MEETING

STATE OF CALIFORNIA

OFFICE OF ENVIRONMENTAL HEALTH HAZARD ASSESSMENT

PROPOSITION 65

DEVELOPMENTAL AND REPRODUCTIVE TOXICANT

IDENTIFICATION COMMITTEE

JOE SERNA JR.

CALEPA HEADQUARTERS BUILDING

1001 I STREET

SIERRA HEARING ROOM

SACRAMENTO, CALIFORNIA

WEDNESDAY, DECEMBER 11, 2019

10:00 A.M.

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

A P P E A R A N C E S

COMMITTEE MEMBERS:

Ulrike Luderer, Ph.D., M.P.H., Chairperson

Patrick Allard, Ph.D.

Diana Auyeung-Kim, Ph.D.

Carrie Breton, Ph.D.

Laurence Baskin, M.D.

Suzan Carmichael, Ph.D.

Irva Hertz-Picciotto, Ph.D.

Aydin Nazmi, Ph.D.

Tracey Woodruff, Ph.D.

STAFF:

Dr. Lauren Zeise, Director

Mr. Allan Hirsch, Chief Deputy Director

Ms. Carol Monahan Cummings, Chief Counsel

Dr. Marlissa Campbell, Reproductive and Cancer Hazard Assessment Branch

Dr. Vincent Cogliano, Deputy Director, Division of Scientific Programs

Dr. Farla Kaufman, Reproductive and Cancer Hazard Assessment Branch

Dr. Poorni Iyer, Reproductive and Cancer Hazard Assessment Branch

Dr. Allegra Kim, Reproductive and Cancer Hazard Assessment Branch

A P P E A R A N C E S C O N T I N U E D

STAFF:

Mr. Julian Leichty, Special Assistant for Programs and Legislation, Proposition 65 Implementation Program

Dr. Francisco Moran, Reproductive and Cancer Hazard Assessment Branch

Dr. Yassaman Niknam, Reproductive and Cancer Hazard Assessment Branch

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

Dr. Lily Wu, Reproductive and Cancer Hazard Assessment Branch

ALSO PRESENT:

Dr. Dale Gieringer, California NORML

Ms. Ellen Komp, California NORML

I N D E X

P R O C E E D I N G S

DIRECTOR ZEISE: Good morning, everyone. I'd like to welcome you all, welcome the Committee, the OEHHA staff, the Office of Environmental Health Hazard Assessment staff, and the audience in the room and online to the December 2019 meeting of Developmental and Reproductive Toxicant Identification Committee.

So we have one main agenda item today, the consideration for listing under Proposition 65 of cannabis smoke and delta-9-THC -- so again, for possible listing as a developmental toxicant under Proposition 65. So the more general endpoint is reproductive toxicity, but we are considering reproductive toxicity in terms of developmental toxicity today.

So the meeting is being transcribed, translated, and webcast. So this is an early reminder that everyone should speak clearly into the microphones, staff, panel, as well as from the audience in making your public comments.

So just a few logistics. The drinking water fountains and restrooms, you go out the door, and turn left, and walk all the way to the end of the hall. In the event of any kind of an emergency, we'll go out the exit door at the back of the room and walk down the stairs and meet in the park across the street.

So with that, I think I've covered all -- oh, and then we'll also be taking breaks for the court reporter.

So to introduce the Panel. We've got Dr. -- on the far end in this direction -- yes, we do have Dr. Patrick Allard from the University of California, Los Angeles, School of Public Health. We have Dr. Diana Auyeung-Kim from Genentech. We have Dr. Carrie Breton from the University of Southern California School of Medicine. Dr. Aydin Nazmi from the California Polytechnic State University, San Luis Obispo.

Oh, I didn't introduce myself. I'm Lauren Zeise. I'm Director of the Office of Environmental Health Hazard Assessment within the California Environmental Protection Agency.

Then to my left is our Chair Dr. Ulrike Luderer from the University of California Irvine School of Medicine. And then Dr. Suzan Carmichael from the Stanford University School of Medicine. Dr. Irva Hertz-Picciotto from the UC Davis School of Public Health -- School of Public Health Science.

COMMITTEE MEMBER HERTZ-PICCIOTTO: School Medicine, Department of Public Health.

CHAIRPERSON LUDERER: Thank you, Irva.

Dr. Laurence Baskin from the UC San Francisco School of Medicine. And Dr. Tracey Woodruff from the UC

San Francisco School of Medicine.

So welcome, everyone.

Now, before we get into today's business and I turn the -- turn over to the Chair the meeting, we're going to have an oath of office for the new members, Dr. Carrie Breton and Dr. Irva Hertz-Picciotto. So if you could please stand up and do the oath of office.

DIRECTOR ZEISE: So Dr. Breton and Dr. Irva Hertz-Picciotto, please raise your right hands and repeat after me.

I, state your name --

COMMITTEE MEMBER BRETON: I, Carrie Breton --

COMMITTEE MEMBER HERTZ-PICCIOTTO: I, Irva Hertz-Picciotto --

DIRECTOR ZEISE: -- do solemnly swear --

COMMITTEE MEMBERS: -- do solemnly swear --

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

COMMITTEE MEMBERS: -- that I will support and defend --

DIRECTOR ZEISE: -- the Constitution of the United States --

COMMITTEE MEMBERS: -- the Constitution of the United States --

DIRECTOR ZEISE: -- and the Constitution of the

State of California --

COMMITTEE MEMBERS: -- and the Constitution of the State of California --

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

COMMITTEE MEMBERS: -- against all enemies, foreign and domestic --

DIRECTOR ZEISE: -- that I will be bear true faith and allegiance --

COMMITTEE MEMBERS: -- that I will bear true faith and allegiance --

DIRECTOR ZEISE: -- to the Constitution of the United States --

COMMITTEE MEMBERS: -- to the Constitution of the United States --

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

COMMITTEE MEMBERS: -- and the Constitution of the State of California --

DIRECTOR ZEISE: -- that I take this obligation freely --

COMMITTEE MEMBERS: -- that I take this obligation freely --

DIRECTOR ZEISE: -- without any mental reservation --

COMMITTEE MEMBERS: -- without any mental reservation --

DIRECTOR ZEISE: -- or purpose of evasion --

COMMITTEE MEMBERS: -- or purpose of evasion --

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

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

DIRECTOR ZEISE: -- upon which I am about to enter --

COMMITTEE MEMBERS: -- upon which I am about to enter.

DIRECTOR ZEISE: Congratulations.

(Applause.)

DIRECTOR ZEISE: Now, I would like to introduce the staff -- oh. Okay. Now, I'd like to introduce the staff of the Office of Environmental Health Hazard Assessment.

So at the end of the table, Allan Hirsch, the OEHHA Chief Deputy Director; Carol Monahan Cummings, our Chief Counsel; Dr. Vince Cogliano, who has joined OEHHA -- the Office. And he is our Deputy Director for Scientific Programs. Welcome, Vince.

Dr. Martha Sandy, who's Chief of the Reproductive and Cancer Hazard Assessment Section; Dr. Francisco Moran,

Farla -- Drs. Farla -- Dr. Francisco Moran, Farla Kaufman, Allegra Kim, Poorni Iyer, Marlissa Campbell, and Yassaman Niknam all within the Reproductive and Cancer Hazard Assessment section. They're all staff toxicologists, except for Dr. Allegra Kim, who's a Research Scientist III. And they'll be presenting to the Committee today.

And then our Proposition 65 implementation program staff, Esther Barajas-Ochoa, Tyler Saechao, and Julian Leichty. So welcome all staff. Julian is over in the corner there.

So now, Carol, would you like to make your introductory remarks now?

CHIEF COUNSEL MONAHAN CUMMINGS: Sure, that's fine.

Good morning. I just wanted to go over a few things. Since this Committee only meets once a year, you might not remember from the last time.

So, first, I wanted to point out that OEHHA takes no position at these meetings regarding whether a chemical or a substance should be listed. Our staff are available to answer questions or locate information, if needed, but they aren't going to recommend whether or not to list a chemical.

The Governor appoints you because of your scientific expertise to be the State's qualified experts

on reproductive toxicity of chemicals. So there's no need for you to feel compelled to go outside that charge. Your listing criteria was adopted by the Committee and it's in your binders. You should base your decision on the scientific principles that are outlined in that guidance and not the consideration of potential future impacts of a particular listing, like whether or not a warning might be required.

The standard for the Committee, of course, is whether or not a chemical has been clearly shown through scientifically valid testing, according to generally accepted principles to cause reproductive toxicity. That standard is a scientific judgment call and not a legal standard of proof.

This Committee can decide to list based on animal evidence only. The chemical need not have been shown to be a human reproductive toxicant or it need not be shown whether the anticipated human exposures to the chemical are high enough to cause reproductive toxicity. Those issues are dealt with in a separate part of the process.

If you need more information today, or need more time to think about the evidence, or to discuss it further before making a decision, there's no requirement that you make a decision today. You may also decide to list one or the other of the two substances that are in front of the

Committee today. You don't have to list both of them, if you don't choose to.

You may also defer a decision on some or all of these chemicals or substances to the group -- in the group to a subsequent meeting.

This process is flexible, so feel free to ask clarifying questions of me or the other staff during the meeting. If we don't know the answer to your question, we'll do our best to find and report it to you.

Any questions?

Okay. Thank you.

DIRECTOR ZEISE: Thank you, Carol.

And with that, I'll turn the meeting over to our Chair.

CHAIRPERSON LUDERER: All right. Thank you, Dr. Zeise. I'd also like to welcome all the Panel members, as well as the staff, and the members of the public who are here both in person or listening via webcast.

I'd like to just remind everyone about public comments. So as per our usual process, every speaker from the public has five minutes, except for those that have made requests in advance and received approval for longer comments. There are blue comment cards available on the back table to my right. Please fill one out if you would like to speak and give it to Esther or Tyler.

Would you like to raise your hand, so everyone knows who you are.

Thank you.

Okay. So we're going to then begin with our staff presentations. And Dr. Martha Sandy, the Chief of the Reproductive Hazard and Cancer Hazard Branch will be giving the first presentation.

Dr. Sandy.

(Thereupon an overhead presentation was presented as follows.)

DR. SANDY: Thank you very much. And if you can put the first slide of the presentation up. So thank you and welcome. I want to provide you with a bit of background on how these two chemicals under consideration today for possible listing have come before you.

So as has been said, the chemicals are cannabis smoke and delta-9-THC. In January 1st, 2018 the adult use of cannabis has become legal under California law. In light of the possible public health concerns related to cannabis use during pregnancy and concerns such use may increase as a result of legalization, the Director of OEHHA, in consultation with the Chair of the DARTIC determined that cannabis and cannabis-related chemicals should be reviewed for consideration for listing under Proposition 65 as causing reproductive toxicity, based on

the developmental toxicity endpoint.

So in March of 2019, OEHHA issued a public request for information on the developmental toxicity of cannabis and cannabis-related chemicals. Nine submissions were received and considered during the development of the hazard identification document, or HID that you have before you.

