma combined were significantly increased in the high-dose group. In testes, interstitial cells tumors were observed with a dose-related trend.

[SLIDE CHANGE]

DR. KATE LI: In the corresponding study in females, tumors were observed in the oral cavity, thyroid glands, and mammary glands. In the oral cavity, squamous cell carcinomas were increased with a dose-related trend.

In thyroid glands, significant increases in C-cell adenomas, and adenoma and carcinoma combined were observed in the mid-dose group.

[SLIDE CHANGE]

DR. KATE LI: Now, I will present you the two-generation studies in Sprague-Dawley, or SD, rats in two slides. Here, male and female parental or F0 rats were treated with vinyl acetate in drinking water starting from 17 weeks of age and continuing for 104 weeks. The offspring or F1 rats were exposed to vinyl acetate starting in utero through lactation, then post-weaning in drinking water until 104 weeks of age. This slide presents findings for the male rat studies.

In F0 animals, pancreatic islet cell adenomas were significantly increased at the high dose with a dose-related trend.

In F1 animals squamous cell carcinomas of the oral cavity and lips were significantly increased in the high-dose group. In forestomach, squamous cell carcinomas were significantly increased in both dose groups with a dose-related trend. Additionally, rare pancreatic exocrine adenomas were significantly increased in the low-dose group.

[SLIDE CHANGE]

DR. KATE LI: This slide presents tumor findings

from the female SD rat studies. In F0 animals, forestomach squamous cell carcinomas were observed in the high-dose group. In the F1 females, squamous cell carcinomas of the oral cavity and lips and forestomach were significantly increased in the high-dose group with dose-related trends. And adrenal gland pheochromoblastomas were significantly increased in the low dose group. In addition, rare tongue tumors were observed in the high dose.

[SLIDE CHANGE]

DR. KATE LI: The next three slides are the two generation studies in Wistar rats. Male and female F0 rats were administered vinyl acetate in drinking water starting from 17 weeks of age and continuing for 104 weeks. F1 rats were exposed to vinyl acetate starting in utero through lactation and then post-weaning in drinking water until 104 weeks of age.

This slide presents tumor findings from the male rat studies. In F0 animals, no treatment-related tumors were observed. In F1 animals, as showing in the table, squamous cell carcinomas of the oral cavity and lips were significantly increased in the high-dose group with a dose-related trend. Tumors of the pharynx, esophagus, and forestomach were observed in the high-dose group. Incidences of pancreatic exocrine adenomas were

significantly increased in the low dose group. In adrenal glands, pheochromoblastomas were significantly increased in the high-dose group with a dose-related trend.

[SLIDE CHANGE]

DR. KATE LI: This slide presents findings from the F0 female Wistar rat study. There was a dose-related trend in lymphomas and leukemia of the hemolymphoreticular tissues. Adrenal gland pheochromocytomas were significantly increased in the low-dose group. Uterine fibrosarcomas were observed in the high dose -- high-dose group.

[SLIDE CHANGE]

DR. KATE LI: In F1 females, tumors were observed in multiple sites. Tumors of hemolymphoreticular tissues were significantly increased at the high dose with a dose-related trend. Squamous cell carcinomas were observed in several tissues. In the oral cavity and lips, the incidence was significantly increased at the high dose with a dose-related trend. In tongue, there was a significant increase at the high dose. In the esophagus, a dose-related trend was observed. In forestomach, tumors were observed at the high dose. Additionally, uterine adenocarcinomas were significantly increased at the high dose with a dose-related trend.

[SLIDE CHANGE]

DR. KATE LI: This slide summarizes the drinking water studies in male and female Crl:CD(SD)BR rats. Animals were exposed to vinyl acetate throughout all life stages starting preconception and in utero to parental animals, and continuing after birth. F1 animals were terminated at 104 weeks of age for examinations. In males, two squamous cell carcinomas of the oral cavity were observed in the high-dose group. In females, no treatment-related tumors were observed

These are all the rat tumor findings.

[SLIDE CHANGE]

DR. KATE LI: Now, I will present you tumor findings in mouse studies.

[SLIDE CHANGE]

DR. KATE LI: In Crj:BDF1 mouse studies, animals was treated with vinyl acetate in drinking water starting at six weeks of age for 104 weeks. In male mice, as showing in the table, in the oral cavity and forestomach, there were significant increases in squamous cell carcinomas, and papilloma and carcinoma combined. In esophagus, significant increases in squamous cell carcinomas were observed in the high-dose group. In addition, rare larynx tumors were observed in the high dose.

[SLIDE CHANGE]

DR. KATE LI: In the corresponding studies in female mice, squamous cell carcinomas, papilloma and carcinoma combined of the oral cavity were significantly increased in the high-dose group. Squamous cell papilloma and carcinomas of the forestomach were observed in the high-dose group. Additionally, significant increases in spleen malignant lymphomas were observed in the low-dose group.

[SLIDE CHANGE]

DR. KATE LI: Now, I will present the two-generation studies in Swiss mice in three slides. F0 animals were treated with vinyl acetate in drinking water starting at 17 weeks of age for 78 weeks. F1 animals were exposed to vinyl acetate starting in utero, through lactation, and post-weaning in drinking water until 78 weeks of age.

In F0 males, no treatment-related tumors were observed. In F1 males, as shown in the table here, tumors were observed in organs of the digestive system, including oral cavity, tongue, esophagus, and forestomach. Significant increases in squamous cell carcinomas of the oral cavity and esophagus were observed in the high-dose group. In forestomach, acanthomas were also significantly increased in the high-dose group, with a dose-related trend.

[SLIDE CHANGE]

DR. KATE LI: Continuing to the tumor findings in female Swiss mice. In F0 animals, as shown in this table, squamous cell carcinomas of the esophagus and acanthomas of forestomach were significantly increased in the high-dose group.

[SLIDE CHANGE]

DR. KATE LI: In F1 females, tumors were observed in tissues of the digestive system in the uterus, lungs, mammary glands, and Zymbal glands. Squamous cell carcinomas of the oral cavity, tongue, esophagus and forestomach were significantly increased in the high-dose group. In forestomach, acanthomas were also signif -- increased -- significantly increased in the high-dose group. And Zymbal gland carcinomas were observed with a dose-related trend. This completes the reporting of tumor findings for mouse studies.

[SLIDE CHANGE]

DR. KATE LI: Here, we summarize all animal tumor findings associated with vinyl acetate treatments, organized by species and strain. The first column on the left is the organ system and then the tumor site. This arrangement makes it easier to compare tumor site similarities across different strains and species.

In each row, M is for male and F is for female,

and rare tumors are noted as superscript R. Bold font for male or female indicates tumors with a significant increase, as determined by pairwise comparison and/or a significant trend. Tumors not in bold include those with a significant trend driven solely by increases observed at the high-dose or the occurrence of rare tumors.

Okay. Great. Yeah. Just a reminder that the tumor findings in SD-derived rats were from inhalation studies as outlined in the blue box, and findings in all another strains were from drinking water studies.

DR. MARTHA SANDY: Excuse me, Kate. The display is cutting off one of the rows at the bottom of the slide.

DR. KATE LI: Right. I don't see it.

DR. MARTHA SANDY: And...

DR. MENG SUN: So Committee members, can you see the bottom row of the table showing immune systems?

No. Okay. So just for your information the bottom row is cut off and it shows immune system and the tumor sites are hemolymphoreticular tissues and there are findings for female rats, in Wistar rats, and also female Crj:BDF1 mice.

DR. KATE LI: Yeah, it's -- both are in drinking water studies.

So as shown here in the respiratory system, nasal tumors were reported in both male and female Crl:CD(SD)BR

rats. There was a significant increase in males and there was only a dose-related trend in females. So the female is not bold. The tumors in both male and female are rare, as marked with superscript R.

Moving down, in the digestive system, oral cavity tumors were observed in both males and females and across three rat strains and two mouse strains. You can also see that tumors were observed in the endocrine system, the reproductive system, and in auditory and immune system, as and Dr. Sun just mentioned. I won't list each tumor site here.

So here, highlighted in the red color are tumors observed in organ and sites distant from the site-of-entry, including lung, liver, pancreas, endocrine, reproductive, and hemolymphoreticular tumors, which are cutoff from the current slide show from drinking water studies -- all from drinking water studies.

In summary, vinyl acetate induced tumor-related tumors in multiple organ systems in both rats and mouse. Some tumor types were observed in multiple strains and in both sexes. In addition, among the tumors reported, several are rare tumors.

This conclude the reporting of animal carcinogenicity evidence. Now, I will turn it over to Dr. Ricker to continue.

[SLIDE CHANGE]

DR. KARIN RICKER: Good morning. So we are now switching to -- sorry, can you hear me now?

Better?

I'm eating it.

(Laughter).

DR. KARIN RICKER: Okay. So we're now switching to the pharmacokinetics and metabolism of vinyl acetate. And I start with a brief overview.

So following inhalation, vinyl acetate is quickly absorbed and distributed throughout the body. And it is largely excreted within 24 hours with the majority excreted in expired air and small amounts in urine and feces. And excretion products include carbon dioxide and acetaldehyde.

The metabolism of vinyl acetate proceeds primarily via two key enzymes. The first enzyme is a carboxylesterase and it metabolizes vinyl acetate to acetic acid and vinyl alcohol. Vinyl alcohol is unstable and quickly rearranges to acetaldehyde a known carcinogen.

In a second step, acetaldehyde is also metabolized to acetic acid via aldehyde dehydrogenase, primarily the aldehyde dehydrogenase 2, ALDH2 for short. And the resulting acetic acid is -- of either reaction is then introduced into the tricarboxylic acid, or Krebs

cycle, where it is further metabolized. There are other metabolic reactions happening as well and we look at these in more detail on the next slide.

[SLIDE CHANGE]

DR. KARIN RICKER: So here is the metabolism of vinyl acetate. Vinyl acetate is shown here in red under lower -- on the middle left side. And we start with a minor pathway, whereby vinyl acetate is conjugated with glutathione.

Moving on to the major metabolic pathway.

In the main pathway, vinyl acetate is oxidized to acetic acid and vinyl alcohol via carboxylesterase, or CES for short, shown here, and vinyl alcohol, as I mentioned, is unstable and quickly rearranges into acetaldehyde, which is a known carcinogen.

In turn, acetaldehyde is further metabolized by ALDH2 to another molecule of acetic acid and, as I mentioned, introduced into the Krebs cycle via Acetyl CoA synthase. The oxidation of acetaldehyde to acetic acid is mainly carried out by the ALDH2 and to a lesser extent by ALDH1. So ALDH2 is a key player in the detoxification of acetaldehyde and we will hear more about this polymorphic enzyme shortly.

Continuing with metabolic reactions. Downstream of acetaldehyde, DNA adducts and DNA-protein crosslinks

can be formed and these have been observed in rodents in vivo and in vitro following vinyl acetate or acetaldehyde treatments. Acetaldehyde can also be oxidized by two additional enzymes. These are the aldehyde oxidase and xanthine oxidase. And both enzymatic reactions can form reactive oxygen species, ROS for short, and xanthine oxidase also produces alkyl radicals. And these radicals can lead to alkylated protein adducts.

[SLIDE CHANGE]

DR. KARIN RICKER: As I briefly mentioned, ALDH2 is polymorphic enzymes in humans. So a single nucleotide polymorphism in the gene, known as rs671, encodes a non-functional protein. And the resulting variant allele is denoted as ALDH2*2.

Individuals that are homozygous wildtype have full ALDH2 activity. Individuals that are heterozygous have less than half activity, as the polymorphic allele is dominant negative, and individuals that are homozygous for the polymorphism have no activity. So with ethanol consumption, accumulation of acetaldehyde leads to various symptoms such facial flushing and is commonly referred to as alcohol flushing syndrome.

The ALDH2*2 polymorphism is mainly found in people of East Asian descent. Up to 40 percent of Chinese, Korean, or Japanese individuals are heterozygous

and another five to ten percent are homozygous for the polymorphism. This polymorphism has also been reported in some Southeast Asian populations at lower frequencies and it is not found in other ethnic groups.

In conclusion, a reduced capacity to metabolize acetaldehyde can lead to build up of this metabolite. And based on census data, OEHHA estimates that this polymorphism could affect at least one million people in California.

[SLIDE CHANGE]

DR. KARIN RICKER: So to summarize the key points for the metabolism: vinyl acetate metabolism generates acetaldehyde. And the balance between metabolic activation of vinyl acetate via the carboxylicesterase and clearance of acetaldehyde by ALDH2 largely determines the overall level of acetaldehyde in the cell or tissue, with aldehyde dehydrogenase 2 playing a critical role as the detoxifying agent. The rapid generation of acetaldehyde coupled with slow clearance can lead to increased levels of acetaldehyde following vinyl acetate exposure. This situation arises in individuals who are heterozygous or homozygous for the rs671 polymorphism. And in turn unmetabolized acetaldehyde can then form DNA adducts, DNA protein crosslinks, reactive oxygen species and acetyl -- alkylated protein adducts.

This concludes the metabolism section and I'm now turning the presentation over to Dr. Cheng who will present the key characteristics for vinyl acetate.

[SLIDE CHANGE]

DR. VANESSA CHENG: Thank you, Dr. Ricker.

We organized the mechanistic data for vinyl acetate by the 10 key characteristics of our carcinogens, or KCs, that are used by IARC and NTP in their evaluations of carcinogenicity evidence. The key characteristics were identified by IARC based on a comprehensive review of mechanistic information for known human carcinogens in IARC Group 1.

As detailed in the HID, there is evidence on vinyl acetate for three of the 10 KCs. Data from humans and animals in vivo, animals and human cells in vitro, and acellular systems were identified for some of these KCs.

A brief overview will be -- of each will be presented. On the bottom left-hand side of each slide, there is a reference to the section in the HID for each KC.

[SLIDE CHANGE]

DR. VANESSA CHENG: Starting with KC1: is electrophilic or can be metabolically activated. In rats exposed to carbon-13 labeled vinyl acetate in vivo, the labeled N2-ethyl-deoxyguanosine DNA adduct was found in

nasal respiratory and olfactory epithelia, as well as in peripheral blood mononuclear cells.

As previously mentioned, acetaldehyde is a metabolite of vinyl acetate. Acetaldehyde has been shown to bind directly to DNA and can form DNA adducts, such as N2-ethyl-2'-deoxyguanosine, 1, n-propano-deoxyguanosine, and N2-ethano-2'-deoxyguanosine.

[SLIDE CHANGE]

DR. VANESSA CHENG: Next KC2: is genotoxic. Some of the effects presented here were observed with non-cytotoxic concentrations of vinyl acetate. For detailed information, please see Tables 29 and 30 of the HID.

A number of studies have reported increased chromosomal effects of vinyl acetate. One human observational study observed increased chromosomal aberrations in lymphocytes of polyvinyl acetate manufacturing workers. Several studies in both animals and human cells in vitro have reported increases in micronuclei, chromosomal aberrations, and sister chromatid exchanges following vinyl acetate treatment. Sister chromatid exchanges were also observed in animal studies in vitro after vinyl acetate exposure.

There are also some data on vinyl acetate-induced DNA damage. Vinyl acetate exposure induced DNA adduct

formation in the nasal epithelial and peripheral blood mononuclear cells in in vivo animal studies. DNA cross-links were observed in human leukocytes exposed to vinyl acetate in vitro. DNA protein cross-links were observed in rat nasal epithelial cells in vitro and an acellular system using plasmid DNA and calf thymus histones incubated with rat liver microsomes.

[SLIDE CHANGE]

DR. VANESSA CHENG: Continuing with evidence of mutations. Vinyl acetate-induced mutations in human TK6 lymphoblastoid cells in vitro and mouse lymphoma cells incubated with or without S9 fraction in vitro at the thymidine kinase locus. No effects were observed at the HPRT locus in human cells. In contrast, no mutagenic activity of vinyl acetate was observed in tests conducted in bacterial strains.

[SLIDE CHANGE]

DR. VANESSA CHENG: Lastly, there were some data for KC10: alters cell proliferation, cell death or nutrient supply. The data below are all from rodent studies in vivo. These finding were observed alongside neoplastic findings from the two-year carcinogenicity studies that were previously presented by Dr. Li. Increased cell proliferation was observed in male rats in the nasal cavity epithelium, nasal olfactory epithelium,

and oral cavity maxillary mucosa. In male mice, increased cell proliferation was observed in basal cells of the mandibular oral cavity mucosa.

Studies in rats and mice have reported vinyl acetate-induced hyperplasia in multiple organs. Basal cell hyperpla -- excuse me, hyperplasia of the nose was observed in male and female rats. Thyroid gland C-cell hyperplasia and hyperplasia of the esophagus and stomach were observed in female rats. In both male and female mice, hyperplasia was observed in the tracheal epithelium, submucosal gland, oral cavity, and esophagus. Dysplasia is characterized as a disordered growth and abnormal proliferation and is more advanced than hyperplasia. Dysplasia was also observed in animals exposed to vinyl acetate.

Squamous cell dysplasia of the esophagus was observed in male and female mice while female offspring of those exposed mice had dysplasia -- excuse me -- present in the tongue, esophagus, and Zymbal gland.

[SLIDE CHANGE]

DR. VANESSA CHENG: I will now briefly highlight shared tumor findings and genotoxic effects between vinyl acetate and its key metabolite acetaldehyde.

[SLIDE CHANGE]

DR. VANESSA CHENG: I will start with shared

tumor findings -- or tumor sites. From inhalation studies, nasal tumors were observed in rats exposed to both chemicals. Laryngeal tumors were observed in rats exposed to vinyl acetate, while these types of tumors were observed in hamsters exposed to acetaldehyde.

From drinking water studies, hemolymphoreticular, pancreatic, and mammary gland tumors were found in rats exposed to either vinyl acetate or acetaldehyde. Most tumor sites from acetaldehyde exposure overlapped with the tumor sites induced by vinyl acetate. However, vinyl acetate exposure targeted several other sites and organs in the respiratory, digestive, and endocrine systems.

[SLIDE CHANGE]

DR. VANESSA CHENG: Vinyl acetate and acetaldehyde also have some shared genotoxic effects. First, both vinyl acetate and acetaldehyde produce micronuclei, chromosomal aberrations, and sister chromatid exchanges in rodents in vivo and human, and rodent cells in vitro. Second, both chemicals produce the same type of DNA adduct and form DNA crosslinks. Third, both induced mutations at the thymidine kinase loci in humans and mouse cells in vitro.

That concludes our presentation for today and thank you for your attention.

CHAIR LOOMIS: Very good. Thanks to all the

staff members for that very helpful summary of the evidence.

At this point, we have an opportunity for the members of the Committee to ask questions of clarification. And I'm going to take the Chair's prerogative and begin by asking a couple of questions.

So we heard about the metabolism of vinyl acetate to acetaldehyde. I have a question about the -- well, and how that metabolism of acetaldehyde by ALDH2 varies according to the polymorphism of that enzyme. How much variation is there in the metabolism of vinyl acetate to acetaldehyde by carboxylesterase? Do we have any information about that?

DR. KARIN RICKER: Okay. We had -- I can answer. We had no specific information on carboxylesterase as there seem to be some indication that some may be causing more activation of vinyl acetate. But I think others did not confirm this, so it's unclear. And it's also unclear which carboxylesterase exactly metabolizes the vinyl acetate. It's either CS1 or 2, but we did not find a clear evidence for either enzyme.

CHAIR LOOMIS: Thank you. One other question really quickly. So describe the -- going back to your description of the metabolism of vinyl acetate or -- sorry, acetaldehyde to its by-products. How much of that

evidence comes from studies of exposed humans?

DR. KARIN RICKER: Are you referring to DNA adducts and reactive oxygen? I think -- I'll double check, but I think it's primarily animal studies, but some products were found in vivo.

CHAIR LOOMIS: Okay. Thanks. At this point, we'll go around the Committee and see if there are other questions. This configuration with all of us lined up in a row is a bit awkward, so I may not see you, if you want to speak. But it looks like Dr. Eastmond is making motions there. We'll begin with you, Dave.

COMMITTEE MEMBER EASTMOND: Thank you and thank you for a very nice presentation. Pretty comprehensive in some aspects as well.

I do have a few questions. I guess the first one relates to the genotoxicity. One of the things that's intriguing for me is that -- so vinyl acetate was induced micronuclei when administered by i.p. injection, but it seemed like when administered by other routes, primarily oral routes of exposure, they didn't seen any micronuclei. Any particular insights as to why that might be the case?

DR. MENG SUN: Looking at the data, I think even for i.p. injection, there's an active study, so I'm not sure if there's a route specificity there, but the database is limited. There are not too many studies of

micronuclei in animals.

COMMITTEE MEMBER EASTMOND: I think there were like three negatives or something like that. It was enough. I mean obviously the data and the mechanisms, there's quite a bit of evidence that it's genotoxic in vitro and it makes sense, but I was just curious about that.

Another point that was raised was just for my information, and this is one of the public comments, was they made an issue about the increase in tumors that were seen were primarily at site of exposure or site of contact. Does that make any difference in sort of the way you assess the risks?

DR. MENG SUN: We actually have a backup slide to show you whether -- which tumors were induced at the sites distant from the site of entry, so I'd like to ask Kiana to share the backup slides, if you want.

COMMITTEE MEMBER EASTMOND: No, I -- they presented it, so it was okay. I mean, I'm just curious. That was made as a -- an issue, but when you -- essentially, you have -- it doesn't have to be vinyl acetate, any chemical, do you make a distinction when you're doing the risk assessment whether it's at site of exposure or a distal site.

DR. MENG SUN: I would say not at the step of the

hazard identification step.

COMMITTEE MEMBER EASTMOND: Okay. All right, that's helpful.

I had one other that's kind of specific, but one of the other public commenters, and maybe that will come up, had comments about sort of study quality, and a lot of these are older studies. But one in particular, they made some comments about the Ramazzini Institute. And it was my understanding that the questions with the Ramazzini Institute were primarily on lymphohematopoietic tumors, and that was pretty well limited, and the other ones seemed to be fine. It was just an interpretation.

Does that seem to impact -- because these seem to be done during that time frame. Is that -- was that taken into consideration when you reviewed?

DR. MENG SUN: Yeah. We also have a backup slide, if you have the time to look at it, but yeah, we considered NTP and U.S. EPA's review, and Pathology Working Group review of the Ramazzini studies. So among the tumors as you've seen today, yeah, there is the -- a hematolymphoid reticular tissue tumors in rats from the Ramazzini studies. You could, you know, make your own judgment on it. But yeah, U.S. EPA continued to consider solid tumor findings from Ramazzini Institute to be valuable and reliable. But yeah, they do consider the

lymphoma and leukemias of the respiratory tract to be unreliable, based on the limited number of studies they reviewed. They did not review the study for vinyl acetate. But yeah, the study for vinyl acetate was consid -- was conducted during the same time period at the Ramazzini Institute.

COMMITTEE MEMBER EASTMOND: Okay. Thank you. And I understand the work that was NTP's pathologists and they're now pretty consistent, but that was during a period of time there was some difference in gradation, anyway.

And I think -- oh, one last thing, and this is for the epidemiology on this recent study from 2024, which was vinyl acetate exposures in Southern California. Do we have an idea what were the sources were for that vinyl acetate? This was a ecological study. They looked at what would be the origins of that vinyl acetate? I mean, if you don't know it, you don't -- it doesn't matter, but I was just curious.

DR. GWENDOLYN OSBORNE: I don't think it's stated in the paper what -- where the exposure is coming from, but yeah.

COMMITTEE MEMBER EASTMOND: Okay. Well, thank you.

DR. MARTHA SANDY: We would just assume it's

industrial, yeah.

COMMITTEE MEMBER STERN: Yeah, if I may comment on that. And they do say in the paper that it's industrial sources and water contamination, that they -- that's what they presume.

CHAIR LOOMIS: I think it's just measured in air and the point sources are not specifically.

Okay. Dr. Eastmond, if you're finished, I think what we'll do to make it easier on me --

COMMITTEE MEMBER EASTMOND: I'm done. Thanks.

CHAIR LOOMIS: You're not.

COMMITTEE MEMBER EASTMOND: Oh, I'm done. Thanks.

CHAIR LOOMIS: You're done. Okay.

To make it easier on me, I think we'll just go with the Committee members on my left, the audience's right, first. So I'm going to look down there and see if anybody else wants to ask a question?

COMMITTEE MEMBER WANG: I wanted to follow up on the epidemiologic study. Can you comment on -- I mean, none of these make -- none of these exposures happen in isolation. So can you comment on the Heck et al. study regarding the correlation with other exposures and how -- or any data they provided on sensitivity and specificity of that exposure?

DR. GWENDOLYN OSBORNE: Yeah. They did look at that. They did look at the correlations and they found that vinyl acetate wasn't highly correlated with any of the measured -- other measured air toxics. That R squared ranged from 0.03 to 0.35. And that was with methyl isobutyl ketone the higher one. So they did look at that, yeah.

CHAIR LOOMIS: Others this way?

Jason.

COMMITTEE MEMBER BUSH: Thank you. Just follow up on Dr. Loomis's comment regarding the ALDH polymorphisms. Maybe in future HIDs, it would be helpful to -- for the Committee if we -- if there is known information on homologous enzymes in the animal models to know whether there is a polymorphism there as well. I mean, generally the animal models are going to be out-crossed and back-crossed to ensure that they are, you know, effectively wildtype. But there might be something there that would give some further insight into some of this -- the metabolic side of things. So maybe there is information. Maybe it isn't known, but if there is, it would be helpful, I think, if there was something to correlate there.

Thank you.

DR. KARIN RICKER: We don't -- we didn't have

those specific data, but we include data on knockout mice that are in the HID.

COMMITTEE MEMBER BUSH: Okay. Thank you.

CHAIR LOOMIS: Anyone else on that side?

Yes, Joe.

COMMITTEE MEMBER LANDOLPH: I very much enjoyed your summarizing this plethora of data. I mean it is a lot of data, so a lot of animal studies done, mouse and rat, a lot of animal carcinogenicity studies' data, and many of them are dose dependent and have some -- many have trend effects as well.

So my occurrence in reading this large summary of data is that there is a large positivity of information on this compound. Am I missing something or is that the way you see it too? I mean, I'm not seeing zeros most of the time. I'm seeing positive studies. So does your team feel that that is a correct interpretation of this data?

DR. MARTHA SANDY: So I'll take a stab at that, Dr. Landolph. We have presented quite a bit of data. You've seen many tables from the animal studies of tumor incidences, but we will remind you that your Committee is the State's qualified experts to make the final judgment, so...

COMMITTEE MEMBER LANDOLPH: Well, that's true, but I'm asking it, since you've lived with the data longer

than we have --

(Laughter).

CHAIR LOOMIS: I think you're putting them on the spot a little bit.

COMMITTEE MEMBER LANDOLPH: I'm sorry, I couldn't hear your comments down there.

CHAIR LOOMIS: They seem to be feeling like you're putting them on the spot a bit here.

COMMITTEE MEMBER LANDOLPH: Well, I am, but not in a -- not in a bad way.

(Laughter).

COMMITTEE MEMBER LANDOLPH: I'm just staying you reviewed a lot of the data and I think I see a lot of positivity in it and I was asking if that's what you saw since you've lived with it for so long.

DR. MARTHA SANDY: I think we have seen quite a bit of it.

COMMITTEE MEMBER LANDOLPH: Okay. That's all. It's not a trick question. That's all I wanted to know. Thank you very much.

(Laughter).

CHAIR LOOMIS: Okay. Dr. Crespi.

COMMITTEE MEMBER CRESPI: Yeah. I had a question about it -- a detail from the Heck paper that I didn't see, and I wondered if maybe the staff had seen it. And

that is the hazard ratios were for one interquartile range increase in exposure. And it wasn't clear to me whether they were using the same interquartile range for all of their analyses or if that interquartile range was specific to each -- to the analysis sample and their various analyses. So I didn't see that in the paper, whether they were specific about that. So I just wondered whether you had seen that or might have insights.