Because of the large volume of data available in the published scientific literature on the developmental toxicity of these substances, OEHHA limited its current review to the evidence on developmental toxicity for cannabis smoke and delta-9-THC.

Other relevant endpoints, such as male or female reproductive toxicity may be considered by this Committee at future meetings. Similarly, other cannabis-related substances may be considered at future meetings.

Several staff within the Reproductive, Toxicology and Epidemiology Section within my Branch will now present an overview of the very large volume of studies included in the HID that comprise the evidence on the developmental toxicity of cannabis smoke and delta-9-THC.

And starting off the presentation will be Dr. Francisco Moran.

DR. MORAN: Thank you. Good morning.

It's good?

In this HID, we compiled and summarized the studies on the developmental effect of cannabis smoke and delta-9-THC. Numerous epidemiology as well as experimental animal studies have investigated the potential to cause developmental harm. The aim is to present data to support an objective and full consideration of the evidence.

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DR. MORAN: Cannabis smoke is a complex mixture of several thousand chemicals. Chemicals identified in cannabis smoke include aromatic amines, polycyclic aromatic hydrocarbons, metals, carbon monoxide, nitric oxide, and over 60 cannabinoid compounds such as delta-9-THC. In pages 15 and 16 of our HID, there is a list of about 350 chemicals identified in cannabis smoke by several investigators. Delta-9-THC is the most potent psychoactive compound present in cannabis.

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DR. MORAN: Exposure could happen by a single or any combination of these methods:

Combusting the cannabis or cannabis mixture and inhaling the smoke;

Vaping and other vaporization methods, which consisting in heating cannabis or cannabis extracts to temperatures below the combustion point of approximately

230 Celsius degree, that result in formation of a vapor and inhaling the vapor;

Dabbing, which consists of heating highly concentrated cannabis or hashish to form a vapor;

And, finally, by ingesting cannabis or cannabis extracts.

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DR. MORAN: Absorption of the delta-9-THC and other constituent of cannabis smoke occurs at multiple sites within the aerodigestive tract, including mouth, nose, throat, portions of esophagus and trachea, and the lungs.

Delta-9-THC is lipophilic and with other cannabis smoke products are distributed widely in the body. The majority is distributed to highly vascularized tissues, such as the brain.

Delta-9-THC crosses the placenta and reaches the fetus and is also present in breast milk and meconium. The two main metabolites of delta-9-THC, 11-hydroxy-THC and the carboxylic form have been detected in umbilical cord.

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DR. MORAN: A variety of Phase 1 and Phase II enzymes are expected to be involved in the metabolism of cannabis. Excretion of delta-9-THC and its metabolites

occurs via the feces and urine, and to a lesser extent, through sweat, saliva, breast milk, and hair.

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DR. MORAN: This is an outline of our presentation today. We will start with an overview of endocannabinoid system followed by developmental toxicity -- presentation of the data on developmental toxicity for both somatic and neurodevelopmental outcomes for human and animals.

Finally, we will summarize epigenetic and other mechanistic data, and a final summary.

Now, Dr. Niknam will present the overview of the endocannabinoid system and its relation to developmental toxicity.

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DR. NIKNAM: Thank you. Good morning.

The endocannabinoid system, or EC system is comprised of cannabinoid receptors, or CBRs, and their endogenous ligands. It has many physiological roles, including maintenance of various stages of pregnancy, reproductive function, somatic development, such as bone growth and differentiation, regulation of the immune system, and neurodevelopment.

There are three different cannabinoid receptors, CB1, 2, and 3, where CB3 receptor is also known as G

protein coupled receptor 55, or GPR55. And these receptors all function as G protein coupled receptors.

CB1R is mainly expressed in the nervous system, but is also found in peripheral tissues.

CB2R is mainly expressed in the immune system, but is also found in other tissues, such as the central nervous system, peripheral nervous system, bone, and female reproductive tissues.

CB3R is expressed in many tissue types including bone and skeletal tissue; however, its role in regulating development is not well understood in literature.

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DR. NIKNAM: Cannabinoid receptors bind their endogenous ligands known as endocannabinoids, or eCBs. The two most prevalent eCBs are AEA and 2AG. They are both synthesized on demand when needed and broken down by the enzymes MAGL and FAAH.

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DR. NIKNAM: There are a multitude of signaling cascades activated through cannabinoid receptors that are important during development.

These pathways are important in: development of the embryo and facilitating successful embryo implantation; bone growth and differentiation; developmental of the immune system; and, development of

the nervous system.

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DR. NIKNAM: Here is an example of the physiological role played by the endocannabinoid system specifically in bone growth. Bone growth is a continuous process that begins prenatally and ends in maturity when the growth plates are fully ossified and involves both osteoblast and osteoclast activity.

Endocannabinoids produced by the -- by the osteoblast bind CB1 receptors in nerve terminals and downregulate noradrenaline leading to a reduction on the negative control that noradrenaline has on osteoblast activity.

It's important to note that both cannabinoid receptors and endocannabinoids are expressed in the epiphyseal growth cartilage, or EGC.

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DR. NIKNAM: Cannabinoid receptors also play a critical role in neurodevelopment and are expressed in different parts of the brain, such as the hippocampus, striatum, and cerebral cortex. The endocannabinoid system can also affect they hypothalamic-pituitary-adrenocortical axis, or HPA. It's important to note that CB1 receptor densities fluctuate throughout gestation and expression of cannabinoid receptors and their roles during development

differ significantly from that of a mature nervous system.

Activation of cannabinoid receptors during development affects neurite outgrowth, growth cone steering considerations, and ultimately synaptic plasticity.

Other endpoints of neurodevelopment controlled by cannabinoid receptors include behavior and locomotor activity.

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DR. NIKNAM: The top part of this figure depicts the action of endocannabinoids as retrograde messengers. CB1 receptors are mainly expressed on inhibitory and excitatory presynaptic neurons and control excitotoxicity during neurodevelopment by acting as gatekeepers. They do this by suppressing neurotransmitter release to prevent hyper-excitation of neurons by repressing excitatory postsynaptic currents, or EPSCs.

The lower half of this figure shows several signaling pathways in which cannabinoid receptors are involved during development. These signaling pathways control cellular transformation, neurite outgrowth, translational control, and actin remodeling.

Some of the receptors and/or ion channels involved in this process include: glutamatergic, specifically the NMDA receptor; G protein-gated inwardly

rectifying potassium channels or GIRKs; voltage dependent calcium -- and voltage dependent calcium channels.

Other receptors also important in the process of neurodevelopment that endocannabinoids system affects includes GABA, acetylcholine, and glycine receptors.

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DR. NIKNAM: Because a large portion of the mechanistic literature pointed to the NMDA receptor as a major target of cannabinoids, here, I've included an adapted adverse outcome pathway, or AOP, for cannabinoid receptor agonists. Starting from left to right, the molecular initiating event includes binding of agonists to cannabinoid receptors during synaptogenesis, which results in inhibition of the NMDA receptors, and several key events later leads to the adverse outcome of impairment of learning and memory.

Now Dr. Allegra Kim will present some of the developmental somatic outcomes reported in human studies.

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DR. KIM: Thank you. Good morning.

In selecting epidemiologic studies to include in the hazard identification document, OEHHA had three main criteria. The first was study design. We included analytic designs with individual exposure and outcome assessment including cohort and case-control studies, and

meta-analyses.

Second, studies that assessed cannabis exposure by biological assay were included.

Studies that assessed cannabis exposure by self-report and included some quantification were also included. If exposure was assessed by self-report only and compared only exposed versus unexposed, the study was generally excluded.

Studies that did not address prenatal tobacco and alcohol use as potential confounders of the association between prenatal cannabis use and developmental outcomes were generally excluded.

In addition, included studies reported original data analyses with sufficient detail to allow determination that the study met the above criteria.

Fifty-seven studies examined birth or somatic outcomes and 68 studies that examined neurodevelopmental outcomes were included.

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DR. KIM: In the epidemiologic studies, exposure from smoking cannabis was assessed. Assessing prenatal cannabis exposure presents some important challenges, which would generally tend to bias findings toward the null.

Exposure to cannabis was frequently assessed by

maternal self-report in interviews, which raises concern about underreporting and validity. Some investigators assayed biological samples, such as urine, for cannabis exposure, which may identify more cannabis users, but may also result in false negatives due in part to elimination of THC and metabolites. Most studies did not report results for different quantities of cannabis exposure.

The prevalence of cannabis exposure among pregnant women was also relatively low. Exposure levels among those who used cannabis were also often low, as many used cannabis infrequently. And both prevalence and intensity of exposure tended to decrease as the pregnancy progressed.

Finally, any given outcome may be linked to a specific sensitive window, which was often not considered or incorporated in analyses.

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DR. KIM: Another exposure consideration is the potency or concentration of delta-9-THC in cannabis, which has increased substantially over time. This chart shows that delta-9-THC concentrations in cannabis increased from about four percent in 1995 to about 12 percent in 2012 through 2014. The lower potency of cannabis when participants in many of the included studies were exposed may hinder the ability to see an association.

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DR. KIM: Three major prospective longitudinal cohorts examined developmental outcomes associated with prenatal exposure to cannabis. The first two, the Ottawa and Pittsburgh studies collected pregnancy data up to 1985 and followed some of the offspring into adulthood. The Ottawa study enrolled healthy women who volunteered to participate. Both of these studies collected self-reported exposure data multiple times during pregnancy.

The Generation R Study in the Netherlands was a larger study that started data collection in 2002.

All of the cohorts used self-report for cannabis exposure assessment. Generation R also had maternal urine for a subsample.

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DR. KIM: I will briefly review the findings for the underlined birth and somatic developmental outcomes of preterm birth, birth weight, birth length, and viability and mortality. Other birth and somatic outcomes shown here are included in the HID. And my colleagues will present neurodevelopmental outcome after the animal somatic outcomes.

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DR. KIM: This forest plot shows risk estimates

for preterm birth and prenatal cannabis use reported by 11 studies and a meta-analysis.

The studies are in chronological order with the earliest at the top. The vertical line represents an odds ratio of one or no change in risk. Blue dots are odds or risk ratios and the horizontal black lines are the 95 percent confidence intervals. At the bottom the plot below the blue line, there is one meta-analysis.

A meta-analysis by Gunn et al. is excluded, because it did not address confounding by tobacco.

With only three stud -- while only three studies reported statistically significant associations with pre-term birth adjusted for tobacco use, most odds ratios are greater than one, suggesting increased risk of preterm birth.

Four studies reported results stratified by tobacco use. Only the estimates for cannabis only with tobacco use -- without tobacco use -- excuse me -- are shown here on this.

And here, the risk estimates for cannabis and tobacco combined exposure are also shown. Adding tobacco exposure resulted in higher risk estimates in three of the four studies.

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DR. KIM: Twenty-seven studies examined the

association between birth weight and prenatal cannabis exposure. Of these, 12 reported statistically significant associations between prenatal cannabis use and lower birth weight adjusted for prenatal tobacco use.

This forest plot shows results from the six studies reporting linear regression coefficients that represent change in birth weight in grams associated with prenatal cannabis use. Asterisks indicate statistical significance.