DR. NEELA GUHA: Hi. My name is Neela Guha. I'm a staff scientist with OEHHA. I'm looking at the Heck paper currently under the methods section. And this is what they say about the interquartile range. We employed Cox proportional hazard models to assess time-dependent air toxic exposures and evaluated its effects on breast cancer risk per interquartile increase. So looking at that, it looks chemical specific for each interquartile increase, but that interpretation would be up to you.

COMMITTEE MEMBER CRESPI: Yeah, I assumed it would be chemical specific. I just wondered whether it was specific to the sample being analyzed in each of their models. I don't think it's specified in the paper, so I just wondered whether you might have seen that or had insights.

DR. NEELA GUHA: I'll keep looking in the paper, but I haven't seen anything.

COMMITTEE MEMBER CRESPI: Okay. Yeah. Thanks.

CHAIR LOOMIS: Yeah. I had a similar question about that paper. Those odds ratios are rather high for an environmental study and I find them hard to interpret without knowing what the zero exposure level would be.

Now, going to my right. Yeah, first question.

COMMITTEE MEMBER ALEXANDROV: Hi there. Thank you for the presentation. Excuse me, I'll have some procedural questions just to -- because it's my first meeting. One of the things was said here was that we need to use generally accepted approaches. Some of those -- the studies we are reviewing are 30, 40 years old. Do we consider generally accepted approaches at the time of the study or generally accepted approaches at this moment?

DR. MENG SUN: I would say a well-conducted animal carcinogenicity study, how you judge that have not changed too much over the years. So if you have any specific question to a study design for some of the older studies, you can let us know and we could try to comment on them.

COMMITTEE MEMBER ALEXANDROV: Okay. So we assume current standards right, that this is not -- okay. And I'll go over that in a second.

The other thing I wanted to ask is when you're selecting the literature that you're reviewing, presumably

you've used predominantly peer-reviewed literature? And the reason I'm asking also, in the Russian article specifically, is there -- and there other articles in the Russian that report out, but you have selected that presumably because it was reviewed in an American journal? Is that the case or do you have any specific -- for foreign literature, do you have any specific set of criteria to search for them?

DR. MENG SUN: I don't think we select a language limitation when we're searching for articles, but we -- yeah, we are looking at peer-reviewed articles.

COMMITTEE MEMBER ALEXANDROV: Which are in things by PubMed, right?

DR. MENG SUN: PubMed and some others. It's detailed in our document.

COMMITTEE MEMBER ALEXANDROV: Okay. So my question there was -- one of the -- well, there's a lot of tables when we're talking about the mouse studies. And there have been a lot of statistical tests that have been done. And I was just wondering if one assumes that these studies are independent shouldn't these p-values be corrected for multiple hypothesis testing?

DR. MARTHA SANDY: The -- this is Martha Sandy. The animal bioassays that -- the way they're analyzed by the National Toxicology Program, and IARC, and other

authoritative bodies, it's -- the concept is you're testing -- you're exposing animals and testing to see if there's an increase in tumors. And it's -- there are no corrections that are typically made. It's generally accepted that you -- that's not the practice for analyzing bioassays, data in general.

COMMITTEE MEMBER ALEXANDROV: But you mean that within a study?

DR. MARTHA SANDY: Within a study, yeah.

COMMITTEE MEMBER ALEXANDROV: What about across the studies?

DR. MARTHA SANDY: We -- each study is different and -- you know, even the same strain of animal -- the study conducted in a different laboratory, the conditions are different, so we're looking at increases in the treated versus the control, the concurrent control. And we do not do corrections across studies that may have been conducted at different points in time and different laboratories.

COMMITTEE MEMBER ALEXANDROV: Okay. Okay. So the other -- the other question I had was about the pathol -- because a lot of this relies on pathology, the mouse or rat, somebody has gone an visually reviewed the actual slides. For these studies, do you know how many pathologists have reviewed each one of the -- of the mouse

tumors to determine whether they're invasive or whether they're adenomas.

DR. MENG SUN: Well, these studies are -- were conducted in different institutes, right, some were in Italy, some were in Japan, some in the U.S. So each study's protocol may be different and we try to provide that information if additional pathology review was provided, other than the publication, so the situation could be different for each study.

COMMITTEE MEMBER ALEXANDROV: I understand. And when I was looking at the papers, there wasn't -- that comes to mind, the generally accepted standards now versus before, because most of those papers, at least when I was looking at them, they did not provide that information. And what I do, especially when it comes to the invasive, because they will report a lot of premalignancies, a lot of adenomas. And there is huge amount of disagreement when you have esophageal squamous dysplasia, especially a high grade dysplasia and esophageal squamous cell carcinoma. You'll get five pathologists to review it, three will say dysplasia, two will say it's squamous cell. It's an invasive one. That's why I was wondering whether there is any specific standard that was used.

Let me see. I suppose the last question I have was about the epi study, the Heck et al. study, and the

question there was -- you showed that there was correction -- there was correction for smoking. Was there correction for alcohol consumption? I don't think there was, but I...

DR. GWENDOLYN OSBORNE: Yeah. All models were adjusted for a whole bunch of confounders. One of them is alcohol use, non-drinker versus drinker.

COMMITTEE MEMBER ALEXANDROV: Okay.

DR. GWENDOLYN OSBORNE: Yeah.

COMMITTEE MEMBER ALEXANDROV: Okay. Thank you.

CHAIR LOOMIS: Neela, did you have something to add to that?

DR. NEELA GUHA: In addition to alcohol use, those models were adjusted for risk factors for breast cancer, the typical risk factors, known risk factors to breast cancer.

CHAIR LOOMIS: Okay. Continuing on this side.

COMMITTEE MEMBER McDONALD: I don't have any questions of clarification for the staff.

CHAIR LOOMIS: Dr. Stern, questions.

COMMITTEE MEMBER STERN: I just have a very quick question, which is more about notation. So I was interested in -- when I look at the animal experiments I was interested in looking at the data for mammary gland, because of the Heck study. So you had it on your slide 20

the -- my understanding is that the notation you're using is that the trend is significant because the p-value is less than 0.05, but the actual number of tumors observed at the high dose compared to the control is not significant and that's why you didn't put an asterisk, is that my understanding, correct? So significant trend, but no significant com -- pairwise comparison. Okay.

DR. MENG SUN: That's correct.

COMMITTEE MEMBER STERN: Okay. Good. I just wanted to understand that.

CHAIR LOOMIS: Okay. Thanks.

Now, we'll go to the two members joining online, Dr. Besaratinia, questions?

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

COMMITTEE MEMBER BESARATINIA: Yes. Thank you very much. Can you hear me?

CHAIR LOOMIS: Now, we can.

COMMITTEE MEMBER BESARATINIA: Okay. Thank you.

First of all, thank you to staff for this report. It was quite informative. I have a few questions. Firstly, with regard to the human study, the single human study, which was also showcased this morning. I understand that the exposure assessment was done using the geocoding data and residential history in order to evaluate the neighborhood air pollution level. And this

was done with a five-year lag time. Considering that early life exposure to endocrine disruptors and mammary gland carcinogen is known to result in breast cancer later in life. Would you comment on that aspect?

DR. GWENDOLYN OSBORNE: Yeah, that is a weakness of the studies that they only looked at it in that specific period and not -- did not account for early life exposures, but that's, you know, what they have.

COMMITTEE MEMBER BESARATINIA: Okay. And the second thing is that if I got it correctly, they exclusively looked at invasive breast cancer, am I right on that?

DR. GWENDOLYN OSBORNE: Yes, and they excluded ductal carcinoma situ I think.

COMMITTEE MEMBER BESARATINIA: Yeah. And actually I want to underscore that fact, because DCIS -- quite significant portion of breast cancer cases are DCIS up to 40 to 45 percent of DCIS advanced to invasive breast cancer. And would you consider this also a major drawback of this study that all the DCIS cases were excluded from this study?

DR. GWENDOLYN OSBORNE: Yeah, they could be missing some cases there. Yeah.

COMMITTEE MEMBER BESARATINIA: Right. And then with regard to -- thank you for your response on the human

studies. I also wanted to see whether there is any additional information with regard to the metabolic pathway of vinyl acetate, since we have put so much emphasis on the key metabolite of this compound acet -- acetaldehyde. I'm wondering, is it known what portion of the vinyl acetate that is taken up by the cells, either in vitro or in vivo experiments is converted to acetaldehyde and subsequently results in DNA adduct formation or DNA-protein crosslinks or reactive oxygen species versus the fraction that is detoxified, for example, by conjugating to reduce glutathione, GSH?

DR. KARIN RICKER: I think the glutathione conjugation very little is known and we just had data from some animal studies where they showed a decrease in the GSH pool, so we don't have any quantitative data on that.

COMMITTEE MEMBER BESARATINIA: So proportionally, we don't know whether the majority of the vinyl acetate is going to turn into acetaldehyde or DNA or protein reactive agent, or it can simply be detoxified and eliminated, is that what you are saying?

DR. KARIN RICKER: Well, I said it depends on your -- you know, the overall amount of vinyl acetate, and also your endogenous levels of acetaldehyde, and the functioning of your ALDH2 --

COMMITTEE MEMBER BESARATINIA: Okay.

DR. KARIN RICKER: -- how well that's tuned to detoxify. And we have studies in animals that show if you have a knockout gene or we have studies in some human cells that show that acetaldehyde levels can increase significantly if the ALDH2 is non-functioning.

DR. MENG SUN: If I may jump in.

COMMITTEE MEMBER BESARATINIA: Sure.

DR. MENG SUN: So in the KC1 and KC2 section of the HID, we do introduce when a study tests animals or cells with both vinyl acetate and acetaldehyde. And in KC1, there are two studies in animals in vivo, where DNA adducts were seen as low as 10 parts per million of vinyl acetate. They also treated animals with acetaldehyde. So if you want detailed information, quantitatively speaking, you can look at the papers. The proportions may be different depending on the study design and study conditions. But in KC2, we also introduce whenever vinyl acetate and acetaldehyde were both treated -- or both used, so you can compare.

COMMITTEE MEMBER BESARATINIA: Okay. Thank you for that note. My last question is with regard to the animal studies. Could you please put in context these doses that were tested in different animal models and kind of let us know how they compared to doses to which humans are exposed on a daily basis, particularly when we are

talking about inhalation experiment. I know earlier we indicated that we are not particularly interested in the dose, but I just wonder if this information is available to be presented to the Committee at this moment or not.

COREY FRIEDMAN: I will let the scientists answer the question to the extent they can, but just again, yes, as far as not being as interested in it, just as a reminder, it's hazard identification.

Thank you.

COMMITTEE MEMBER BESARATINIA: Yeah.

DR. MARTHA SANDY: As we look at the exposure section, we -- of the document, we have discussed that probably the most exposed folks are in the occupational setting. And I don't think we have any recent information on what those levels might be in the workplace.

COMMITTEE MEMBER BESARATINIA: Okay. Thank you. That's all I have for now.

CHAIR LOOMIS: Okay. Thank you.

And let's go over to Dr. Felsher.

COMMITTEE MEMBER FELSHER: Thank you. Can you hear me?

CHAIR LOOMIS: Yes.

COMMITTEE MEMBER FELSHER: Fantastic. Yeah. I have a variety of questions, and a couple details probably I could clarify. First, I think -- I want to compliment

the scientists in the group. I've read a lot of reports like this. It was coherent, organized, very easy to read and unusually concise for the amount of information. So I found it a pleasure to read this report. So thank you.

I think the ALDH2 is really important. You recognized it as being important. You mentioned it throughout the report. There are a few things I think that should be asked to clarify. One important thing is because we know this is the enzyme that detoxifies perhaps really the most important metabolite, the acetaldehyde. Really, the question I have for you is to what extent did you look to see the spectrum of tumors observed in people mutant for this gene or the spectrum of tumors that we've seen associated with vinyl acetate?

DR. MENG SUN: Unfortunately, we don't have any direct evidence regarding vinyl acetate exposure in conjunction with this polymorphism, ALDH2 and tumors.

COMMITTEE MEMBER FELSHER: Well, that was my third question I was going to ask you. My first question is if you just look at the tumors you saw in rats and mice, to what extent does that phenocopy, the tumors you see say in the mice that are knocked out, we all know -- you know that I've worked in animal models for decades. I know you know that there are models. We know humans have been studied for years with this mutation. I've been to

conferences just on ALDH2. There was one hosted at Stanford that I spoke at, just a few years ago. To what extent does it map? You might predict that if vinyl acetate is a carcinogen, you would expect to see almost the same spectrum of tumors you see in humans who have this mutation or in mice who have this mutation. I'm just asking you did you look?

DR. MARTHA SANDY: I don't think we have that information at hand, no. And I think we have to consider route of exposure and the metabolism -- intracellular metabolism.

COMMITTEE MEMBER FELSHER: Sure.

DR. MARTHA SANDY: For each chemical that might be metabolized to acetaldehyde.

COMMITTEE MEMBER FELSHER: That's a fair point. The other thing I wondered is there a reported increased risk of breast cancer in humans who have a mutation of ALDH2. It's not as great as a relative risk as what Heck reported. Probably you -- that would be the same answer. It's not really an equivalence.

DR. MENG SUN: Yeah. In the HID, we do have a paragraph talking about this polymorphism and people's risk of cancer. But again, we don't have any data with vinyl acetate exposure in humans, and this polymorphism and risk of cancer.

COMMITTEE MEMBER FELSHER: We do know though that the ALDH2 mutant is much more common amongst these Asians. You highlighted that. In the study -- in the Heck study, was there any effort to look to see if people of East Asian descent had a higher relative risk? I mean the only thing I could see is they looked at Japanese Americans.

DR. GWENDOLYN OSBORNE: Yeah. And I think the paper said they attributed it more to like higher exposures based on where you might live than, you know, the actual like differences in genetic susceptibility.

COMMITTEE MEMBER FELSHER: For the human studies, we talked about the lag time being five years. It is confusing to me they chose that. Lag time also allows you to look at latency. I -- what was the duration range they felt people were exposed?

DR. NEELA GUHA: Let me check. I have that on a backup slide.

COMMITTEE MEMBER FELSHER: I found it confusing reading the Heck study to know what they thought the mean duration of exposure they thought was.

DR. NEELA GUHA: Yeah. I'm looking through the methods section of the paper again and just the years of the NATA models that were taken. Geocoded addresses for 1998 to 2000 and 2001 to 2003 were then linked to the 1999 and 2002 NATA models, according to the 2000 census tracts.

So that's the information we have on that.

COMMITTEE MEMBER FELSHER: The thing is we'd like to have an idea of what they thought for this population -- what was the range of which they were exposed to air that had chemicals in it, to know whether or not there was sufficient time for latency from exposure to having the disease cancer that uses that as a endpoint.

DR. NEELA GUHA: Yeah. I mean, you have the information of when the exposure was assessed and you know when the cancer time points occurred.

COMMITTEE MEMBER FELSHER: So I'm just asking, can you -- what was the -- what's the time difference. How many years were they assuming it took for breast cancer to occur?

COMMITTEE MEMBER STERN: Can I provide a comment? Is that okay for me to comment on this, at this point?

So the way the study is done as the team explained is they geocoded their residential address with a five-year lagging time, right, between the measure of exposure and the incidence of a case. They also know -- they have information about residential history on these participants, so they were able to classify participants based on whether they had lived at that residential address for most of the time, or as adults, or not. And they did an analysis, a sensitivity analysis stratifying

patients -- participants based on whether they had moved or not and they did not see differences.

So they did take into account whether patients were -- had -- not patients, everyone had lived in that address for the five years only that they had considered or longer, or if they had moved earlier in their life and they didn't see that that had a difference. So that may be a. --

COMMITTEE MEMBER BESARATINIA: Mariana, if I may say, I think what Dr. Felsher and both I were concerned that we don't know how far back they went to assess exposure and see the duration of time these individuals, who were diagnosed with breast cancer were exposed to that particular chemical. So that is quite vague. The description in the article doesn't really clarify it.

COMMITTEE MEMBER STERN: Yeah. My understanding is that they consider a minimum of five years.

COMMITTEE MEMBER BESARATINIA: Yeah, which would be extremely --

COMMITTEE MEMBER STERN: So that's the minimum done and it could be more.

COMMITTEE MEMBER FELSHER: Extremely short latency.

COMMITTEE MEMBER BESARATINIA: Extremely short. For any type of cancer that would be extremely short as

far as I know.

COMMITTEE MEMBER FELSHER: Yeah.

COMMITTEE MEMBER STERN: Yeah, but in that case, you would expect that you would not see an association, right, if it were too short.

COMMITTEE MEMBER BESARATINIA: And if you do see, then you might think twice what this association is about.

COMMITTEE MEMBER FELSHER: I mean, it's possible that we're not talking about tumor initiation. We're talking about progression. And you're accelerating -- like you brought up thoughtfully DCIS, which is the precursor to anywhere from a quarter to two -- three-quarters depending on which person's study you look at. That's all -- that's all we're trying to get at is that there's a loose end in terms. It would have been nice to say on average, this is what we thought people were exposed to polluted air to. The other -- the other aspect of this is that the NATA data has been used by lots of people and there -- and I know it was brought up. I believe in the report there's a Niehoff study in 2019 that came to a different conclusion.

It's also a very interesting paper using the data in a different way. And it seems like the main difference is the population was different. That this particular study, the Heck study, focused on a focused population in

LA. But I wondered if you'd thought about -- because the Niehoff study I don't believe specifically focused on vinyl acetate. It focused on many other carcinogens.

CHAIR LOOMIS: So is this a clarifying question? I feel like we're drifting a bit into discussion of causal inference here and --

COMMITTEE MEMBER FELSHER: Sorry.

CHAIR LOOMIS: -- we don't need to go there just yet. Other people are eager to jump in. I can see, but maybe we'll -- we should hold that discussion until later.

COMMITTEE MEMBER FELSHER: I apologize for making the discussion too broad. Those are the questions that I had.

CHAIR LOOMIS: Okay. Neela, did you have something to clarify there in response to those questions?

DR. NEELA GUHA: Yes. We just had an additional point of clarification again looking at the paper. The exposure lagging was presented for five years only, but it was also conducted by 5, 10 and 15 years. And the NATA -- the exposure models were considered at the earliest time period that the NATA estimates were available.

COMMITTEE MEMBER BESARATINIA: But they indicated that the 10 and 15 years data were not sufficient for any type of analysis. That's why they excluded and exclusively used five years lag time.

DR. NEELA GUHA: That is correct. Those time periods have sparse data.

COMMITTEE MEMBER BESARATINIA: Yes.

CHAIR LOOMIS: Okay. Any other questions from the -- from you, Dr. Felsher, are you finished?

COMMITTEE MEMBER FELSHER: One quick question about the animal studies. I wasn't clear. I think this was -- this was kind of asked, but I wasn't clear how they chose what doses to use. I have no problem with the doses. I just wasn't sure how -- was it clear there's some, because the doses -- the dose range that was chosen was consistent amongst the different studies. Was there -- was there a reason?

DR. MENG SUN: Again, these studies were conducted by different institutes, but you can see studies of the Ramazzini Institute probably chose consistent dosing. They probably did previous short-term dose finding studies, but I can't comment on all of them. In the JBRC study, they typically include a short-term dose finding study as well.

CHAIR LOOMIS: Okay. Let's do a quick survey of the Committee and see if these discussions have brought up any other questions of clarifications, but not yet discussion on causal inference.

Dr. Crespi, you've got one.

COMMITTEE MEMBER CRESPI: I had a clarification -- or informational question. So in the Heck air pollution study, the cancer case ascertainment was from the California Cancer Registry, I believe. And is it -- ductal carcinoma in situ, is that reportable to the California Cancer Registry or not?

CHAIR LOOMIS: Maybe while they're checking, we can see if there are any other questions on --

COMMITTEE MEMBER STERN: It should be reportable. It is -- if it's -- if it's cancer, it's reported as localized.

COMMITTEE MEMBER CRESPI: Okay. Because I was trying to determine whether it's reported and then the authors chose to not include it as a cancer outcome in this paper versus it wasn't available.

COMMITTEE MEMBER STERN: That's my understanding, because based on my own experience working with the California Cancer Registry, localized cancers are reported.

COMMITTEE MEMBER CRESPI: Um-hmm. Okay. Thank you.

CHAIR LOOMIS: Okay. Other questions on my left? Anything else?

It doesn't look like it.

On the other side?

No.

All right. I'm going to recommend that we break for lunch at this point. And when we do that, it's my duty to remind you that even during the lunch break, we're still governed by the Bagley-Keene Open Meetings Act, so you are not allowed to discuss the subject matter of the meeting among yourselves or to have phone calls, texts, or other electronic communications about that. You're also asked not to speak to third parties about the items under discussion. But if you do so, you'll be asked to disclose that and to describe the discussion that you had, so that can be part of the public record. So bottom line, best not to talk about it during lunch. Talk about, you know, sports, or the weather, or whatever you like.

So with that, we will break for lunch for 45 minutes. And I think that means we come back at -- well, let's say it's 12:40-ish, 12:40. Okay. That's when we'll come back.

(Off record: 11:52 a.m.)

(Thereupon a lunch break was taken.)

AFTERNOON SESSION

(On record: 12:43 p.m.)

CHAIR LOOMIS: Okay. All right. That's better. They have changed out my microphone because I understood or the staff understood that people online were having trouble hearing me, so we'll try this. Let me know if it's working any better.

Okay. So at this point, we'll move to that part of the agenda, where we hear from those of us designated as initial discussants of the evidence. So we'll begin with the human evidence and hear first from Dr. Crespi and Dr. Stern on cancer studies in humans. Then Jason Bush and Tom McDonald on the animal cancer studies. And after that, Dr. Felsher and I will talk about pharmacokinetics and metabolism. And finally, Dr. Alexandrov and Dr. Wang on the key carcinogenics of -- key characteristics of carcinogens.

So Dr. Crespi, I think you're up first as initial discussant on cancer studies in humans.

COMMITTEE MEMBER CRESPI: Okay. Thank you.

Yeah. So -- well, the staff this morning had a very good summary of the -- well of the highlights of the epidemiological studies. So I don't want to repeat everything that they went over today. I don't think they talked much about the occupational exposure studies, but

there wasn't really much there. They were very, very limited. So the study I think that is most relevant for our deliberations is the Heck study of ambient air toxic exposure in breast cancer, which I think has a number of strengths -- notable strengths, including the study population.

It was a large population-based prospective cohort study -- the multi-ethical cohort study. It's a very well studied cohort with unlikely to have a lot of selection bias associated with it. There -- sorry. I was going to pull up my notes, so I'm a little behind on my notes. Let me pull up my notes.

I think a few things to add, some things that popped to my mind about the study as we were having some discussions this morning. Some relevant facts about the study is that they enrolled individuals when they're ages 45 to 75. So most of the women who were enrolled were postmenopausal or close to menopause, which makes it particularly well suited for studying postmenopausal breast cancer, which was their outcome, which they assessed. Another strength of the study was the inclusion of the multiple ethnicities and they had a diversity of socioeconomic status within the cohort. So I think their study population was very well suited for the study.

They also had a very robust collection of

potential confounders and risk factors, lifestyle factors, et cetera, that they collected by questionnaire. So it's self-report, but a very good robust collection of confounders that they adjusted for in their analyses. So that's definitely a strength, and also their residential histories. Having that available is also a great strength of the study.

So, the exposure assessment, I think there were some concerns or issues raised this morning about how exposure was assessed at perhaps one or, I think it was, two points in time like three years apart essentially in the air toxics modeling. And that it wasn't -- the exposure assessment wasn't assessing exposures that were farther back in the life history of these individuals. But I think that, you know, the epidemiological studies, you have to take the data that's available. And these data just aren't available going back into the early life of these individuals.

So -- but I think we can take their exposure assessments as a marker or an indicator of exposure, rather than, you know, holding it to some high standard that they -- we don't trust the study unless they have exposure histories going far back. We just don't have the luxury of that very often in epidemiological studies.

Let's see, some other points I wanted to make are

that the vinyl acetate -- I think it was mentioned it wasn't highly correlated with any of the other studied chemicals, so -- so we can't really associate those high hazard ratios with the correlation with other chemicals that were studied. So I think that, you know, my assessment of that study is that it has -- it was a well-conducted study with a lot of strengths. There's some information that's missing that I wish was there. So, it's not perfectly reported.

Some other things that I wish they had done. Like I don't understand their increment that they use to calculate the hazard ratio. It's not that clear to me, but that hazard ratio is very high and it's high and across all of their stratified analyses and all their sensitivity analyses. And it's hard to think of some source of bias or confounding that would create a hazard ratio that high in this kind of a study. So, I guess that I find the study is very informative to us in making our decision here today. So that's my comments.

CHAIR LOOMIS: Okay. Thank you, Dr. Crespi.

Dr. Stern, anything to add?

COMMITTEE MEMBER STERN: Yeah. I share the same comments as Dr. Crespi and I agree that the study from multi-ethnic cohorts is very well designed and done. And, you know, aside from doing an interventional study, which

would be the gold standard but would be unethical. I think doing a prospective study like this one, a cohort study, is really the gold standard in epidemiology. And I think I share the same view as Dr. Crespi that I think of the exposure here as an indicator of what the exposure that they had likely before and the analysis they did considering people that may have moved over their lifetime I thought was very well thought out and kind of shows that the findings remain the same.

So, I thought that they did a very good job of considering all possible confounders. And the other comment I want to make about this study is that the limitation that they did not assess exposures earlier in life or that there could be some residual confounding due to other unmeasured factors would be non-differential, meaning that it would affect everybody in the cohort. So it means that when you're comparing the cases to the controls, likely it is biasing the results towards the null. So it's actually -- it may actually tell us that the real estimated association may even be higher than what we're seeing. So that's an important point to keep in mind when we think about these kind of biases.

The other thing I want to mention is that they did a pretty thorough job of looking at -- they considered over a hundred and eighty potential agents that they could

measure. And they did a careful job of selecting those that they thought could have a biological mechanism by which they could lead to breast cancer and also that they were prevalent in the LA basin. And that's how they ended up with those 15, so -- and there's no -- and they did -- as the team shared before -- the OEHHA team shared before, they look at correlations between these agents and there really isn't a strong correlation between vinyl acetate and the other 14 compounds that they looked at.

For the other compounds they didn't look at, they didn't look at them, because they were not really prevalent in the area. So I think that it's telling us that it is unlikely that what we're seeing is led by another compound that is commonly present in the LA basin, since they pretty much consider, you know, a lot of other compounds that were not included in the final analysis. So I agree that this study is very well done and it gives us very useful data.

I also wanted to make a very quick mention to some of the studies from the occupational studies that were not really discussed. And, you know, they were all very small. The assessment was through occupational records, so there's a lot of -- some issue with that. But I wanted to mention one study that caught my attention, which are the studies that were done on brain tumors,

because these studies were done by NIOSH, because there was a report of a cluster of brain tumors among workers of one particular factory.

So NIOSH did this study and it was very small. They didn't really present estimates, but they did find some evidence that there was higher levels of exposure among those who had cancer compared to those who did not. And then the company, Union Carbide Corporation, they published an independent study reanalyzing the data from the cohort, and they confirmed that for vinyl acetate, there was an excess of exposure among the cases. And they also did an independent case control study, where they found that 60 percent of the cases were exposed to vinyl acetate compared to 47 percent of controls, so it's about a twofold increase.

They didn't present the estimates, but the OEHHA team calculated them. So numbers are super small, but -- and the assessment, you know, there's some limitations with the way that the assessment was done. But again, any issues with the assessment would be non-differential. They would affect everybody in that factory, not just the people who developed the brain tumors. So again, they probably are biasing the results towards the null. So I thought it was worth mentioning that study, because it was repeated by different teams, including the same company

where these workers had been diagnosed. And they confirm that there seem to be an excess of exposure among those with brain cancer. So I wanted to highlight that.

There was also another study done also with occupational exposures that showed a positive association with non-Hodgkin's lymphoma. Similar limitations, occupational exposure measures through work records and small numbers, but I think it was worth mentioning that.

So I'll stop here.