Most of these studies reported either a decrease in birth weight or no change associated with prenatal cannabis use, as indicated by the majority of the blue dots being to the left of the vertical line or at the line.

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DR. KIM: These six studies reported mean differences in birth weight in grams associated with prenatal cannabis use. Again, most of these studies reported either a decrease in birth weight or no change associated with prenatal cannabis use.

Two studies reported mixed results, which included the significant associations with higher birth weight shown. The three studies that reported multiple exposure levels reported decrements in birth weight associated with their highest cannabis exposure, although

one was not statistically significant. There are also two meta-analyses below the blue line.

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DR. KIM: Woops. Okay. Sorry. Chabarria et al. reported that cannabis use alone was not associated with odds of birth weight below the 25th percentile. But tobacco use alone and cannabis and tobacco co-use increased the odds of lower birth weight.

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DR. KIM: Saurel-Cubizolles et al. reported generally lower birth weight associated with more frequent cannabis use and the addition of tobacco use, and Howard and colleagues reported lower birth weight associated with a positive test for cannabis exposure at delivery.

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DR. KIM: The infant's birth at -- length at birth was examined in 14 studies. Five studies reported statistically significant associations between prenatal cannabis exposure and decreased birth length. Three of these five included bioassays for cannabis exposure.

One study reported mixed findings: cannabis use once a week before or during but not throughout pregnancy was associated with an increase in length, but a similar decrease in length was associated with more frequent cannabis use before and throughout pregnancy. Although

that did not reach statistical significance. Eight studies did not report statistically significant associations with birth length.

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DR. KIM: Eleven studies examined offspring viability and mortality. Five of these reported no significant associations. No studies reported associations with spontaneous abortion alone.

But spontaneous abortion and stillbirth combined were examined in one study. The odds ratio for prenatal cannabis use -- prenatal only, excuse me, compared to no use, was 12.1. Stillbirth by itself was examined in four studies, though three were unable to adjust for tobacco.

Petrangelo et al. with 12 and a half million births reported a statistically significant adjusted odds ratio of 1.5 and that was adjusted. Two studies reported only unadjusted odds ratios of 2.34 and 1.74. One study reported excess stillbirths among weekly and daily users, but there were still too few to analyze and report.

Two studies examined sudden infant death syndrome, or SIDS. One reported no association between maternal cannabis use and SIDS.

A well-conducted case-control study focused solely on SIDS reported no associations with maternal cannabis exposure, but paternal cannabis use before the

conception period and possibly the pregnancy was associated with the odds of SIDS.

Now, Dr. Campbell will present somatic developmental studies in animals.

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DR. CAMPBELL: Thank you.

We will be presenting summaries of four main subtopics of available data on the animal developmental toxicity of cannabis smoke and delta-9-THC.

The information on early embryo development and implantation was prepared for the HID by Dr. Lily Wu. I will be presenting that information, along with sections on the whole animal studies, and evidence on immune development and bone growth. And a bit later, Dr. Poorni Iyer will present the animal evidence on neurodevelopmental toxicity.

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DR. CAMPBELL: The EC system may regulate early developmental events such as oviduct transport, embryo development, and implantation. Cleavage stage embryos have been found to express mRNA for both CB1R and CB2R. A 1995 in vitro study by Paria et al. reported that delta-9-THC delayed mouse embryo development in a dose-dependent manner. Between 60 and 89 percent of two-cell mouse embryos failed to reach the blastocyst

stage after exposure.

A series of in vivo studies from the same group investigated effects of THC on implantation of mouse embryos. Delta-9-THC exposure alone under the conditions used had no affect on implantation frequency. But when THC metabolism was blocked by co-treatment with a cytochrome P450 inhibitor, implantation frequency approached zero.

When THC was given with metabolism inhibitors and a CB1 receptor blocker, then implantation frequency recovered. Implantation frequency was also normal when THC and metabolism inhibitors were given to mice having a knockout mutation for both CB1 and CB2 receptors.

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DR. CAMPBELL: We identified and retrieved 38 whole-animal toxicity studies investigating multiple potential effects of prenatal exposure to cannabis smoke or delta-9-THC by the oral or injection routes. These apical-type studies were published between 1971 and 2017. The majority were conducted during the 1970s with only two published after the year 2000.

And following this slide, the next few slides will show the most frequently observed effects by route of exposure.

This slide also includes a brief overview of some

of the most common methodological and reporting deficits affecting confidence in the available data set. Inadequate sample size and failure to analyze data on a per litter basis, or to otherwise account for litter influence, were the most common of these.

Because the maternal animal is the exposed individual and litter membership is a strong determinant for offspring outcomes, such as viability, fetal or birth weight, and frequencies of morphological anomalies. The failure to account for litter effects can allow a small proportion of outlier litters to give a skewed impression of a dose group especially when combined with small sample size.

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DR. CAMPBELL: This slide shows results from inhalation exposure to cannabis smoke in animals. Taken together, the results of these studies appear consistent with an effect of prenatal exposure of -- to cannabis smoke on both pre- and postnatal growth. Delays in acquisition of postnatal developmental landmarks also suggest an association between exposure and generalized developmental retardation.

However, all the studies shown here as reporting significant adverse effects performed their analyses on a per dose group not a per litter basis. Where analyses

were performed on a per litter basis, statistical significance was not achieved.

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DR. CAMPBELL: This slide shows results of oral exposure to delta-9-THC. And again, the reported results appear consistent with adverse effects on offspring viability, weight deficits, and in some studies effects on the male reproductive system of exposed offspring. Again, overall confidence in the data set is undermined by generally poor reporting of methods, including failure to note the number of animals per group or to account for changes in group size between the original treatment and the final analysis.

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DR. CAMPBELL: One of the better studies performed by the oral route was this one Fleischman et al., 1980. They reported on three experiments conducted in rats and a fourth experiment in mice.

The rat studies tested doses ranging from 12.5 to 50 milligrams per kilogram per day of delta-9-THC in sesame oil, with sacrifice for evaluation every three days between gestation days eight and 19. Mice were treated similarly but using much higher doses.

For both species, viability decreased with increasing dose. And those were affects that were

statistically significant on a per litter basis. Although it should be noted that the data for animals sacrificed on different gestational days were lumped together by dose group, such that animals in a group were exposed to the same daily dose, but not necessarily the same total gestational dose, and then the same potential windows of sensitivity wouldn't have been covered.

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DR. CAMPBELL: This slide shows injection exposure to delta-9-THC. Studies that were performed in rodent -- rodents or rabbits reported results including adverse effects on offspring viability and weight. Although, again, overall confidence in the data set is constrained by limitations in experimental design and reporting. Most used test groups of marginal size and failed to perform statistical analysis on a per litter basis.

An additional study was conducted in five sexually mature female rhesus monkeys. That was the Asch and Smith, 1986. They gave delta-9-THC by intramuscular injection starting on the day pregnancy was confirmed and continuing on throughout gestation.

Four out of five pregnancies were lost in the treated animals: three by early spontaneous abortion, and a fourth was stillborn. Vehicle controls produced five

live born infants out of five pregnancies.

Other test groups in the study involved treatment at later stages of gestation. And those experiments resulted in predominantly live births, suggesting that early gestation may be the most sensitive period for these animals

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DR. CAMPBELL: In an elegant series of experiments Lombard et al., 2011 used pregnant C57 black 6 mice to of the studies the effects of gestational exposure to delta-9-THC on development of offspring thymic cellularity and function. Gestation day 16 corresponds to the initial stages of T cell development in fetal mice, and so was selected as a sensitive window for disrupting the developing immune system.

Specific experiments documented:

First, that fetal -- mouse fetal thymocytes express high levels of CB1 and CB2 receptors. The figures shown on this slide shows total thymic cellularity in gestation day 17 mouse fetuses following THC treatment on the previous day. Other experiments demonstrated caspase-dependent apoptosis causing thymic atrophy and altered T cell subpopulations following THC exposure. In vivo receptor blocking experiments showed that pre-treatment with antagonists attenuate a delta-9-THC

induced immunological changes. Significant functional immune dysregulation was demonstrated postnatally in five week-old pups following gestational THC exposure with a treated animal showing decreased proliferative and antibody responses to human immunodeficiency virus gp120 antigens.

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DR. CAMPBELL: As mentioned earlier in the presentation on the EC system, the EC system has an important role in the processes of bone growth and remodeling at all stages of life, but particularly during periods of rapid bone growth. These processes begin prenatally and continue postnatally until growth is complete. Delta-9-THC exposure has been reported to affect bone growth and remodeling, both in vitro and in vivo.

The figure on this slide shows microcomputed tomography of femurs from female mouse pups at 11 weeks postnatal age. Now, in this case, delta-9-THC treatment was given daily between the ages of 5 and 11 postnatal weeks, which is the very rapid period of bone growth in these animals.

THC exposure was associated with decreased femoral length wild type or CB2 minus, minus female pups, while CB1 minus, minus or double mutant mice knockout for

both receptors were unaffected.

Thus, the TH -- delta-9-THC appears to interact with CB1 receptor specifically in affecting linear bone growth. As obviously, the study was conducted postnatally, it provides only indirect evidence for a potential prenatal effect of THC on bone growth. It should be remembered that mice do not develop secondary ossification centers, which are the precursors of the epiphyses until after birth, while in humans this may occur prenatally.

Additional results for the same animals showed that, just as for reduced bone growth, delta-9-THC was associated with reduced overall body weight gain, but not for fat weight, which was measured separately, and only in female mice having functional CB1 receptors.

And that concludes my presentation. And I will hand over to Dr. Farla Kaufman to talk about neurodevelopmental outcomes in humans.

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DR. KAUFMAN: Now we turn our attention to those neurodevelopmental studies in humans.

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DR. KAUFMAN: This slide provides an overview for some of the neurodevelopmental outcomes studied in association with prenatal cannabis exposure, including

central nervous system maturation, visual perception and functioning, attention, and intelligence and achievement.

Below each of these categories one can see the preponderance of studies emanating from the two large longitudinal cohorts, the Ottawa cohort and the Pittsburgh cohort. These studies from -- the studies from these cohorts were well-conducted and of good quality.

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DR. KAUFMAN: In this table, the neurodevelopmental categories studies are shown on the right with the ages at which the children were tested across the top. For CNS maturation, most of these associations were assessed during infancy.

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DR. KAUFMAN: Presented here are the studies that examined CNS maturation. All the studies were found to be significantly -- found significant associations.

In the Ottawa cohort, the findings included decreased habituation and response to light, and increases in startles and tremors in neonates, although these outcomes normalize by 30 days of age.

In a study of children with an average age of four, increased variability binocular indices were observed. In the Pittsburgh cohort, one study observed increased P1 wave latency in one month old infants and

eight[SIC} month old toddlers. P1 wave latency is a measure of visual evoked potential, and is used as an estimate to brain maturation in clinical practice. Increased disturbances in sleep were observed in one to two day old infants and three year old children

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DR. KAUFMAN: The of the studies examining attention were conducted in children one to 22 years of age, with outcomes highlighted here.