CHAIR LOOMIS: Very good. Thank you. This was, for the benefit of the new members, a really good illustration of how we like to do the discussion here. With the initial discussion, we ask that they not read from detailed notes verbatim, but give a quick summary of their overall views of the evidence, with the second discussant adding to that anything omitted or other interpretations of the evidence.

So with that, let's move on to studies of animals and Jason Bush.

COMMITTEE MEMBER BUSH: Thank you, Dr. Loomis. Firstly, I'll start with comment and credit to Dr. Sandy and Sun. I want to congratulate you on the quality of the HID. Having reviewed these things now for over 10 years, this was particularly sophisticated, so I very much appreciate that. So kudos to your team for the effort,

the continued dedicated due diligence that you performed in putting these things together.

Secondly, I have read the public comments from -- that were submitted, notably the Vinyl Acetate Council. They have several compelling counterarguments that, you know, do have merit. So I am considering those in my determination.

Now, let's dig into it.

So I'm going to remind you we're dealing with 24 animal studies, so six rat and eight mice, and I'm going to take a more macroview of -- I think the OEHHA team did a good job digging into the data. I'm going to really paraphrase in terms of my determination. So based on the information provided in the animal studies, vinyl acetate demonstrates a pattern of carcinogenicity across multiple animal studies. And I'm coming to that based on six points. It could be more, but I'll be quick.

Okay. First, statistically significant tumor induction. Vinyl acetate exposure was associated with significantly -- sorry, statistically significant increases in various tumor types, including rare and malignant tumors across multiple species, strains, sexes and exposure methods. These include the squamous cell carcinomas, adenomas, adenocarcinomas in diverse tissues.

Secondly, dose response relationship. Many

studies identified significant dose-related trends in tumor incidences, strengthening the causal link between vinyl acetate exposure and carcinogenic outcomes. There's consistency across studies. Tumor formation was observed in multiple animal models, rats and mice, under both inhalation and the oral exposure conditions. This consistency enhances the reliability of the findings in my opinion.

And the relevance of rare tumors, the induction of rare tumors, like the squamous cell carcinomas of the forestomach, oral cavity, and esophagus is a notable indication of some carcinogenic potential. I appreciated the table related to the different plasias that you were seeing in the data. And I think that adds a level of credibility. We know that metaplasia, dysplasias, hyperplasias are fairly good surrogates for the carcinogenic potential. And so highlighting those, I think is a particularly important aspect of the HID.

And then, of course, the issue that we've talked about the acetaldehyde connection with vinyl acetate. Yes, it's a complicated metabolism. Yes, there are other things that contribute to endogenous levels of acetaldehyde. Diet can be one of them. But that connection I think is very strong evidence of why vinyl acetate ought to be considered as a carcinogen.

And so in conclusion, weight of evidence from these studies supports classifying vinyl acetate as a carcinogen, in my opinion, due to its consistent tumorigenic effects across multiple animal models and exposure scenarios.

With that, I'll yield my time.

CHAIR LOOMIS: Thanks, Dr. Bush.

Dr. McDonald, it's over to you now.

COMMITTEE MEMBER McDONALD: Thank you very much. Can you hear me fine or should I bring this closer?

CHAIR LOOMIS: Closer.

COMMITTEE MEMBER McDONALD: Okay. Once again, thanks to the OEHHA staff. They've -- for pulling together such a large amount of information on vinyl acetate carcinogenicity. It always is an immense amount of information that you compile. And I concur this was a very well written report. Thank you.

I'd also like to thank the public comments. They were also very informative and provided some points that were not covered in the HID, and so I appreciated that.

I'm going to structure my remarks in the following way. I want to first discuss the authoritative body with respect to the animal calls. And then I'll go into the studies themselves. Just -- I don't want to rehash, but try to just highlight again the consistency

there.

And then I also want to spend some time discussing the limitations and criticisms of the animal studies, which reduce the impacts on what -- and I think the Committee should all discuss that as well.

So let's start with IARC. We heard earlier today that, you know, it's limited evidence, but that was based on its transformation to the putative metabolite, acetaldehyde, and they both, acetaldehyde and vinyl acetate, cause nasal tumors. IARC covered eight bioassays. But as you saw in the HID, we have 24. I think also the HID stated that EPA hasn't looked at it, NIOSH and NTP haven't formally looked it up, and FDA as well. I did see in the Vinyl Acetate Council comments that the FDA does permit the esterification of starch by vinyl acetate. And so I assume that that's a reaction and there's some monomer left, so that -- but that's not a formal hazard ID.

Although not an official Prop 65 authoritative body, the European Chemical Agency looked at this formally in 2011. And I think it's worth noting that that authoritative body stated that vinyl acetate was carcinogenic in two animal species and in both sexes. It also demonstrated in their opinion inhalation and oral carcinogenicity. So I think that's worth noting here.

So let's first take a look at the cancers -- the bioassays. I won't go into the detail, but I'd like to just try to focus on consistency and then -- and then criticism. I saw little evidence throughout that the maximum tolerated dose was exceeded. This conclusion is also consistent with a European Joint Research Centre. They did a formal analysis and suggested that the MTDs were not exceeded in these animal studies.

There is high non-linearity in the data. The high dose group is often the only one that showed tumors. And this may relate to the mechanism of action, which we can talk about -- I'm sure we'll talk about later. So I want to just briefly, you know, tick off some of the findings in the studies. I don't want to rehash what's been already presented, but I just wanted to talk about the consistency.

In the inhalation studies in rats and mice, we saw nasal tumors in the male rats and suggestive evidence by statistical trend in the female rats. But there was negative studies in the mice, but there was also preneoplastic proliferation lesions in those studies, but no tumors.

In the oral studies looking at juvenile dosing through adulthood in rats, you know, there was the study of Lijinsky and Reuber, and the males were not -- there

were no tumors there. But in the females, even though the tumors were rare, these were endocrine carcinomas. They were rare and statistically significant by trend, but what's interesting is when you look at the author's discussion of those, they were very large, and invasive, and metastasized throughout the peritoneum. So this is a very unusual finding.

Also, the studies from the Japanese Bioassay Research Center showed the oral -- squamous cell carcinomas. Minardi, you saw the forestomach carcinomas. And then you had the oral studies where they started early life and then all the way through adult dosing. The studies by Bogdanffy et al. in rats were negative, but there were two squamous cell carcinomas of the oral cavity. And then the studies by Minardi and Belpoggi, which these are the Ramazzini Institute studies, were all positive showing statistically significant tumors by pairwise and trend tests of the oral and lip, tongue, forestomach, consistent all the way through. And then in the Belpoggi females a uterine adenocarcinoma. So consistency is what we're seeing here.

And then when we move to the oral studies in mice, starting at juvenile all the way through adult dosing, we see the same sort of thing, oral cavity, esophagus, forestomach those point of contact tumors being

quite substantial. And then in the Maltoni Swiss mice, we see the same sort of thing in males and females. The oral cavity, the tongue, esophagus, forestomach, all those point of contact sites.

I did want to spend a couple minutes talking about the criticisms of the studies. You know, that all sounds very, you know, powerful and consistent. There were some discussions about the lifetime dosing and natural -- watching the animals to a natural death. Several studies specifically the Ramazzini Institute studies did that where they have a protocol. That protocol has been -- has been criticized by some, because it can lead to high background incidences of spontaneous tumors. However, for these studies of vinyl acetate, you know, the tumor incidences in the controls were at or near zero, so that really doesn't follow as a valid criticism for these studies.

And we also -- (cleared throat) -- excuse me -- talked about the fact that the Ramazzini Institute studies were suspect. You know, this would relate to the Maltoni study, the Minardi study, the Belpoggi study. As noted, the EPA IRIS Program has stopped using those studies for its analysis. And the NTP has gone through an audit back in 2011.

I read that audit report, and, you know, it is

around methanol, MTBE, ETBE and vinyl chloride. So it's about the same era, but they're different chemistries. But I was struck by the fact that NTP had -- was worried about that both of the studies, there were chronic inflammation in the nasal cavity, air canal, and trachea, and lung indicating an infection of one of more respiratory pathogens, chronic airway inflammation due to mycoplasma pulmonis and perhaps other pathogens may have led to differences in opinion in the responses. Malignant lymphoma, which was mentioned, but also squamous cell carcinoma, and osteosarcoma.

So anyway, it's interesting also that the European Union when they analyzed acetaldehyde, there was a study by Soffritti in 2002, the same era as these studies, and the European Food Safety Administration took that study off the table for its analysis, because they were worried about this background infection rate.

So how should we view this criticism? For me, you know, background information inflammation can clearly drive the tumor responses that we're seeing. But, you know, I don't agree that with the EU that we should completely eliminate these from the analysis. The way I look at these is the target tumors and the tumor types of the Italian studies, the oral cancer studies are reasonably consistent with those from the Japan and even

the U.S. studies. So, even if we put them as a supportive evidence, I think the Ramazzini studies all point in the same direction as the other studies. So I'm still on board with that.

Then the final criticism is around the un -- the instability of the dosing solutions. I don't think that's really been discussed here. All of the studies started with solutions that were of high purity, but all of them were unstable, specifically the Lijinsky and Reuber, for example, lost eight and a half percent, but from volatilization by every day and the solutions were only made twice weekly.

And the Umeda and the JBRC study, the Japanese study, produced twice a week daily -- twice weekly dose solutions, and they estimate somewhere between 70 and 80 percent of the vinyl acetate was lost to volatilization.

So, you know, it -- and then the Bogdanffy studies in comparison made their solutions daily, so they have less of a concern. But everybody is choosing the best article as they go along.

I mean, for me, it creates some concern that you don't know the exact dose, but, you know, and this tends to just lower the overall dose to the animals and makes it less likely to see a toxic effect. But admittedly, you know, we still saw statistically significant induction of

malignant tumors even with the lower doses. So my bottom line is that given the concern over the studies, I think the overall picture is less strong, than we -- that we'd take a first look. However, the totality of data, the positive tumor findings seen in two species, even though the studies have some concerns, there's overall consistency that support a weight of evidence. And I think we shouldn't forget that the tumors from acetaldehyde overlap the same tumor types and tumor locations overlap with vinyl acetate.

So I would conclude that vinyl acetate is clearly shown to be an animal carcinogen, but I'll keep my mind open to hear public comments and Committee discussion for a final decision.

CHAIR LOOMIS: All right. Thanks to both of you. We'll move on now to pharmacokinetics and metabolism. And Dr. Felsher, you're up first on the agenda, so if you'd give us your summary of the evidence as you see it.

COMMITTEE MEMBER FELSHER: Thank you. Oh, shoot. It just freeze for you guys. Okay. Sorry it froze for a second.

Thank you for the chance to talk. I think the issues of the pharmacokinetics and metabolism were very nicely and thoughtfully organized as presented to us earlier today. There are basically four kinds of issues I

think that are worthy for our consideration. It's important to consider the fact that we have an idea of how this putative chemical carcinogen is bioactivated and how it's metabolize and eliminated.

Certainly, there are considerations in terms of how it gets distributed through the body and considerations about whether or not it actual reaches target organs of consideration of carcinogenesis. As had been described already, it's clear that this is a chemical that we have a pretty significant understanding of how it gets distributed in the body. There's excellent studies in animals in particular that have explored its ability to be absorbed through multiple routes, including inhalation and gastrointestinal, and through skin, in some circumstances, exposure. Then it had already been described.

We also have a good idea in cases where in animal studies, in particular radioactive, vinyl acetate has been used that -- an idea of where it actually physically gets distributed into animals and the kinetics at which it gets distributed. And those don't really support that the chemical, when consumed or exposed through different routes, is widely distributed through the body and it's distributed to organs in which there is evidence for carcinogenesis, as has been already summarized.

In particular, we've already heard a discussion of how vinyl acetate gets bioactivated. And, in particular, it's a chemical that gets metabolized to acetaldehyde, that this is a very important, because of course as we've just already been discussing, acetaldehyde there's already significant evidence of its carcinogenic properties. And we know that acetaldehyde is also further metabolized by the ALDH2 gene. And we've discussed already and heard how that's a very important way in which this chemical is inactivated, and provides more understanding in terms of the mechanism and ultimately how it's eliminated to acetic acid and carbon dioxide and released from the body.

One thing that perhaps hasn't been talked about, in terms of aspects of how the chemical can be bioactivated and contained within the body in a dangerous way is that radioactive studies of vinyl acetate have also been used to actually explore whether or not -- when it is bioactivated to acetaldehyde it actually does form adducts with other chemical compartments, most notably does it form stable binding components with DNA. And there is evidence that that occurs in these same studies that have explored the pharmacokinetics and metabolism.

So I think on balance this study suggests that we have a good understanding of how this chemical can get

taken into the humans or animals, and how it gets biodistributed, and how it gets activated and how it gets eliminated to provide us a framework for considering whether or not the carcinogenesis that's been observed in animal studies and has been associated in epidemiologic studies is it consistent with what we understand about this chemical.

One thing that we haven't discussed that may come up in the discussion is that most of our understanding of the carcinogenesis of this chemical is in its form of acetaldehyde, but it isn't that there aren't studies suggesting that vinyl acetate itself may, in some circumstances, have some dangerous qualities, and that perhaps something that is worthy of discussion.

So those are the comments that I was prepared to provide to you. Thank you.

CHAIR LOOMIS: Very good. Thank you. Well, I'll add a bit to that. So having heard from previous discussants that there is evidence of carcinogenicity in experimental animals and knowing that the human epidemiological evidence is sparse at best in terms of numbers of studies available anyway, I think that what you make of the metabolism of vinyl acetate to acetaldehyde is kind of a key piece of causal inference with respect to this listing. And with that in mind, it may be helpful to

think a bit about previous Authoritative body evaluations of acetaldehyde in vinyl acetate. We don't necessarily have to follow those in this instance. But it is interesting to note that when vinyl acetate was evaluated by IARC in 1995, at that time, there was limited evidence of carcinogenicity in animals, inadequate evidence in humans, and yet, the working group made an inference, based on studies of acetaldehyde in animals, that because there's sufficient evidence of carcinogenicity of acetaldehyde in animals at that time, and this was in 1987, I think, they upgraded the evaluation from what would have been group 3 to 2B.

So, since that time, acetaldehyde was evaluated again, also classified in Group 2B based on sufficient evidence in animals and inadequate evidence in humans. And then the next evaluation of acetaldehyde was really interesting, because it was done in conjunction with evaluating the carcinogenicity of alcoholic beverage consumption. And so, in that case again, the IARC working group inferred that because individuals with the ALDH2*2 allele produced more acetaldehyde and have higher incidence of cancer that acetaldehyde, in conjunction with alcoholic beverage consumption is carcinogenic to humans.

So that is a really important inference, but I want to point out that, you know, it is an inference and

there isn't direct evidence in humans of a link between production of acetaldehyde and development of cancer. And so, I think you could look at this two ways. You could say, well, you know, I'd really like to see that direct evidence or you could think, well, this is the way science works, isn't it, that we have this piece of evidence, this piece of evidence, and another piece of evidence, and we can make a link between those.

And I think -- I think that link is there and that the evaluations that IARC working groups have made over the years are kind of a guide to how you could proceed through that inference. I think they were done according to IARC's protocols. Again, we don't have to follow those, but it is informative to know what they did.

One other thing I would add is that I think it's important for this Committee to consider the evidence on susceptible groups. And as we heard in the very helpful presentation by the staff, there are at least a million Californians who may have heightened susceptibility to the potential carcinogenic effects of vinyl acetate, because they possess that ALDH2*2 allele, that inactivates or partially inactivates the metabolism of acetaldehyde.

(Noise in the background).

CHAIR LOOMIS: Well, that's a way to focus attention. I think we'll wait for this to stop before we

move on.

Okay. That may be it.

Let's go on to key carcino -- key characteristics of carcinogens. Dr. Alexandrov, you're up first on the agenda.

COMMITTEE MEMBER ALEXANDROV: Thank you so much. And again, I want to also thank the OEHHA staff for the very well written report and the presentation.

(Noise in the background).

COMMITTEE MEMBER ALEXANDROV: So I will wait. So when I come -- when it comes to the key carcinogens, there were four key carcinogens that were presented, where there's some evidence. I have to say from my perspective, it was very refreshing to hear all the other Committee members talking about the different evidence on the different considerations.

So when it comes to the key characteristic of carcinogens, just to remind you, the fact that something has a characteristic of carcinogens does not mean it's a carcinogen. When it comes to the key carcinogen -- carcinogen, one, it's electrophilic or can be metabolically activated. When I also look at the evidence, there were multiple papers that were supporting that I felt that this was quite compelling. I think it was quite clear.

But when we come to the key carcinogen -- key characteristic of carcinogen 2, the genotoxicity, I personally felt that the evidence there was a bit weaker. When it comes to chromosomal effects in humans, that was that was relying on one study from the Soviet Union in Armenia, which was quite old. I have a number of concerns about the -- the sample size was small, even though they took a hundred cells per patient. And again, it didn't seem particularly well conceived. And also, it was hard to judge some of the corrections, if any, that were done, whether the patient -- whether the individuals were age match, sex match, tobacco smoke match, et cetera.

In contrast, when it comes to the micronuclei formation and the sister chromatid results, there were multiple studies that both in vitro and in vivo and I personally found them very convincing. From my perspective, it was very clear that we can see genotoxic effects in experimental systems. The DNA damage was a bit of a mixed bag. There were studies that were showing that there is no DNA damage effect. There was crosslinks, but not specific crosslinks being mentioned. I think it's very clear that there is adduct formation, but whether this adduct formation leads to somatic mutagenesis, and whether that somatic mutagenesis is relevant to carcinogenesis, that wasn't particularly clear.

And the last part of the genotoxicity is the mutations. And again, I found there that the studies, even though the most recent studies was in -- from 2013, I believe it's about 10 years old, they were using reporter genes. There wasn't that particularly strong evidence. That wouldn't be the way one would conduct this study today, if one conducts it. So when it comes to somatic mutagenesis, I didn't find that there was sufficient evidence there.

When it comes to the key characteristic of carcinogen, the 10th one, alter proliferation, cell death or nutrient supply, I thought that this was crystal clear, at least from my perspective, that is very clearly cell proliferation. The multiple in vitro -- or sorry, in vivo studies show hyperplasia, they showed dysplasia. I thought there was absolutely no concern there, that that's a very, very clear good result to me.

What I worry and what I will express in the discussion section is that being able to create this dysplasia and hyperplasia may be confounding some of the mouse results that exist. And that has been my main concern, as part of the mouse studies, but we can discuss that later.

This is the summary of my remarks. Thank you.

CHAIR LOOMIS: Thanks. Dr. Wang.

COMMITTEE MEMBER WANG: Thank you for that summary. That was great. And I largely agree with those comments. I'll just add a few things so my comments will be brief. I agree that for the three that were considered key characteristics and the Characteristic one that it is electrophilic and particularly that it's metabolically activated is -- I think that has been clearly stated, based on the studies. And I found what was particularly compelling is that these adducts are often identified in the route of exposure, so in nasal, respiratory and olfactory epithelial.

I want to point out that for KC2, I actually found the data sound. I do want to remind the Panel that genotoxicity was already supported by the IARC report in 1995 and -- but I do agree that there was new data that was presented that were published in 2013. And those data were a little bit not as robust. But overall, I found that the -- I would agree with the original IARC report that there were numerous studies on all of these genotoxic effects that on the whole were consistent and robust.

And for the third charac -- Key Characteristic 10, I also agree that the data demonstrating cell proliferation, hyperplasia and dysplasia are robust, and also found in both the inhalation and oral exposure routes.

CHAIR LOOMIS: Very good. Thanks to all the Committee members for those helpful comments.

At this point, we will turn to public comments on the vinyl acetate agenda item. And I will describe how this works, while we look at a slide.

Sorry, I'm being reminded there's opportunity for the Committee to say more things, if they want to. So, I'll look on this side first, any other remarks?

Seeing nothing.

This side?

Yes, Dr. McDonald first.

COMMITTEE MEMBER McDONALD: Yeah. I just wanted to ask if there was any discussion that needed to happen around the endogenous or background adducts that seem to be coming from foods and alcohol that are much higher than what you get from -- that are very high. You'd have to have pretty good vinyl acetate exposure to even reach those background levels. Does anybody have an opinion or a thought whether those are relevant in this discussion?

CHAIR LOOMIS: I think I made a note somewhere that they probably were not relevant, but perhaps Dr. Felsher could add to that.

COMMITTEE MEMBER FELSHER: I think it's a very worthy comment to bring up and to discuss, because it is often challenging, and particularly confusing to explain

to non-scientists why there would be circumstances where we would not worry about the same chemicals when it's endogenous versus when it's exogenous. But to my interpretation, the simple answer would be that some of these metabolites are made endogenously in the context that there hasn't been reason to believe that they would be in the same way dangerous simply because of some of the mechanisms that we've been describing that have provided a way to deal with them.

And so we can't think of them -- we have to think of them -- the exposure in terms of context. We talked about, for example, an association between exposure through nasal and gastrointestinal exposure in cancer. That's a context that would not be anticipated biologically. But I think it's a -- I think you're bringing a very thoughtful and complicated issue that's worthy of the whole panel considering and discussing. Thank you for the chance to make some comments.

CHAIR LOOMIS: I think my note about that referred to epidemiologic studies primarily. And the idea would be that unless that endogenous production was associated with environmental exposure, it wouldn't affect interpretation of the epidemiologic studies. I see Dr. Eastmond also wants to make a comment and we'll turn it over to him.

COMMITTEE MEMBER EASTMOND: I guess this is the way I think of it. If I think of the dose to the individual, and this is now exogenous. Now, we're talking about ethanol alcohol consumption. The dose of acetaldehyde has to be so much higher to those individuals, because they're drinking gram levels of alcohol, as compared to very low levels of vinyl acetate by inhalation. So while there is an association between alcohol consumption and breast cancer, it tends to be relatively modest and happens with very high alcohol consumption levels.

So it's hard for me to reconcile this sort of ecological study, while the cohort study with vinyl acetate where the doses tend to be very, very low versus those seen with alcohol where there's many studies. So those estimates are fairly precise. So I don't put as much stock in that one epidemiological study, because of the acetaldehyde relative levels, in my opinion.

COMMITTEE MEMBER EASTMOND: I hope that made sense.

CHAIR LOOMIS: Yeah. Thanks. So is there discussion by the Committee down here?

Dr. McDonald, yeah.

COMMITTEE MEMBER McDONALD: I have one more question. Sorry. One thing that I haven't heard in the

discussion as it relates to the mechanism of toxicity, especially as ATSDR describes it, that, you know, the carboxylesterase reduces it to acetaldehyde an acetic acid. And then at high doses, they suggest it is the acetic acid which is creating a high -- highly acidic tissue and that's what's driving proliferation. So it's almost a threshold mechanism, but I don't know if that also happens with acetaldehyde, because I know acetaldehyde itself is then converted to acetic acid, but I haven't heard that discussed in terms of importance to the tumorigenicity and the neoplastic effects. Does -- can anybody speak to that?

CHAIR LOOMIS: Anyone.

COMMITTEE MEMBER EASTMOND: I believe that was the hypothesis generated by Bogdanffy and colleagues. But I don't know much more than that, as that was their proposed mechanism for the effects they were seeing was due to basically increased acidity proton generation.

DR. MENG SUN: May I say a few words regarding acidification?

CHAIR LOOMIS: Yes.

DR. MENG SUNG: Yeah. To us, it remains a hypothesis. As far as we know, there's no study studying vinyl acetate decreasing intracellular pH and increasing mitogenic cell proliferation. So it's a hypothesis, but

it has not been validated for vinyl acetate.

CHAIR LOOMIS: Any other Committee discussion, members online?

COMMITTEE MEMBER WANG: I'm not sure if this is the right forum, but I know we all discussed the individual components separately, but at what point do we try to synthesize them together? Because the one thing that I -- I don't know. You can stop me if this is not the right -- we have -- we're going to have a different discussion, but I guess what I'm still having -- what I'm trying to reconcile are the animal data versus the human data, right?

So we won't see -- we see a threshold effect in the animal data where it's only in the highest group. And then the human data, the magnitudes of risk are just astounding, and it's by increments. So I think that -- the question that was asked previously about what are those increments is really important. So that's -- I just want to bring that out.

CHAIR LOOMIS: Yeah. That's a really important question. So let's hold that thought until after we hear the public comments and we'll come back to that discussion before we vote. Anything else from the Committee before we move on?

Nothing this way.

Nothing that way.

Online?

Don't see anyone coming off mute. Okay. So now it is that time for public comments and in a moment we're going to see a slide on how to do this. But as a reminder, if you're here in person and you wish to make an oral comment, you're asked to fill out a blue comment card. It looks like this. They're at the back of the room and we'll call on those present to provide comments. So, when you're called, please come to the microphone, giving first your name and affiliation and then your comment.

If you're joining virtually and make -- wish to make a comment on Zoom, please use the raise-the-hand function that you'd indicate that you'd like to speak. And then when your name is called, you'll be prompted to unmute yourself and do the same, state your name and affiliation and give your comment. I'll remind you that public comments are limited to five minutes. I have a timer on the desk in front of me that will keep track of your time. When you get to four minutes, if you're still talking, I'm going to wave my hand at you, so that you can wrap up. And we will terminate those comments after five minutes.

So we'll go ahead and see if there are any

additional public comment cards. I have one on my desk. Are there any more?

No. Okay. So let's go ahead with the comment from Dr. Barranco.

DR. WADE BARRANCO: My name is Wade Barranco and I'm a senior toxicologist at LyondellBasell Chemical Company and serve as the Chair of the Vinyl Acetate Council. The Vinyl Acetate Council has sponsored decades of research and testing on vinyl acetate, including many of the key studies addressed in the hazard identification document. All of our research is published in peer-reviewed literature journals. We appreciate that you've reviewed our written comments and considered them today.

We would like to reemphasize one key additional point. As stated by ATSDR, the European Chemicals Agency and Health Canada, tumor formation in animals following vinyl acetate exposure is occurring only at high doses or exposures. Thus, vinyl acetate should be considered a threshold carcinogen assuming CIC judges it as such.

Thank you for the opportunity for providing a comment today.

CHAIR LOOMIS: Thank you very much.

Are there any comments on Zoom?

No comments on Zoom.

Is there anyone else who'd like to provide a comment from the public?

Okay. Hearing none. Does the Committee have any questions of clarification for the public commenter for Dr. Barranco?

No.

Okay. That means we move on to the Committee discussion of the evidence. And what I might do, Dr. Wang, since you raised the issue, do you want to bring that up again and propose that we -- see if we can -- we can help you figure out where we go with this?

COMMITTEE MEMBER WANG: My comment was on reconciling the animal data with the human data, of which we only have one, so it's a -- I mean, what the animal data clearly show based on the nice presentation this morning was that there is a clear threshold effect, where you don't see any association or tumors until the very -- the highest quartile of exposure. Whereas, the single human data that was provided, the hazard ratios are by increment. And that was at a very high magnitude of risk. So those two data don't seem to reconcile. And I just wanted to try to understand or wrap my head around, you know, how we consider the -- I think I -- what I consider the wealth of animal study data and in vitro studies compared to the single human study.

CHAIR LOOMIS: Well, that is a very important question and reconciling those data streams is exactly what we're about right now. I think I would add one thing that might be helpful and that is that this is hazard identification, so we don't really have to be concerned with dose and trying to reconcile, you know, whether this agent has a threshold or not. But let's see whether other Committee members would like to jump in and try to deal with that question or raise others.

Dr. Alexandrov.

COMMITTEE MEMBER ALEXANDROV: So I -- well, I do have one question for the Committee first and then I have a number of concerns related to them -- the animal studies. But my question is about the epidemiological study. This is a recent study published this year, right, and it does report quite strong effect sizes. But when I was reading it, and again I'm not an epidemiologist, I wasn't sure to -- and I heard comments that this is a very well conducted study. But one of the things that's -- I found concerning is in the discussion they were talking about breast cancer and the risk of air pollution, PM2.5 for example, and they said the evidence there is mixed. We're going to -- and they cited five studies where they had positive evidence, another five or six studies that had negative evidence between breast cancer risk and

PM2.5.