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DR. KAUFMAN: Twelve studies observed significant associations, two reported no significant findings. Specific outcomes included increases in attention problems in girls -- excuse me -- 18 months of age, decreased sustained attention and increased impulsivity in children six years of age up to those 22 years of age. A dose response relationship was reported in one of the studies in six year olds.

Only one study reported an increase in sustained attention, although the authors postulated that this may reflect the children needing more time to complete the task. However, this could not be tested as data on reaction time was not recorded. One other study observed increased behavioral regulation. This study relied on teacher's evaluations

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DR. KAUFMAN: Intelligence and achievement was studied in children 1 to 18 years of age with outcomes highlighted here.

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DR. KAUFMAN: All but one study observed significant associations. In children one to four years of age, studies -- shown on the left-hand column, the outcomes included decreased language comprehension, decreased memory and vocabulary test scores -- sorry. Sorry. It didn't click. Yeah. Thank you -- in children one to four years of age, shown in the left-hand column here.

The outcomes included decreased language comprehension, decreased memory and vocabulary test scores in the Ottawa cohort, as well as decreased verbal reasoning and short-term memory in African-American children in the Pittsburgh cohort. In the Ottawa cohort, decreased -- decreased language comprehension was also observed in six to nine years olds, along with decreases in phonologic scores, and abstract reasoning, and mental flexibility in nine to 12 year olds.

Pittsburgh cohort studies in six to ten year old children observed decreases in composite intelligence, verbal and quantitative reasoning, academic achievement,

and learning and memory.

In children 13 years and older, shown in the right-hand column, associations were observed in -- with lower abstract design and Peabody spelling scores in the Ottawa cohort and lower school achievement in the Pittsburgh cohort.

One study in high school students observed increased metacognition. This was the study that used teachers' evaluations.

The studies highlighted in green were studies that controlled for postnatal cannabis exposure in the home.

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DR. KAUFMAN: The outcomes for visual functioning and processing are highlighted here.

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DR. KAUFMAN: Five of the studies examining the outcomes observed significant associations. One study conducted in four and a half year olds observed an improvement in global motion perception thresholds. Two studies in nine to 12-year olds observed decrease function and processing on a number of measures shown here.

Two studies, one from Ottawa and one from the Pittsburgh cohort examined function in children 18 to 22 years old and 16 years old, respectively. Both studies

observed decreased interhemispheric coordination, while one study also found de -- increased visual motor coordination and the other observed decreased processing speed.

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DR. KAUFMAN: The next few slides show some other outcomes which were studied. These were presented in tables D.13 and D.14 in the hazard identification document. They include substance use as shown on this slide. One study examined e-cigarette use in adolescents and observe significant -- one significant association. Three of four studies examining early initiation frequency of cannabis use observed significant associations. Three, other studies of early initiation only also observed significant associations.

One study examining cannabis and tobacco use reported a significant association, as well as one for drug use disorders. So six of the seven studies shown on this slide observed significant associations either by direct or indirect pathway using path analysis. No significant association was observed in one study.

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DR. KAUFMAN: Mood disorders, specifically depression, anxiety, or psychotic symptoms and experiences were examined in six studies. Four studies observed

significant associations, one reported a marginally significant association and one found no significant association.

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DR. KAUFMAN: Nine studies examined various aspects of behavior, five of which observed significant associations with child behavior problems. One study observed an association with increased aggression in girls. One reported early sexual behavior. Another study reported an association with negative adult roles. And two studies observed associations with emotional problems, no significant association was observed in a study of behavioral resilience.

Eight of the nine studies reported significant associations through direct or indirect pathways. One study reported no significant association.

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DR. KAUFMAN: Six studies used neuroimaging to examine either structural differences or functional outcomes, three of which looked at brain morphology and structural changes using magnetic resonance imaging. A study in children six to eight years of age from the more recent Gen R cohort in the Netherlands reported significantly thicker cortices, specifically in the superior frontal area of the left hemisphere, as well as

significantly thicker frontal pole in the right hemisphere.

There was no significant differences -- there were no significant differences between the cannabis exposed and unexposed groups for volumetric measures of total brain, gray matter, or white matter. A study from the Pittsburgh cohort conducted in 18 to 22 year olds examined the structure of the caudate nucleus. The focus of the study was prenatal alcohol exposure. Prenatal cannabis exposure was considered as covariate and no significant association was observed.

The focus of the study in 10 to 14 year olds was prenatal cocaine exposure. Cannabis exposure was considered as a covariate. The study included only three children with cannabis-only exposure and no significant association was observed.

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DR. KAUFMAN: Three studies used functional MRI to examine executive functioning. These studies were conducted in the young adults of the Ottawa cohort. A study in -- by Smith et al., 2016, this -- the data of two -- included the data of two of the earlier studies by Smith et al., 2004 and 2006. They were combined and reanalyzed with a more rigorous up-to-date method.

Sixteen young adults aged 18 to 22 prenatally

exposed to cannabis and 15 unexposed were tested on four executive functioning tasks, while in an FMRI scanner.

Performance on the tasks were not significantly different between the two groups, except where the exposed adolescents made more errors on commission -- errors of commission.

The findings did show that all four executive functioning tasks - in those, the prenatally exposed group had significantly more brain activity compared to the non-exposed group, specifically in the left posterior region of the brain. The author stated that this suggests a need for a compensatory response whereby either additional brain regions were required to perform the tasks or more activity in typically activated regions is necessary.

Prenatal cannabis exposure was associated with neurophysiological processing in several distributed neural networks that underline multiple types of executive functioning.

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DR. KAUFMAN: Dr. Iyer will now present the studies of neurodevelopmental outcomes in animals.

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DR. IYER: Good morning. So a number of studies were conducted in animals to investigate the

neurodevelopmental effects of exposure to either cannabis smoke, cannabis extracts, or delta-9-THC. These included a large number of studies in rats, with three studies in mice, and one study this rhesus monkeys, and there were four studies in the zebrafish model.

Exposure to cannabis smoke via inhalation was tested in three studies, exposure to delta-9-THC was tested by oral and parenteral routes in multiple studies, and exposures to hashish and cannabis extracts were tested in single studies by the oral and parenteral routes respectively.

As shown here, the studies differed in design according to when exposures occurred. For example, in some the exposure occurred prior to conception, in another, exposures occurred in utero, and in others exposure occurred perinatally or postnatally.

Studies with postnatal exposures may be directly relevant to human prenatal exposures because the developmental stage of the neurological structure affected by postnatal exposure in the rodent may correspond to the gestational period in humans.

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DR. IYER: This next slide provides an overview for some of the neurodevelopmental effects studied in animals after preconceptional, or prenatal, or perinatal

cannabis exposure. These include behavioral effects and effects examined at the molecular level.

The reported effects on behavior include changes in locomotor and exploratory activity; cognitive function, such as learning and memory; emotionality, including social interaction and anxiety; and effects expressed at later life stages, such as susceptibility to addiction. Other behavioral effects such as auditory startle have been described in the published literature and are cited in the HID.

In addition, some studies reported effects at the molecular level. Several studies examined multiple endpoints and effects. And the number of studies examining these endpoints are shown on this slide.

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DR. IYER: Of the studies that examined locomotor and exploratory behavior, seven studies after pre-conception, or prenatal, or perinatal exposure to cannabis smoke or delta-9-THC reported altered spontaneous locomotor and exploratory behaviors, and four studies reported no effects.

In some of the studies that reported effects increased locomotor activity was observed in young animals but not adults. Also, some studies reported sex-specific effects.

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DR. IYER: Ten studies examined a variety of cognitive endpoints utilizing a number of different tests with individual studies focusing only on some of these endpoints. The animals were exposed to delta-9-THC or cannabis extract preconceptionally, or prenatally, or postnatally. Cognition includes memory and learning as well as acquisition.

In this first slide, findings in five studies related to impaired memory and learning are shown. There were three studies that reported no significant effects on spatial learning and memory.

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DR. IYER: In this second slide on cognition, effects of other aspects, such time taken to complete tasks or deficits in attention are shown. These effects were reported in four studies.

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DR. IYER: Four studies examined several aspects of emotionality after prenatal or perinatal exposure to debt-9-THC using different testing paradigms. The findings could vary within the same study for different measures of emotionality. The tests included various measures of social interaction and anxiety. Findings related to social interaction were reported in three

studies and one study observed no effects on emotional reactivity. An increase in separation-induce ultrasonic vocalization in young pups was reported. And changes were reported in open fetal behavior in offspring evaluated as adults.

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DR. IYER: Eleven studies examined the potential for increased frequency of drug-seeking behavior after preconceptional, prenatal, or perinatal, or just postnatal exposure delta-9-THC. Also, one study observed lower sensitivity to natural rewards.

Two studies reported new effects on either food consumption -- food or morphine self-administration, or ethanol self-administration following perinatal exposures to delta-9-THC.

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DR. IYER: Four studies in the zebrafish model assessed neurodevelopmental effects, as well as some morphological endpoints after exposure to detla-9-THC. The authors interpreted the neurodevelopmental effects shown here on the top part of the slide to be an indication of anxiogenic behavior.

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DR. IYER: This slide has examples of effects reported at the molecular level with TH -- delta-9-THC

exposure. Many of the studies that reported effects at the molecular level also tested for behavior and typically publications include this aspect in an attempt to understand the mechanisms involved in contributing to the behavior observed.

Exposure was do delta-9-THC or cannabis extract, and was preconceptional, or prenatal, or perinatal. These molecular findings focused on both concentration or temporal aspects of expression. Alterations in gene expression was evaluated by measuring protein levels and/or mRNA levels. Alterations of gene expression of delta-9-THC responsive genes affected gene ontology categories that impacted various parameters of neurodevelopment.

Altered mRNA and protein levels related to neurotransmitters were reported, such as a decrease in cortical extracellular levels of glutamate and noradrenaline. And in one case, in one experiment an increase in tyrosine hydroxylase mRNA.

A number of these alterations were reported in brain regions known to be involved in drug-reinforcing behavior, such as the nucleus accumbens.

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DR. IYER: The changes related to cannabinoid receptors were age-dependent given that there are patterns

during development of the expression of cannabinoid receptors and different neuronal lineages may be affected, and frequent co-localization of the opioid and cannabinoid receptors with overlapping expression between the opioid and cannabinoid systems were observed.

Now, that concludes the presentation of the neurodevelopmental data animals. And now my colleague Francisco Moran will present the findings from the epigenetic data.

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DR. MORAN: Okay. Epigenetics effects data were prepared in collaboration with Andres Cardenas and Anna Smith of the University of California Berkeley. This is a very busy slide presenting a summary of the information presented in the HID on epigenetic and related findings after exposure to cannabis smoke and delta-9-THC in humans and animals.

I'm going to highlight a few findings here.

Effects were reported in sperm in human and rats, on effects in rat brain as a result of exposure of the fathers prior to conception.

Changes in DNA methylation were reported. For example, lower methylation levels were reported in human sperm DNA; and differentially methylated regions were reported in rat sperm DNA.

Highlighting another set of findings all related to alterations in dopamine receptor associated methylation, gene expression, and protein expression. Increased DNA methylation in the promoter region of the dopamine receptor D2 and D4 genes were observed in exposed adult humans, and also decreased dopamine receptor gene expression in some brain regions in man. In animals it was also reported decreased expression of dopamine receptor 2 among other genes and altered profile of a specific histone methylation marks at the dopamine receptor 2 locus.

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DR. MORAN: We'll conclude this presentation with a brief summary of what was presented today before you.

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DR. MORAN: This is a summary of the developmental somatic outcomes.

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DR. MORAN: And this is a summary of what was presented for you on neurodevelopmental outcomes.

That's all we have today. Thank you.

CHAIRPERSON LUDERER: Thank you very much for those wonder -- excellent overviews and for all the work that went into this -- putting together this very comprehensive document.

Do we have any -- I guess we have some time maybe for some clarifying questions, if any, from Panel members?

No. All right.

Then we will move on to Committee discussion. There are two discussants for each of these areas. Although, the agenda lists one order, I think it makes sense to go in the order that the presentations by staff were done. So we'll -- do you have a questions or

COMMITTEE MEMBER WOODRUFF: Yes. I had a question about some of the materials that were in the presentation, like the graphs. Are all of these -- not all of these are included in the -- right.

I guess it would be helpful to get them ahead of time, because it's hard to -- well, actually, I think that we should have more graphics and graphical elements in the HID documents. And so I -- I'm going to save my general comments for later. But I just think that there's better approaches to being able to extract some of the data from the -- to extract the data from the presentation -- from the papers and to include them in a way that it's easier to visually read them.

And I wanted to just comment that I thought the presentation on the neurodevelopmental outcomes was very helpful, but I thought it was -- would have been very helpful to have it written in a more clear and categorized

approach for the animal studies. So I felt like the writing -- the way that the epidemiological studies were covered in the document were -- was pretty good, but should have used the same approach where we had better tables about outcomes and similarities across outcomes and -- and reporting for the animal studies, because they're just -- actually, let me just say this, the non-human studies, because they're basically similar animal studies, but just in -- not in humans. And I think the inconsistency across the document between those sections made it difficult to really read some of it.

So that was it.

CHAIRPERSON LUDERER: Thank you.

Any other comments or questions from the Panel?

Okay. All right. Then we will move on, as I said, to our Committee discussion. So we'll start out with the human studies of developmental effects. And the first discussant for those is Dr. Suzan Carmichael.

COMMITTEE MEMBER CARMICHAEL: Okay. Good morning, everyone. And thanks again to everyone who has -- who put all the hard work into the preparation of these materials for us. That's always hugely helpful especially with a literature this large.

So just basically a brief outline of what I'm going to talk about. Very briefly mention a little bit of

background about use and then highlight some of the challenges, which will echo some of those that were mentioned by the OEHHA staff; challenges to studying this issue of cannabis exposure and birth outcomes, and interpreting the literature. I want to briefly mention what current recommendations are from professional organizations about use during pregnancy. And then I'll go -- give a summary of findings -- summary of findings of the epidemiologic literature on maternal and infant birth outcomes. And then I'll put that in the context of the tenets of causal inference.

So basically just as has been said, we've got a backdrop of increasing prevalence of use and increasing potency of the products over time, and legalization, which is -- in other places has been shown to be leading to further increases in use.

Currently, estimates vary on prevalence of use, but it may be around six to eight or higher during pregnancy and at least 10 to 15 percent in the year before pregnancy. Although, some estimates are, you know, up to at least twice that.

It goes down markedly by the end of pregnancy. So especially before a woman knows she's pregnant, the use may be more comparable to the pre-pregnancy use, but still during pregnancy.

These -- this usage likely varies regionally. It's higher in the youngest and the lowest socioeconomic status women. And so those are just -- that's just some of the context we're working in.

Some of the challenge -- the main challenges to studying cannabis use and repro -- and birth outcomes, and interpreting the literature. I want to really emphasize how limited the exposure assessment has been in many studies. Most of the studies have minimal detail. It's typically -- it's typically just any or no use during pregnancy. And so frequency isn't typically known. The type of product is -- there's very little examining any detail on that, which does make it a challenge to compare -- to think about what different types of products and as product -- use of different products is changing.

Some studies did try to sort of compensate for that, saying use of hashish, for example, is equivalent to a certain multiplier for -- versus smoking other products. And there's really not information about e-cigarette -- e-cigarette use versus other use.

And then timing, there's very -- since it's usually any versus none, there's very limited information about that. But as we know, effects on development can vary depending on timing of exposure. And there have been varied approaches. Typically, self-report. Some studies

just did things like medical record review, ICD-9 codes from discharge records, some have tox screen results or other biomarker results. And biases could occur with any of these approaches. It's hard to know in which direction those biases may occur.

It depends on how standardized data collection was and the circumstances. For example, it could vary from an interview during prenatal care that is standardized and confidential to interview data collected right at labor and delivery.

And then the increasing potency of products over time presents challenges to comparing results of older versus newer studies. And then another -- so exposure assessment is difficult and then correlation with tobacco use is a challenge. It's hard to isolate. Most -- many -- a large percentage of women who report cannabis exposure also smoke cigarettes, and so that makes it difficult to separate out the effects of one versus the other.

However, it's also notable that cannabis smoke contains many of the same toxins as tobacco smoke and often at several fold higher levels. And the same with carbon monoxide exposure.

And I just wanted to briefly mention what current recommendations are, before I move on to summarizing the

actual literature. The National Academy of Science, Engineering, and Medicine in January of 2017 concluded there's substantial evidence of a statistical association between maternal cannabis smoking and low birth weight, and limited evidence of an association with pregnancy complications for the mother.

And the American College of Obstetrics and Gynecologists issued a recommendation in October of '17. Just a quote, "Women who are pregnant or contemplating pregnancy should be encouraged to discontinue marijuana use". And the American Academy of Pediatrics a year later, September of '18 quote, "Marijuana should not be used during pregnancy". And then a Surgeon General report in August of this year refers to both of those AAP and ACOG statements and the effects of the endocrine -- on the endocannabinoid system and birth weight and quote, "No amount of marijuana use during pregnancy or adolescence is known to be safe. Until and unless more is known about the long-term impact, the safest choice for pregnant women and adolescents is not too use marijuana".

So now I'll move on to summarizing the findings from the epidemiologic literature. I'm going to start with maternal health. And again, these are rather large literatures, so I'm kind of cutting to the chase and referring to the systematic reviews that have been done,

as well as the more recent studies.

So Gunn in 2015 included maternal pregnancy-related morbidities in its review. And it only included studies that excluded women with other illicit substance use. So narrowed it down in that way.

And the main -- the main -- the outcome with the most studies was anemia. And they reported findings on six studies related to maternal anemia. Five were null, but the -- but one -- one -- the one study that was actually large was -- had a positive finding. So the meta-analysis results showed an in -- a significantly increased risk of 40 percent. However, that was not adjusted by any potential confounders like cigarette smoke.

And then there were a few studies of hypertensive disorders during pregnancy. They tend to be small and older and they were not significant. And that was based on three studies they reviewed. Other studies of maternal -- other miscellaneous maternal health outcomes tended to have from like one to three studies each at most, and basically inconclusive.

And there's a review by Conner in the same -- in 2016 or '15. And they refer to placental abruption. And found -- and there were five studies and found that the unadjusted odds ratio was 1.8, so 80 percent increased

risk. But that was not adjusted and they did not -- I don't believe they presented and adjusted risk estimate.

And then as for more recent studies, there's a study by Chabarria in 2016 using study -- using samples from the Baylor PeriBank it's called. And they surveyed women at labor and delivery about their use of cannabis during pregnancy. And one of the interesting things in that of the studies is that they split their analyses based on women who were only exposed to cannabis, which was 58 women and versus women who were exposed to -- reported both cannabis and tobacco use, which was 48 women. And then they also showed results for 194 women who only smoked tobacco.

And the odds ratio -- the adjusted odds ratio for maternal hypertensive disorders was 2.6 for women who used both, but it was closer to 1.3 for women who only used cannabis or only used tobacco. And this is where it's just -- it's just difficult to interpret even with an analysis that's trying to differentiate and stratify, based on -- to get around this potential confounding or interaction with tobacco. It's difficult to separate out the effects due to sample size. And also, they did not take into consideration whether co-use was associate -- was actually a marker for increased intensity of exposure. So women who used both may be -- may be higher users of

one or the other. But again, it just shows the limitation of -- of these -- of getting at intensity of exposure and independence from tobacco.

And then there's a study Petrangelo in 2018 used, I believe, data from the National Inpatient Sample, and looked at a number of maternal morbidities. And they were all non-significant, but they used ICD-9 codes to assess cannabis exposure. And that's basically codes used at a hospital discharge. And it's very underreported. It wasn't collected in a stand -- or reported in a standardized way.

So basically, in summary, there's really limited -- very limited evidence about -- not enough evidence to make firm conclusions about maternal health and cannabis use during pregnancy.

And then there -- I will summarize studies on structural congenital malformations. There have been a handful of studies in the last couple of decades. They tend to be limited in their ability to examine specific phenotypes or specific types of congenital anomalies. And this is especially important because they are -- they are heterogeneous in their etiology and different structures develop by different mechanisms.

And just to note, even one of the stronger studies had challenges with sample size, given that

specific congenital anomalies tend to be relatively rare. So there was study using -- by van Gelder using data from the National Birth Defects Prevention Study, a population-based, multi-state, case-control study, which has very good stan -- it's retrospective, but it has standardized interviews to assess exposures and very good ascertainment of the birth -- of the congenital anomalies themselves.

That out of 20 birth defects, it only saw an association with anencephaly, which was of 1. -- and odds ratio of 1.7, but the confidence interval included one and only included 12 exposed cases.

So even with one of these more rigorous - although it does have limitations as well - one of these studies, it was still difficult to actually assess associations with congenital anomalies. So again, unfortunately, I think there's not enough evidence to rule in or out whether there's an impact on this important set of outcomes.

And then I'll discuss studies related to pregnancy loss and perinatal and postnatal mortality as a group. And here, I would include spontaneous abortion and stillbirth, infant mortality, and SIDS. And again, there were not that many studies. I believe 11 were covered in the OEHHA summary, the report that we received before

today. Very limited evidence. Many small sample sizes. But I will summarize a few studies here.

So Petrangelo, the 2018 study that used the Nation -- the National Inpatient Sample did find an odds ratio of 1.5, which was significant for quote "fetal demise". And that was adjusted for smoking.

However, this was, as I said, I believe, smoking and cannabis exposure were based on ICD codes and not assessed in a more standardized way than that.

And then Varner in 2014 using data did -- from the Stillbirth Collaborative Research Network, which was a very rigorously conducted study focused on stillbirth. They found an odds ratio for cannabis exposure based on tox screens was 2.8, and that was significant. And those were in singleton babies with no congenital anomalies.