What worried me is that one study -- I don't know if we're five years in the future, whether there won't be three studies that show the effect size and three studies that are not showing it. And I don't know when a study is too early to judge that it's conclusive being a single study.

CHAIR LOOMIS: Good point. Anyone want to address that concern or raise something else?

Dr. Eastmond, you're looking like you want to say something.

COMMITTEE MEMBER EASTMOND: Just going to say in the animal studies, many of those showed a positive trend. And so that the effects weren't only seen at the highest dose. No, a number of them, the effect was seen at the highest dose only, but quite a few of them, there was positive trends across doses. And I am confident when OEHHA looks to evaluate dose response analysis, they'll look at these issues.

But as the Chair indicated, largely, you know, dose response is a separate step in the risk assessment that happens after the hazard identification step. But I think it's relevant to look at sort of those issues related to threshold, et cetera, when OEHHA gets to it.

CHAIR LOOMIS: Other discussion?

Dr. Alexandrov again.

COMMITTEE MEMBER ALEXANDROV: Yeah. So I wanted to bring the concern I had about the animal studies. So at first when I read them, I said amazing, so much supportive data. And then one thing that concerned me was seeing the things in Table 8 that were shown about the non-neoplastic preneoplastic lesions, which are very, very clearly increasing. And they're increasing in much higher rates than the neoplastic. You have one single, two, three, whereas you're going to have 40, 50 preneoplastic lesions. And what I am concerned about is my understanding is our mandate is to use generally accepted evidence to show that this leads to invasive cancer.

And my concern is that if we take that all the experiments were done correctly, then you eventually have a pathologist that's going to look at the lesion and is going to judge that lesion, whether it's precancerous or cancerous. And we know now because of the boom of digital pathology, that human pathologists make mistakes. And that mistakes is not trivial. That could be, you know, as much as five to 10 percent for some common cancers. For rare cancers that we mentioned multiple times, the disagreement between pathologists is significant.

So what I got increasingly concerned is that, yes, we see a lot of cell dysplasia. You see a lot of

hyperplasia. Is it possible that a lot of those invasive tumors that we are seeing are just the pathologists making a mistake and just misannotating something that's precancerous. It hasn't invaded the base membrane to something that's cancerous.

And none of those studies have had two pathologists or a third adjudicating pathologist, which would be, you know, the generally accepted standards at least when you deal with human patients. So that has been -- and when I started judging the animal studies from that, is it possible there is a pathologist's error which is 10 percent. You know, 10 percent of the preneoplastic get classified as neoplastic or if it's cancerous, then all of a sudden, I -- these things are not as conclusive. And I don't know what my fellow Committee member think about it. That was my main concern about all the animal studies.

CHAIR LOOMIS: And so as I hear you raising a concern about the animal studies and perhaps other Committee members can help with this. Dr. Bush, I'm looking at you or --

COMMITTEE MEMBER FELSHER: I certainly could have some comments.

CHAIR LOOMIS: Okay.

COMMITTEE MEMBER FELSHER: So I think these are

all thoughtful comments. And certainly, you have to take animal studies with the limitations of the studies. Generally, animals metabolize carcinogens more, especially alkylating agents. That's what's been reported. So generally, animals don't live as long as humans. The studies are much shorter. We know the general duration of exposure is actually a much -- usually a much important parameter for genotoxic agents than quantity.

There are issues in the difference of pathology unequivocally. But I -- but I actually think, if anything, the animal studies would underestimate effects. And the fact that so many studies show that there's a cause of cancer. If the question were being asked is can this cause cancer? To me, it is quite compelling. There's not one or two studies. There are multiple studies done by different investigators. The cancers have a logic to them. I agree that you -- that they can be misdiagnosed as early lesions, but actually in a two-year study, I suspect they're missing actually neoplastic lesions, because you can't -- you certainly -- they couldn't afford to do a whole body histological analysis to find occult cancers.

And all of us would expect there to be preneoplastic lesions in animals that whole bodies are being exposed to a carcinogenic agent where the cancer

process will go through multiple steps. So I'd say the evidence isn't perfect, but compared to other examples I've seen, this is pretty good -- this is really good evidence. There's lots of different studies.

The second consideration is I think it's -- you have to be careful using animal studies to try to estimate a hazard threshold for two basic reasons. The metabolism is very different and the second reason is the numbers are smaller. And it's very easy to -- there is a trend here, but the reason I asked about the dosing was we didn't -- we really weren't given a range to know in animals what was the expected range. They didn't -- of what makes sense in terms of the metabolism. But what we -- we did see some examples of a dose effect.

And when you're only talking about a hundred animals -- I know we're not here to talk about hazard. We all look at hazard, especially as -- when I'm wearing my MD hat, I'm thinking about hazard. But we know that when -- if we were going to talk about hazard, we're not talking about hazards. We're trying to determine between 20 and 30 percent. An animal study with 50 mice, 100 mice isn't going to detect a one percent hazard. It's impossible.

But a one percent -- if we thought we were talking about something that would be a one percent

hazard, that would be a huge hazard in terms of a population. I do think that the question raised by, I believe it was Dr. Wang in terms of the concern about the epi versus the animal studies is disjoint. I think -- I think it was you, Dr. Loomis, but it could have been several people commented that the actual hazards seen in our one epi study is high. It's a big number. It's unusual to see such a high number where there are no other studies, but I trust the colleagues who reviewed this, their description that we -- there's not a reason that we found that there's a flaw in the study. It's reasonable to say other studies may not see the same amount of hazard.

They try to give reasons in the study why they saw perhaps more than other people had seen. So those are my thoughts on the animal study. All important thoughts. I certainly don't disagree the pathology can't be confounded, but it could also be confounded both ways. I don't think that we can easily say there's a threshold here. I think it's thoughtful to remark that we don't see a dramatic dose response, but there's some evidence of a dose response. And I do think it's legitimate, but it doesn't change the value that there's a disjoint between the animal data and the amount of hazard we saw in this one good epidemiologic study. Thank you for the chance to

share comments.

CHAIR LOOMIS: Yeah. Thanks, Dr. Felsher, and let me add for the online participants, you know, I'm trying to watch everybody in the room, as well as both of you. And I may not notice your little red microphone disappearing indicating you want to say something. So, if you do want to say something and I don't notice, just speak up, or wave your hand or something, and I'll get to you.

I think we had more comments in the room.

Dr. Eastmond looks like he's -- has one.

COMMITTEE MEMBER EASTMOND: I always do.

One of the points in this sort of guidance criteria that was discussed many years ago, about 20 years ago actually, is that while the -- essentially the -- our charge is to identify chemicals that cause cancer and invasive cancer. If it's -- if we see a benign tumor of the type that is known to progress to become invasive, that is counted as the same. Usually, that's combined in making that determination, so that it's a combination of both benign and malignant oftentimes are used in making decisions. I hope that's clear.

CHAIR LOOMIS: Okay. Thanks.

Further discussion?

Dr. Stern.

COMMITTEE MEMBER STERN: Yeah. I just wanted to provide some additional insights or comments reflecting on the literature provided and just to remind everyone that even though we are focusing mostly on the study by Heck et al. and the multi-ethnic cohort, because it's really the most valuable informative study because of the size and characteristics, all of the other five studies that were all occupational cohort studies or case control studies within cohorts, two of them -- one of them that I mentioned before, a brain cancer study that was repeated a few times, does show evidence of an association. And there's the other one that shows evidence for association for non-Hodgkin's lymphoma, so I think we shouldn't forget that with all the caveats that were already made about the way the exposure is measured. But again, in my view, such misclassification, if anything, might be reducing the estimates that we are seeing, not inflating them.

The other thought that I had when I review all these materials is, you know, you're thinking about causal inference, we tend to think about different aspects, one of them being analogy biological plausibility. And with all the discussion we had previously about acetaldehyde and the comments that Dr. Loomis made, I really think there's something important there to consider, given that in particular for breast cancer alcohol is an established

risk factor. There's convincing evidence that alcohol causes breast cancer and the main mechanism is supposed to be through acetaldehyde.

So if we use that logic of analogy with this compound that we've been discussing leads to the accumulation of acetaldehyde and the carcinogenicity of that, then that's something that makes me think that this is something we need to worry about, even if as you are talking about, this is one study, it's true, but it's a well-designed cohort study, which we tend to consider our gold standard in epidemiology. So, yes, it would be ideal to have multiple cohort studies, so that we can see that they all find the same, we don't have that, but we have this one that we know we think is showing us an -- and I agree with Dr. Felsher, we rarely see alteration of hazard ratio of five with a dose response, which is another criteria we use for causal inference, right. We want to see a dose response.

So putting all that together, I think this is concerning and we need to take this evidence pretty seriously, I think, even though it's just one study, right, which is not ideal.

CHAIR LOOMIS: Other comments.

Dr. Bush.

COMMITTEE MEMBER BUSH: Yeah. Thank you. And

maybe this might help rectify some of the information, Dr. Wang, but you know -- and for our newer Committee members, remember that our guidance criteria, as was laid out as per statute, the weight of the scientific evidence clearly shows that a certain chemical causes invasive cancer in humans or that it causes invasive cancer in animals. So just reminding you of that statute.

CHAIR LOOMIS: Thanks for that important information.

I want to add to the discussion on causal inference. Appreciate the comments from Dr. Stern. I would also add that here we have compelling evidence of carcinogenicity in animals. I would certainly like to see more human epidemiologic evidence. But what we have is reasonably consistent in spite of the small number of studies. And then we have evidence that there are -- that this agent shares several key carcinogenic characteristics with other agents known to cause cancer.

So I think another causal criterion is coherence. I think all the evidence hangs together and points in a consistent direction suggesting that this agent also, vinyl acetate, is carcinogenic to humans.

Further discussion from the Committee?

Yes, Dr. Landolph.

COMMITTEE MEMBER LANDOLPH: Thank you. Yeah, I'm

not particularly concerned that humans are more resistant. I mean, they're more resistant to almost anything. And this is undoubtedly why throughout evolution we've been able to grow, you know, to roughly an 80-year lifespan. And one of the reasons, among many, for that is that the humans have a real resistance to maintaining chromosomal integrity and chromosomal stability. Whereas, if you work in cell culture, those of us know that there are like orders of magnitude difference in the rate at which you get chromosomal aberrations in mice versus humans. It's extremely small in humans. You have to work extremely hard to get it. So you would ex -- I would expect that it would be more -- humans would be more resistant to many of these agents than they are. And that's not a surprise. That's a plethora of data that's grown up over the last 40 years or so more recently. So I wouldn't get hung up on that at all.

CHAIR LOOMIS: Thank you.

Further discussion. Dr. Alexandrov again.

COMMITTEE MEMBER ALEXANDROV: Just one last thing for me. I suppose I remain unconvinced that there is convincing evidence for invasive tumors in mice. I think that there is a high chance of pathologist mistake. But one question I wanted to ask for colleagues who work on mouse models, if there were invasive cancers -- and my

understanding, because most of those studies did not find difference in mortality between the -- between the controls and the exposed mice. If there were invasive cancers, wouldn't one expect to see difference in mortality?

CHAIR LOOMIS: Anyone care to answer that?

DR. MENG SUN: May I jump in regarding the -- your doubt on the pathology. So I do want to mention that in the HID, we do mention that for the Bogdanffy and the Lijinsky studies, independent pathology reviews were conducted. So, they're in the table footnotes for these studies. Yeah. No comment on the mortality.

CHAIR LOOMIS: I guess you don't get an answer to that.

COMMITTEE MEMBER ALEXANDROV: That's fine.

CHAIR LOOMIS: Are there any other issues the Committee would like to bring up before we vote?

This way.

That way.

Online?

I don't see anything.

So I'm going to propose that we move to the vote now, unless there are any objections?

Hearing and seeing none, let's go ahead and do that. And so for the vote, we have to consider the

following formal question. Has vinyl acetate been clearly shown through scientifically valid testing, according to generally accepted principles to cause cancer?

So I'll now call each of your names and ask you to vote yes, no or abstain. And we'll go in Alex -- in alphabetical order, beginning with Dr. Alexandrov

COMMITTEE MEMBER ALEXANDROV: Yes.

CHAIR LOOMIS: Dr. Besaratinia?

COMMITTEE MEMBER BESARATINIA: Based on the totality of evidence, I would say the epidemiologic data and human studies are inadequate, particularly the study which was discussed -- the latest study by Heck, there are major drawbacks in that study, which gives me pause reading the conclusion. Having said that, the animal studies, although have their limitation as was also discussed by panel, they show consistency in results. And we see positive results in different strains of rodents, both mouse and rats, different genders. What is particularly important is the rarity of tumor incidence in a majority of those animal studies together with in vitro data.

And with the KC finding two out of three, I think KC1 and KC10, which made a good case, I would stay with the conclusion of the IARC that was a classification as a group 2B carcinogen. But since we don't have that luxury

to specify it, my vote would be yes.

CHAIR LOOMIS: Okay.

ACTING DIRECTOR EDWARDS: Just a quick clarification. If we can limit the responses to yes, no or abstain, that would be great. Thank you.

CHAIR LOOMIS: Thank you. Yeah. Okay. So that was a yes vote.

Dr. Bush how do you vote?

COMMITTEE MEMBER BUSH: Yes.

CHAIR LOOMIS: Dr. Crespi, your vote?

COMMITTEE MEMBER CRESPI: Yes.

CHAIR LOOMIS: Dr. Eastmond?

COMMITTEE MEMBER EASTMOND: Yes.

CHAIR LOOMIS: Dr. Felsher?

COMMITTEE MEMBER FELSHER: Yes.

CHAIR LOOMIS: Dr. Landolph?

COMMITTEE MEMBER LANDOLPH: Yes.

CHAIR LOOMIS: I vote yes.

Dr. McDonald?

COMMITTEE MEMBER McDONALD: Yes.

CHAIR LOOMIS: Dr. Stern?

COMMITTEE MEMBER STERN: Yes.

CHAIR LOOMIS: Dr. Wang?

COMMITTEE MEMBER WANG: Yes.

CHAIR LOOMIS: Very good. Six votes are required

to add a chemical to the list. And we now have a unanimous vote in favor of listing, so the chemical will be added.