The authors -- that's the unadjusted result. The author said that the results -- the odds ratio decreased more than ten percent after adjustment for cotinine levels, but that result -- that actual result is not shown.

And in 2019, Howard and others conducted a study -- conducted a study and it included some results for perinatal mortality. And they based exposure on a woman being positive for a screening that was done using urine samples at both during a prenatal care appointment

and at birth.

So women who were positive at both -- for both had -- there was an adjusted odds ratio of 4.2, and that was significant. And -- but again, those numbers were relatively small. There were 18 deaths in the THC negative women and nine in the THC positive women.

And it says it's adjusted, but it doesn't state what it's adjusted for. And I'm not sure what the time frame is for perinatal mortality. Then again, it was concerning given the high odds ratio.

And then there's one study I wanted to point out on SIDS, and -- by Scragg in 2001. And that was a nationwide study in New Zealand, case control study, included 393 cases. And one of the advantages in that study was that they did look at frequency of use. And they found that the odds ratio for at least weekly use was 1.8 for SIDS. And so that was adjusted for race, ethnicity, and tobacco. And that is a partially-adjusted model. It was not significant in their fully-adjusted model. But that model also included birth weight and gestation, which could be considered sort of intervening or on the causal path. So for the purpose of thinking about the association -- the overall association with SIDS itself, then I believe the odds -- the odds ratio of 1.8 is more representative of that in particular.

So, in summary, there are some concerning results, I think, in this relatively small literature. But it is -- these are basically very few studies per outcome. So it's difficult to make any firm conclusions.

And then we'll go to birth weight. There's definitely the most studies there, probably at least 30 studies. And reviews results have been mixed. Many studies tend to show a reduction in birth weight. An important question is to figure out whether that's independent of tobacco or interactive with tobacco possibly.

The two reviews published in -- it's 2016, the review by Gunn included 24 studies and concluded that there is an -- there's substantial evidence for an association with lower birth weight. And the other review in 2016 by Connor included 31 studies and concluded that there was not an association after taking into -- after taking -- after looking at results that were adjusted for cigarette smoking.

So they were -- so that's what the conclusions were. However, given the co-occurrence of the two, it's still -- it's still difficult I think to tease apart or know if the -- or to know if the actual -- actually, typically frequency is not taken into account, adjusting for cigarette smoking could actually be sort of a proxy

for adjusting for intensity of exposure, and therefore an overadjustment.

And just to point out, even with all of these studies, it's still difficult. In Connor, they tried to especially focus on -- or pull out the studies that actually looked at frequency of exposure. And out of all the studies that they reviewed, there were only two of low birth weight that actually they cited as analyzing results, including frequency rather than just any versus none. And only five of the preterm birth studies were able to do that. And that resulted in basically in this meta-analysis, only 49 women who had the outcome and weekly exposure, and actually zero reported with daily exposure. So it just shows you how limited the literature is on that point.

And they also pointed out -- highlighted studies that stratified by tobacco exposure. So again, like the earlier study I was mentioning trying to -- another way to isolate the effects of cannabis by looking at cannabis over -- cannabis only, or cannabis plus tobacco, or tobacco only exposure. There were no low birth weight studies that did that and only two preterm birth studies, which resulted in only eight exposed cases.

I wanted to highlight a few more recent studies. There's a study by Crume in 2018 using data from the

Colorado PRAMS, or Pregnancy Risk Assessment Monitoring System, study. It's a survey that's done across many states. And they did find an association with low birth weight. The -- a 50 percent increased risk, and that was significant, even after adjustment for several variables including late pregnancy, exposure, or cigarette smoking. And that study did not find that associations with other outcomes, such as small for gestational age or preterm birth.

And then there's the study by Howard in 2019 at the -- out of Cincinnati that had the exposure based on urine samples during prenatal care and at birth. And they did find that birth weight was lower in women who were exposed. It was lower by about 150 grams for women who only showed a positive screen during prenatal care, and by about 450 grams by women who only were positive at delivery. There were only 27 exposed women in that group.

And then it was -- birth weight was reduced by over 100 -- or wait, no. Sorry. About 300 grams in women who were positive both prenatally at a prenatal visit and at delivery. And that was about a little over 100 women.

And they say that these results were -- these were the unadjusted results. In the text, they say that the results were still significant after adjustment. They actually provide the P values for that, but they don't

actually show the difference. Although, these unadjusted differences are substantial.

And then Chabarria in 2016 did the study using the Baylor samples. It had used exposure assessment based on self-report. Less than one percent of women actually reported use during pregnancy. And they found that the results were not significant for birth weight for the women who only showed exposure to cannabis. But they were -- so the odds ratio was around 1.3. But it was significant for women who used both tobacco and cannabis.

So, in conclusion, I would say there's limited evidence that does suggest an association with birth weight. The limited information on associations with cannabis among women who do not smoke and limited information on intensity and timing of exposure, and limited information from more contemporary studies make it difficult to make definitive conclusions.

And now I'll talk about preterm delivery or -- and gestational age. They were probably around 20 -- 25 studies -- or more than 20 studies. Results are more mixed than for birth weight. Many of the studies -- so there's not a prepon -- many of the studies don't show an association. Some do. The meta-analyses by Connor and Gunn both -- actually sorry, the meta-analysis by Connor showed a significant association with preterm delivery of

30 percent increased risk. But after adjustment for tobacco, it was only a ten percent risk and that was not significant. And then the review by Gunn concluded that the association was not significant.

And, in summary, the evidence for gestational age and preterm delivery is less suggest -- less suggestive of an association with preterm birth than with birth weight.

And there have been a number of studies looking at other aspects of fetal growth from length at birth to head circumference, to small for gestational age. It's relatively -- I think the findings are rela -- and the limitations are relatively similar to what we've seen for gestational age, but with somewhat fewer studies, and somewhat more variable definition and the outcome -- how the outcome is defined. And so I'd say there's insufficient evidence for an association there.

And then just to put this into context of sort of how we think about synthesizing the weight of the evidence and causal inference. As our colleagues have summarized, and I'm sure there will be more in the subsequent presentations, the -- in detail -- in more detail, I think the biologic plausibility is extremely strong. And it's -- there's also plausibility based on -- by analogy based on similarities in cannabis and tobacco exposure, as far as some of the toxins that are present and carbon

monoxide exposure as well.

And as far as consistency of findings, results are not very consistent across -- for many of these outcomes, I'd say the most consistent is for birth weight across different designs, and populations, and definitions.

The strength of association is moderate from -- tending to be from around 1.5 to two-fold increased risks. But again, the limitation being that usually it's an "any" or "none" comparison in the literature. And it would be really helpful to have more information on -- more information about intensity of use.

And as far as dose response, there's again very little on dose response. To add to this synthesis, temporality is clear. And then I think as far as coherence being another tenet, coherence of the human with the experimental animal studies and mechanistic studies. I think we'll hear more about that in subsequent presentations.

So in summary, I'd say there's certain -- it's certainly plausible based on mechanistic effects and similarities to tobacco. And there is some evidence, although limited, of a statistical association between cannabis use and some birth outcomes especially low birth weight and insufficient evidence to support or refute a

statistical association between cannabis and many of the studied outcomes, especially maternal, pregnancy-related health outcomes.

That's it. So I will end there.

CHAIRPERSON LUDERER: Thank you very much, Dr. Carmichael for that discussion and summary.

I think we'll have the -- our second discussant Dr. Breton present next, right?

COMMITTEE MEMBER BRETON: Um-hmm.

COMMITTEE MEMBER WOODRUFF: Can I ask a question? Were all the papers that you mentioned at the end, the Colorado study, was that in the references? What did you say the same of -- that was Crume?

COMMITTEE MEMBER CARMICHAEL: The Colorado one is Crume, C-r-u-m-e.

COMMITTEE MEMBER WOODRUFF: Was that in the references in here, in the document?

COMMITTEE MEMBER CARMICHAEL: I'm pretty sure it was, but I'm --

DR. KAUFMAN: I think it might have been identified after our cutoff. We have to cutoff the search for studies much earlier, because it takes a long time to produce a document.

COMMITTEE MEMBER WOODRUFF: Oh. Did you -- I didn't see a cutoff date in the document for when you cut

off your search. Is there a date when you cut off your search?

DR. KAUFMAN: I'll have to look in the HID, and I'll get back to you on that one.

COMMITTEE MEMBER CARMICHAEL: It was 2018.

COMMITTEE MEMBER WOODRUFF: Was your search during 2019 or '18?

COMMITTEE MEMBER CARMICHAEL: So I'm thinking that one was in there, but I'm sorry. I don't remember for sure. I can look for that.

DR. KAUFMAN: We'll bring an answer back to you.

COMMITTEE MEMBER WOODRUFF: I don't -- well, I don't see it. That's why I was looking for it.

How did you find it?

COMMITTEE MEMBER CARMICHAEL: Okay. Are you looking in the report itself?

COMMITTEE MEMBER WOODRUFF: Yeah.

COMMITTEE MEMBER CARMICHAEL: Okay.

COMMITTEE MEMBER WOODRUFF: Where else am I supposed to look? Is there another place?

COMMITTEE MEMBER CARMICHAEL: No. I thought maybe you were looking at like -- I know that some of the articles -- the PDF. If you were looking like in the folder of PDFs. If you were looking there, maybe -- it may not be there.

COMMITTEE MEMBER WOODRUFF: Oh, yes. No, I know that too.

COMMITTEE MEMBER CARMICHAEL: Just that -- because all the PDFs weren't there.

COMMITTEE MEMBER WOODRUFF: It's just -- I will make this comment later, but I just -- I appreciate some of the documentation of the search, but I felt that there's a lot more that can be done to clarify the search and obtaining of the studies, because there were -- there's a lot of -- I think the methods can be improved by which the studies are identified, documented, and made available to us. I mean, that's an example of one. I have several examples of studies that were -- either I found in references or were listed in the document and not available on the website. And there's a -- I think we need to see some improvement in the tools used, so that the -- you know, the underlying database is accessible.

That Crume study sounds -- or did I -- I don't know if I pronounced that right. It sounded very interesting and important, so -- because it's taking place in a -- in a -- in Colorado where they have recently legalized marijuana. So it seems like it's more relevant than maybe some of the older -- I mean, a lot of these studies are quite old, so...

CHAIRPERSON LUDERER: Thank you.

Dr. Breton.

COMMITTEE MEMBER BRETON: Thank you. So thank you, Dr. Carmichael, for a very comprehensive summary. So I don't want to repeat things that she has already said, so I do have a few additional comments that I would like to make. I'll start with birth weight, because as she said, I do believe that the -- there's the greatest level of evidence for birth weight and low birth weight.

So just a couple other points that I wanted to make with regard to that are that of the meta-analyses that were done, the three most recent ones - and by recent, I define that as post-2000 - found -- did all find evidence for cannabis associated -- being associated with lower birth weight.

And that, you know, while the literature on dose response -- dose response is limited, the ones that did exist, looking at urine biomarkers, do show evidence for a dose response. So I think that that's worth keeping in mind that some of the more recent studies are starting to move in that direction, trying to assess exposure a bit better or trying to look at dose response.

And also in thinking about recent versus older studies in light of the potency for THC changing over time, the seven out of the ten studies from the last decade all show statistically significant lower birth

weight -- associations with lower birth weight.

And so they may be slight -- slightly more relevant or point to the fact that we've crossed some threshold in terms of potency that matters when we're doing population studies. So that's all I wanted to say about birth weight.

With regard to preterm birth where -- and I think that's sort of the next one in terms of level of -- literature and level of evidence potentially in support of an association, it is -- I agree with Dr. Carmichael that, in general, it's very mixed. And if you look at just the overall numbers of studies, only six out of 19 find statistically significant positive associations with risk for preterm birth, and including one meta-analysis in that count.

But again, if you look at the ones that have any evidence for dose response, four out of six of them that looked at dose response see evidence for a dose response. So again, I think that that's -- that's a strength in the literature and is something to consider in the larger context and also when looking at meta-analyses that try to really summarize the state of literature at that given point in time. The meta-analyses also suggest positive associations.

And then with regard to pre- and postnatal

mortality and so risk for spontaneous abortion or stillbirths, I would agree that the -- the evidence is just too thin to really draw conclusions. These are really challenging studies to do in human populations. So I think that the results may be suggestive, but at this point are just too thin.

And then the only other one I want to -- the only other one -- category I want to mention has to do with birth defects. And, you know, the challenge with birth defects research of course also is that there are many -- there -- it's a very heterogeneous group. They're often quite rare. So in trying to do this in human studies, they can be very challenging.

So on the whole, only five out of 13 studies of any type that were down found any sort of association, but they were with different birth defects and different types. And I think that -- so the distinction that -- or the one point I wanted to make here that I think wasn't mentioned is that some of these were secondary analyses, and -- but of these studies that specifically set out to study birth defects, and so they were specifically designed as a population of studies to look at birth defects, they -- those studies tended to find statistically significant associations with exposure and the outcome.

And so -- so I think thinking -- you know, it's hard to dive into the heterogeneity of these, but I found that the evidence with regard to the VSD or the ventricular septal defects might be suggestive, in that large -- within the context of the larger body of literature that on the whole is not very -- is really quite thin for birth defects.

And then I agree with Dr. Carmichael in the sense that all of the other outcomes look -- that have been looked at so far, the studies are just too thin and inconclusive at this point in time.

So I'll end there.

CHAIRPERSON LUDERER: Thank you very much, Dr. Breton.

Dr. Kaufman

DR. KAUFMAN: Yeah. I'd like to respond to Dr. Woodruff's question. The Crume et al. study 2018 was acknowledged in the HID on page 405. It'a cross-sectional study and it was excluded, as per our criteria that we outlined in the HID.

COMMITTEE MEMBER WOODRUFF: Would you say that -- was it --

DR. KAUFMAN: It was -- we excluded the cross-sectional studies. And that is on page 42 as outlined in tabulation and summarization of epidemiologic

studies. And the cutoff date for our search was November 8th, 2018.

COMMITTEE MEMBER WOODRUFF: I'm sorry. So on page -- I'm sorry. Can you say again on page 42?

DR. KAUFMAN: Yeah, sorry. Page 42 outlines the criteria for inclusion and exclusion. Ecological studies, cross-sectional studies and case studies were excluded -- or case series were excluded.

COMMITTEE MEMBER WOODRUFF: So there's no cross-sectional studies listed in the document?

DR. KAUFMAN: There are -- there could be some, but it's -- this is the rule that we -- we didn't include them in the analyses that we presented due to the nature of -- the cross-sectional study you can't establish temporality and that's pretty -- pretty standard.

COMMITTEE MEMBER WOODRUFF: But -- so I guess -- so, I'm sorry, in the summaries -- I'm sorry, you excluded studies in the document that were cross-sectional or in your summary?

DR. KAUFMAN: Well, some are shown here as excluded in the document. We specified which studies we excluded on page 405. In our detailed study summaries and in our summaries of outcomes, we did not include cross-sectional studies.

CHAIRPERSON LUDERER: Okay. I think now would

be --

COMMITTEE MEMBER WOODRUFF: Okay. Can I just say one more thing.

Yes, because I am reading this. And I actually did have a comment about this in my comments. This is what it says, "Detailed summaries were developed and included in the appendices for analytic epidemiology studies with individual exposures and outcome assessment, such as cohort and case-control studies". So is it yes or no? "Such as" is like "for example".

I guess what my point is -- I mean, I know you did a lot of work and this is a really important topic. I think my point is is that I would like to see a more -- better clarity on what the exclusion and inclusion criteria are for the studies, because "such as" implies to me that sometimes they are and sometimes they aren't.

And my recommendation would be for the next document to have something a little more clear, like -- like what you would have in a systematic review, like a PECO statement that says here's the things we're going to do, and we -- if we're going to exclude cross-sectional studies, here's the exact reasons and how we decide.

So I -- you're right, I did read this, but then it says they were excluded "such as" or they were excluded. So one could interpret that in two different

ways, so that's just --

DR. KAUFMAN: Well, we put "such as", because some people are very specific. This was general, a cohort and case-control studies. Some people identify cohorts as longitudinal studies or retrospective studies. So that's the "such as". But as I pointed out, it goes on to specifically say ecological studies, cross-sectional studies, and case-control studies were excluded.

So I will note -- we will note in the future to be more specific. And instead of "such as" we will list all of what was --

COMMITTEE MEMBER WOODRUFF: Okay. Great. That's helpful. Thank you.

DR. KAUFMAN: -- very clearly included.

COMMITTEE MEMBER WOODRUFF: Okay. But I mean, then this one too, "Studies that did not address potential confounding were also excluded with few exceptions, where this was noted and detailed in the appendix tables". Again, I just think it's -- you know, you either are going to include them or not include them, and -- so now this says sometimes also. And I think it's -- it makes it easier to evaluate the literature and be more -- have better clarity and reduce the bias in evaluating it if it's -- there's a more clear decision rule.

So you sometimes included these studies that had

confounders or sometimes you did not. So I just think that, again, being -- having more clearly written rules, somewhat like a PECO statement, would help that, so it would be clearer which studies were in and out.

Because then it's going to matter, right, when we do the evaluation, because there's this issue about the potential for confounding by tobacco. So how do we evaluate that?

CHAIRPERSON LUDERER: Okay. Thank you, Dr. Woodruff.

Do we have -- I was just going to ask for additional discussion by the Panel.

Dr. Hertz-Picciotto, did you have a comment?

COMMITTEE MEMBER HERTZ-PICCIOTTO: No. I -- I mean, it seemed to me that this was a very comprehensive tabulation of studies. I didn't get a sense of selection going on by the staff as to what went in and what went out. I mean, it seemed -- you know, there's a ton of studies here and I'm speaking for the more developmental outcomes. And they were virtually all cohort studies, which I think is appropriate, given the importance of having the temporality of exposure prior to -- assessed prior to the outcome.

So, you know, it didn't strike me as particularly unclear, but, you know -- and "such as" to me means "for

example", so...

COMMITTEE MEMBER BASKIN: I would just echo that I thought the analysis was pretty spectacular with an emphasis on the cohort longitudinal studies, which we're going to talk about in the next discussion and the prospective ones are what we have to emphasize. And every one of these meetings there's a -- we have to review many articles that are basically worthless. The ones that aren't, we need to focus on.

COMMITTEE MEMBER WOODRUFF: I totally agree that it's better to pick a set of studies that are useful for this analysis. But when your discussion point said, oh, I looked at this Crume -- whatever this paper -- I don't think I'm pronouncing this persons's name right -- Crume. So that indicates to me that there might be some value in this study. And so that kind of backs up into, well, what is our selection criteria? Are we going to consider cross-sectional studies as a valuable input into this or not?

I'm not disagreeing that you guys did a tremendous amount of work, and it's very useful, and there's a lot of studies. But when we start to discuss them individually and we're getting down to thinking about the body of evidence, and that there's differences in the body of evidence depending on the type of studies, this

type of thing actually, when I listen to the discussion, makes a difference. So I do think it's worth being clear in the document about those types of things.

COMMITTEE MEMBER CARMICHAEL: Yes. And, you know, I could be clearer also in the study design, so --

COMMITTEE MEMBER WOODRUFF: I wasn't -- I wasn't saying that. I was just saying -- I'm just saying it's like it becomes clearer --

COMMITTEE MEMBER CARMICHAEL: Yeah.

COMMITTEE MEMBER WOODRUFF: -- that there's a discussion going on, because if we don't have clarity about what the studies are or are not, then people have different maybe understandings of what the body of evidence is. That's all my point is.

CHIEF COUNSEL MONAHAN CUMMINGS: Dr. Luderer. Sorry. If I could just say again that it's -- it's totally fine to look at any evidence that you all have found that may be in addition to the work that the staff put together. And the fact that they may have excluded a study, it's okay to consider that one, if you think it's appropriate from a scientific perspective.

But -- so you're not constrained by the document that we created or the way we might have presented it. You can apply your own scientific judgment to what the material is and anything additional that you may have

found.

DIRECTOR ZEISE: Yeah. And I -- I think another issue is I -- that was raised was the presentation of the animal data. And basically, we followed the approach used that was discussed by the Committee earlier. And so this Committee may now decide that they'd like to see the evidence presented differently. And we can talk about that later. Perhaps after we discuss -- after you discuss the chemical more. But what we're -- you know, we're open to hearing from the Committee about ways of presenting the information that you find particularly useful.

CHAIRPERSON LUDERER: Dr. Hertz-Picciotto.

COMMITTEE MEMBER HERTZ-PICCIOTTO: Yeah. Just to point out, I actually had meant to say this earlier and I forgot. I had written it down when you were asking for comments after the initial presentation. And the one thing that I think I would kind of take issue with in the presentation of these outcomes was that there was a -- one of the slides was about spontaneous abortion and stillbirth. And it talked about one study that had an odds ratio of 12.1. And then it went on to show that others had much more, 1.7, things likes that.

If you looked at that study, and I never read the study. I've never seen it, but all you needed to do is look at the confidence interval, which went from 1.03 to

141.8. Now, if you get a confidence interval in which the upper limit compared to the lower limit is ten-fold, at that point, you already know that they're small cells, probably -- they're small cells. There's at least one cell that's five or smaller. And when you've got something over 100, there's a zero cell most likely or at most there's a one in that cell. And to draw any conclusion from any epi study where you've got a cell with one person - and we know epidemiology is full of all kinds of problems with misclassification, things like that - it means that you could lose or add one -- one more, and it would totally change your results.

So it's -- I would say take it out. I never let my students publish if there's a confidence interval that's bigger than ten. Take it out.

COMMITTEE MEMBER WOODRUFF: I have another.

Yeah, I just want to go back to because you also referenced the excluded and included studies on page 405 and 406. So we did look at that. And I just want to see if I have these numbers right. There were 435 references that you had from the Swift screening. And so you included 142 studies, is that right, and excluded 74?