I don't think we need to tally them up.

The agenda says we can break here for 15 minutes, so let's do that and return at 2:15.

(Off record: 2:02 p.m.)

(Thereupon a recess was taken.)

(On record: 2:16 p.m.)

CHAIR LOOMIS: Let's try to reconvene the Committee here please. If you're all in the room, please take your seats. It is 2:15 and we're going to try to wrap up.

Okay. Everyone is here or nearly, so, so we will take up the third item. That is the consent item updating the California Code of Regulations Title 27, section 27000 list of chemicals, which have not been adequately tested as required. So we'll take that now. The Committee is being asked to affirm changes in response to submissions from the U.S. EPA's Office of Pollution Prevention and Toxics. The California Department of Pesticide Regulation and EPA's Office of Pesticide Programs have indicated there are no changes. So this consideration is a ministerial duty of the Committee. We rely on information provided to OEHHA by the Department of Pesticide

Regulation and U.S. EPA in order to identify the chemicals that need to be added or removed from the Section 27000 list.

And so to move on to that item, I invite Environmental Scientist and the Implementation Committee, Kiana Vaghefi to give the staff presentation.

(Slide presentation).

KIANA VAGHEFI: Hi, everyone. Oh, perfect. Thank you, Dr. Loomis.

Proposition 65 requires the State to publish and update annually a list of chemicals that are required to be tested under State or federal law for carcinogenicity or reproductive toxicity that have not yet been adequately tested as required. This list can be found in Title 27, Section 27000 of the California Code of Regulations, and is commonly referred to as the Section 27000 list.

It is separate and distinct from the Proposition 65 list of chemicals known to cause cancer or reproductive toxicity. The Section 27000 list has no regulatory impact. It does not require that any testing be done. Rather, it is a source of information concerning chemicals that need further testing pursuant to State or federal law.

To update the list, OEHHA requests information from the California Department of Pesticide Regulation and

the U.S. Environmental Protection Agency's Office of Pollution Prevention and Toxics, and the Office of Pesticide Programs. OEHHA staff reviewed these responses and identified one recommended change to the Section 27000 list, addition of 2,2,3-trifluoro-3-(trifluoromethyl)oxirane, also known as hexafluoropropylene oxide, or HFPO. Based on information received from U.S. EPA's OPPT, further carcinogenicity, reproductive toxicity, and developmental toxicity testing are required.

The letter from OPPT, along with additional background, response letters from DPR and OPP, and a mock up of the proposed changes are available in the staff report provided to the Committee and posted online on November 27th. The proposed change is also shown on the slide.

As Dr. Loomis mentioned, this is a consent item and a ministerial duty of the Committee, in that the DARTIC and CIC committees use the information provided by DPR and U.S. EPA to identify the chemicals that need to be added or -- added to or removed from the Section 27000 list. We ask the Committee members to vote in favor of the proposed change, so OEHHA can update the list.

And I'll turn it back over to Dr. Loomis and we're happy to take any questions.

Thank you

CHAIR LOOMIS: Are there any questions of clarifications from the Committee? I'll remind you that this is a consent item, so we don't need discussion, but for your information. Is there anything?

Nothing that way.

Nothing that way.

Online, nothing.

Since there are no questions, we'll turn to the vote. The question before us is should Section 27000 of Title 27 of the California Code of Regulation be amended as indicated in the staff report? I'll now call your names and ask you to vote yes or no. Again, as with the vote on listing, this is simply yes, no or abstain vote, without justification or explanation of why you're voting as you are.

Dr. Alexandrov?

COMMITTEE MEMBER ALEXANDROV: Yes.

CHAIR LOOMIS: Dr. Besaratinia?

COMMITTEE MEMBER BESARATINIA: Yes.

CHAIR LOOMIS: Dr. Bush?

COMMITTEE MEMBER BUSH: Yes.

CHAIR LOOMIS: Dr. Crespi?

COMMITTEE MEMBER CRESPI: Yes.

CHAIR LOOMIS: Dr. Eastmond?

COMMITTEE MEMBER EASTMOND: Yes.
CHAIR LOOMIS: Dr. Felsher?
COMMITTEE MEMBER FELSHER: Yes.
CHAIR LOOMIS: Dr. Landolph?
COMMITTEE MEMBER LANDOLPH: Yes.
CHAIR LOOMIS: I vote yes.
Dr. McDonald?
COMMITTEE MEMBER McDONALD: Yes.
CHAIR LOOMIS: Dr. Stern?
COMMITTEE MEMBER STERN: Yes.
CHAIR LOOMIS: Dr. Wang?
COMMITTEE MEMBER WANG: Yes.
CHAIR LOOMIS: Very good.
Unanimous again. The change is affirmed.
So the next item is staff updates. That will provide current information on Proposition 65 listings, regulations and litigation that have taken place since the last meeting. Again, Kiana will present those listings and safe harbor levels.
(Slide presentation).
KIANA VAGHEFI: Hi, again. Thank you, Dr. Loomis. I'll be providing you with an update on important Proposition 65 developments since the last CIC Committee meeting. I'll start by going over the chemicals or endpoints to be listed or under consideration for

potential listing. Then I'll review the proposed safe harbor levels. After that, I'll turn it over to our counsel, Corey Friedman, to provide a brief update on other regulatory actions.

[SLIDE CHANGE]

KIANA VAGHEFI: Last week, the Developmental and Reproductive Identification Committee considered listing BPS for male reproductive toxicity. The DARTIC unanimously voted yes on the question, has Bisphenol S been clearly shown through scientifically valid testing, according to generally accepted principles to cause reproductive toxicity based on male reproductive toxicity. And so the male reproductive endpoint will be added to the listing of this chemical.

In December of last year, BPS was added to the Proposition 65 list for reproductive toxicity based on the female reproductive endpoint.

[SLIDE CHANGE]

KIANA VAGHEFI: BPS remains under consideration for listing as causing developmental reproductive toxicity. Information from the BPS data call-in will be used in preparation of a hazard identification document for a future DARTIC meeting on this endpoint. And recently, OEHHA issued a data call-in on n-methyl-n-formylhydrazine to solicit information related

to its carcinogenicity. The comment period ends January 10th, 2025.

[SLIDE CHANGE]

KIANA VAGHEFI: Since the Committee's last meeting, we propose to adopt a no significant risk level for exposure to titanium dioxide airborne unbound particles of respirable size, where both of the following intake levels must be met, 440 micrograms per day for airborne unbound titanium dioxide particles with diameters of 10 micrometers or less and 44 micrograms per day for airborne unbound titanium dioxide particles with diameters of 0.8 micrometers or less. We're still in the regulatory process for this proposal.

And now, I will turn things over to Corey.

COREY FRIEDMAN: First of all, thank you all for your patience with the construction sound effects earlier.

Hopefully, that won't interrupt this. But if it does, thank you, all.

[SLIDE CHANGE]

COREY FRIEDMAN: Okay. So first in October, OEHHA finalized regulations to provide an additional safe harbor warning option for businesses that cause significant exposure to acrylamide from foods.

Second, in February, we at our -- at your last meeting, we told you about a proposed rulemaking that

amended existing regulations and added some new sections to the Safe Harbor Warning regulations. This proposal has been finalized and approved. It amends the sections visible on that slide there. And that takes effect on January 1, although there is a three-year implementation period before it's fully effective.

These regulations make the short-form warning more informative to consumers by requiring at least one chemical name in a short-form warning. So to give an example, instead of just saying, "Warning, Cancer", the short-form warning would say something like, "Warning, can expose you to formaldehyde a carcinogen," and then the website where people can learn more.

The regulations also provide additional warning content options for businesses to select from and provides businesses that currently rely on the existing short-form warnings three years during that phase-in period to transition to the new safe harbor warning content for short forms. The regulations make explicit that short-form warnings may be used to provide safe harbor warnings for food products, provide a 60-day transition period during that three-year implementation period for retailers to give them 60 days to update online short-form warnings when they get notice from a manufacturer that the new short form is -- they've updated to the new short-form

warning. This regulation package also provides new tailored safe harbor warnings for passenger or off-highway motor vehicle parts and recreational marine vessel parts.

So I'm next going to talk about some of the significant litigation.

[SLIDE CHANGE]

COREY FRIEDMAN: So, I mentioned the safe harbor Warning for acrylamide in food that is relevant to ongoing litigation which existing members, who are not new to this meeting heard about previously.

California Chamber of Commerce versus Bonta involves a first amendment challenge. For the new members, in recent years, there have been several challenges to the Prop 65 Safe Harbor Warning content. The general argument is that they violate businesses' First Amendment rights. This case, Chamber of Commerce, is currently proceeding. There is a preliminary injunction in place, which prevents enforcement of the warning requirement for acrylamide in food. This Chamber of Commerce has filed a summary judgment motion, which if successful, would result in a permanent injunction. And the hearing for that motion is scheduled for January 23rd. So the next time this Committee meets, we should -- we may have the results on that or at least on the summary judgment motion. If the summary judgment motion is not

successful, the case continues to trial.

In Personal Care Products Council versus Bonta, this concerns titanium dioxide airborne unbound particles of respirable size, in that the Personal Care Products Council filed a First Amendment challenge to warnings for that listed chemical for cosmetic and personal care products. In that case also, a temporary injunction is in place and a summary judgment has been filed, but there's no hearing date for that motion, so the court could rule at any time.

And then in Physicians Committee for Responsible Medicine versus Newsom, a challenge is pending to the decision not to list processed meats as a carcinogen. Processed meats was the subject of an IARC monograph, but OEHHA has not listed it. And that case is still pending in Sacramento Superior Court, but I don't have any significant developments to report. We do not have a hearing date in that matter.

Just to let you know, outside of the Proposition 65 context, businesses are challenging government mandated disclosures in other contexts. So it is possible that the -- that decisions that are not about Prop 65 in particular could have an effect on California's ability to require Proposition 65 warnings, particularly in consumer products. Does anyone have any questions about those

updates?

COMMITTEE MEMBER McDONALD: Can you tell me -- say again what you just said about the last point of a possible pre-exemption or exemption? What was your last point you made?

COREY FRIEDMAN: Oh, just that First Amendment questions and the extent to which government entities can require business disclosures. That issue is being litigated in context outside of Proposition 65. And so it's possible that a decision could be issued in a non-Proposition 65 case that would also have an effect on the ability of California to mandate Proposition 65 warnings for listed chemicals.

COMMITTEE MEMBER McDONALD: Thank you.

CHAIR LOOMIS: So where is that litigation in the federal court system now?

COREY FRIEDMAN: Well, the two cases that I mentioned are at -- currently at the trial level. There have been, in the past, appellate decisions, that have been reported to this Committee. But those two cases are at the trial level.

CHAIR LOOMIS: So which court are they in?

COREY FRIEDMAN: Oh, which district?

CHAIR LOOMIS: District.

COREY FRIEDMAN: I can get you that information,

but I'm afraid I don't remember --

CHAIR LOOMIS: That's okay. It's --

COREY FRIEDMAN: -- off the top of my head.

CHAIR LOOMIS: You know, the districts are different, right? And so --

COREY FRIEDMAN: Yes.

CHAIR LOOMIS: -- if it comes from the Fifth District, it might be an interpretation that's highly consequential, for example.

COREY FRIEDMAN: Yeah. I mean, we'll see what happens. Also, it's possible they could go back up to the Ninth Circuit again, but we don't know that at this point. And as you can see from their case names, OEHHA is not a party to those cases. It is the Attorney General's office that is litigating them. We are a party in the processed meat case.

Any other questions?

Okay. Then that is the end of my presentation. So, Chair Loomis, if you would like to continue.

CHAIR LOOMIS: Thanks to both of you.

At this point, I'll ask Acting Director Edwards to summarize the Committee Actions today.

ACTING DIRECTOR EDWARDS: Great. Thanks, Dana.

All right. So today, the Committee considered and deliberated at length on whether to add vinyl acetate

to the Proposition 65 list as a carcinogen. By a unanimous vote, the Committee approved to list vinyl acetate.

The Committee also voted on a consent item to add two 2,2,3-trifluoro-3-(trifluoromethyl)oxirane, also known as hexafluoropropylene oxide, or HFPO, to Section 27000 list. That's published in the California Code of Regulations. The vote here was also unanimous and so the chemical will be added to that list.

I want to give thanks and acknowledgment for the work that the Committee did to prepare for this meeting. We really appreciate your effort and preparation. And, of course, I want to add my thanks to the staff for all of their work to put that document together and also to the audience and commenters today.

We do have one final item, and that is that Dr. Thomas McDonald has informed us of his intention to resign from the CIC committee after his seven years of service on this Committee. So this is Dr. McDonald's last meeting. It's a tremendous service to the people of California. So I would like to allow some time for the Committee members and OEHHA staff to express their thanks to Dr. McDonald and wish him well.

(Applause).

COMMITTEE MEMBER McDONALD: Yeah. Thank you very

much. Yeah, I am retiring in January and I'm going to try to make it a clean break with work as well as other toxicology.

CHAIR LOOMIS: That's hard to do, I can tell you. (Laughter).

COMMITTEE MEMBER McDONALD: Yeah. Yeah.

Many of you may not know that I started my career at OEHHA in 1994. I was there for 11 years and I really enjoyed my time there, especially working with very impressive scientists. I had to smile and chuckle a little bit when you were talking about acrylamide and food litigation, because I think I did the first NSRL on acrylamide.

Anyway, I've been -- yeah, I enjoyed the last seven years on the Committee and I appreciate that I was allowed to serve.

Thank you.

ACTING DIRECTOR EDWARDS: Thank you.

I will now turn it back to Dr. Loomis to adjourn the meeting.

CHAIR LOOMIS: Well, thanks, Dave. I'd like to echo the appreciation for all the hard work of the staff producing an excellent and really clear and concise risk identif -- hazard identification document. Really, really helpful for our discussions. Thanks too to the members of

the public who joined and gave comments and especially to the Committee, new members, continuing members, and retiring members. Really appreciate all your work on this.

I now declare this meeting adjourned. Thank you very much.

(Applause).

(Thereupon the Carcinogen Identification Committee adjourned at 2:36 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 11th day of January, 2025.

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