I just said there's 219 studies that I just -- are not accounted for in this. So I think the other thing I would also recommend for next time is to have a flow

diagram of how you start off with the number size. You have the total number of the studies that you started with in the table. But then how you got to the final number need -- should -- there should be a flow diagram that says, okay, we did this title and abstract review, then we did this full text review, and show how many papers were at each step, because -- I mean, maybe those 200 studies aren't really useful. I don't know, but they could be so. So that was also -- I didn't really have a -- that was a kind of a gap here.

CHAIRPERSON LUDERER: Do we have any additional discussion on the epidemiological studies related to pregnancy outcomes?

Well, no.

All right. So, it's -- I was planning on, as I said, moving on to the animal studies of the related developmental endpoints next. And so one question is what time do we want to break for lunch or start on that? I'm wondering if we --

DIRECTOR ZEISE: So you can -- the Committee can either decide to break for lunch now and come back in 45 minutes to an hour. And then take the animal studies at that point or take a quick -- or take a quick break of ten minutes to give the court reporter some time and break for lunch.

CHIEF COUNSEL MONAHAN-CUMMINGS: Give him at least 15.

CHAIRPERSON LUDERER: Anyone on the panel opposed to taking a break for lunch now and would prefer to do that? 15 short break or

DIRECTOR ZEISE: So shall we take a ten minute break.

COMMITTEE MEMBER WOODRUFF: So are we going to each lunch, did you say?

CHAIRPERSON LUDERER: I was actually suggesting the opposite of that.

DIRECTOR ZEISE: Oh, sorry.

(Laughter.)

CHAIRPERSON LUDERER: Since I apparently wasn't clear. We could have a show of hands who would -- on the Panel who prefer to have lunch now?

(Hands raised.)

CHAIRPERSON LUDERER: Okay. All right. It looks like we have a lot of unsure, so let's just decide now that we'll break for lunch and then we'll reconvene in one hour.

All right.

CHIEF COUNSEL MONAHAN CUMMINGS: Excuse me. Just a reminder, too, that Committee members that during lunch please don't discuss among yourselves the subject that

you're considering today. Maybe just talk about the weather or something.

Thanks.

(Off record: 12:00 p.m.)

(Thereupon a lunch break was taken.)

A F T E R N O O N S E S S I O N

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

CHAIRPERSON LUDERER: Oh, now it's on. Okay. All right. Now, you can hear me, right?

Okay. The green light was on, but it was not doing any amplification.

All right. Well, I'd like to reconvene. I hope everyone had a good lunch. We are going to continue now in the afternoon session with a discussion of the animal studies of the other developmental endpoints kind of to complement the epidemiological study discussion that we had in the morning. And so the first discussion on those endpoints is going to be from Dr. Auyeung-Kim.

COMMITTEE MEMBER AUYEUNG-KIM: Thank you.

So I'm going to follow the same -- the same order that Dr. Campbell discussed this morning for the animal studies.

And so the conduct of embryo development and implementation -- implantation studies are limited to in vitro models and also a study in mice. As mentioned, the Paria laboratory ran a series of experiments on the possible estrogenic effects of THC in mice. The lab studied the presence of cannabinoid ligand receptors, CB1 and CB2, signaling in the embryo and uterus during early pregnancy.

The results suggested that THC is capable of producing modest project -- pro-estrogenic and anti-estrogenic effects in the mouse uterus and demonstrated ligand receptor signaling with endocannabinoids and is intimately associated with embryo-uterine interactions during implementation. The study, however, is limited, in that it is know -- unknown whether this mechanism is applicable to other species, since only the mouse model was used and whether the physiological significance of the signaling pathway is relevant to humans.

And so based on this -- the studies that were presented for early embryonic and development implantation, I don't believe that it clearly indicates whether THC has an effect on early embryonic development or implantation, because of the limitations in the data available.

With regards to the general effects in whole animal studies, the inhalation route was first discussed. And it's the relevant route of exposure in animal studies. And the animal studies were conducted in both mice and rats, as previously mentioned.

The limitations of the study are that there was a small number of animals. All but one study had an N of ten or less. And animals whole -- also animals -- in most

of the studies the animal whole body was exposed. The animals were exposed in chambers where their whole body was exposed. And so therefore, there is a potential for ingestion as well. And in most analysis conducted, they were on a per group basis and not on a per liter basis, as previously mentioned.

Only a few studies indicated maternal toxicity, which was the decreased body weight gain, while others did not report or there were no maternal toxicity.

As mentioned in the Charlebois and Fried study in 1980, some of the developmental tox observed with the cannabis exposure included decreased birth weight and delayed incisor eruption and delayed eye opening, which may be related to maternal malnutrition. As mothers are exposed to cannabis may not eat well.

Now, I'm going to go over -- there is -- the one study that had a robust number of animals was the Rosenkrantz study in 1999. And it had an N of 30 for inhalation in mice and rats. Maternal toxicity was not mentioned. Exposure to smoke via the nose cone -- and this one is also -- exposure was not a whole body exposure. It was only through the nose cone -- was performed during day six to 15 of gestation. And overall, I think the study was well designed and controlled and targeting the doses that would be seen in heavy users

exposed to cannabis smoke.

There's no teratogenic effects were observed in the Swiss Webster mice or the Fischer 344 rats after exposure to the marijuana smoke, but embryo toxicity was prevalent in the mice.

For the mothers, there were no significant adverse effects on the conception rate, dam growth -- dam growth rate, total number of implants, or the number of implants per dam.

On the other hand, the number of dams with early fetal resorption was significantly increased in a dose-related fashion among marijuana-exposed mice, but it was not observed in the rat. So the study was -- had mixed results in whether or not it was a mice-only effect or whether -- because it was only seen in the mice and not the rats. No other species was reported.

So there was -- and for the oral studies, there's a greater number of oral studies conducted in mice, rats, and hamsters, and a chimpanzee study was also conducted. Most of the studies also did not have a sufficient number of animals or some of the finer endpoints evaluated were limited to just that study, where it was like the altered sex ratio, the reduced postnatal weight gain, and increased external malformations. There were also studies where the analysis was conducted on a total group basis

rather than per liter.

And so I'll review a few papers that I considered to have a sufficient number of animals and had adequate methods or study design. In the same paper discussed previously for inhalation, the Rosenkrantz paper, they treated the CD-1 mice -- and they changed the species for the rat to the Fischer 344 rats. Oh, sorry. I had to -- oh, no, they kept the same.

They changed the model for the mice not the rats. Sorry. And these were larger doses. And the larger doses was -- or the doses were between 150 and 600 milligrams per kilograms per day. The dam growth rate was significantly inhibited. But the loss in dam weight was related to resorption of the fetuses and not maternal intoxication in both the mice and rats.

In the Abel study, which was conducted in 1999, Long-Evans rats were treated with 10 or 25 mg/kg of THC, presumably by gavage from GD 6 to parturition. The THC lowered the maternal weight gain -- or the results of the study indicated that THC lowered the maternal weight gain and the weights of the offspring at birth, and at 21 days of age, but it did not affect the litter size.

There was a study conducted by Hutchings in 1987, where there was up to 20 Wistar rats treated with up to 50 mg/kg of THC during gestation GD 8 to GD 22. In this

study the pups were actually cross-fostered to untreated dams. And then the study showed that there was a -- there was a decrease in maternal food and water intake in the THC-treated groups.

The THC-treated groups produced embryolethality and fetotoxicity. But the extent to which these affects is due to the THC or what the maternal toxicity needs to be considered. Although THC did not significantly reduce the birth weight independent of the maternal undernutrition, it did produce dose-related effects on the rate of growth.

Whereas, the body weights of the pair-fed controls caught up to those not treated group within a couple days. The body weights of the 50 mg/kg group were significantly less than those not -- in the not treated group throughout most of the study.

By comparison, the THC 15 mg/kg group showed inhibited growth only during the first five days following the growth spurt, so they caught up to the controls by day 11 of life. And by postnatal day 32, there were no significant differences amongst groups. So although the animals did have decreased birth weight that they -- when cross-fostered to -- when they were not exposed postnatally, they -- their weight resumed to normal.

The Fleischman paper in 1980, they used Fischer

rats, or CD-1 mice. And treated the animals from GD 6 to GD 15 up to -- let's see the rats were treated up to 50 mg/kg per day and the mice were treated up 600 mg/kg per day. And for the control animals, they were either Sham treated or treated with sesame oil control. The animals were sacrificed at approximately ten per group during gestation. And there was no signs of intoxication in the dams and the growth rates were normal in all the studies.

In both rats and mice, there was a decrease in the number of live fetuses per litter and increased resorptions in all treated groups. But the statistics were not reported for the mice cohorts, but they were reported for the rats. And thus in this study, embryocidal effects were observed in both the rats and mice.

The last paper I'm going to review is the Wright paper, where rats were treated with a lower dose of THC at 5 -- up to 5 mg/kg per day at various time points. Mating and infertility indices were similar for controlled and treatment groups, but there's no difference in -- between the control and treatment groups were seen. And so that may be a result of the -- due to the lower concentrations that were used in the study. The average number of pups delivered viable at birth did not differ among the control and treated groups. And the pup survival was unaffected

by treatment. And there's no evidence that teratogenic activities obtained for either the rats -- for -- in the rats.

This paper also covered New Zealand white rabbits -- or a study in New Zealand white rabbits that were treated. And there was a decrease in weight gain in the mothers. And similar to rats, there was no evidence of teratogenic activities in rabbits. However, there was a decrease in implantation sites and decrease in viable fetuses in litter.

And so these oral studies show that there is -- there is a trend that at -- that there is a decrease in body weights. But however, due to the limitations of some of the studies, whether it's the number of animals or the -- the number of animals or that the statistics were conducted -- or calculated per group versus per litter calls into question whether or not -- whether -- the clarity of whether there is a direct effect.

In the injected studies were conducted in mice, rats, hamsters, and monkeys. And so this was not necessarily the relevant route of exposure in humans. But in most of these studies, maternal toxicity was not reported. But those that did showed a decrease in weight gain. And the number of animals in the study were also small. In general, the studies show that THC was

embryocidal as well, and -- but for the same reason above, it could be that embryocidal effects were due to maternal toxicity.

The one study I did want to discuss a little further was the one conducted in the rhesus monkey by Asch and Smith in 1986. And this was a study in which there was only five animals per group. And they were assigned to either vehicle or 2.5 mg/kg THC. And so in the THC treated group, there were three early abortions, one stillborn out of the five treated monkeys in the control group.

Now the -- and there was a paper that was not in our packet, but that I was made aware of was by Henry et al., which looked at the pregnancy loss in rhesus monkeys at the California National Primate Research Center. And it showed that the pregnancy loss in rhesus is approximately 17 percent and it's a U shaped -- it's U shaped, in that you have more losses early and late in pregnancy. And so the average in the first trimester, which is generally through gestation day 50, is about five percent.

And so there is variability in the study just because there is a small number -- very small number of animals used in this of the studies And so, while it may appear that there is a test article effect due to the

number of animals on this study is called into question whether it may potentially be based on the historical rates.

For immune system effects, there was one study that was conducted in vivo that showed that the EC -- the endocannabinoid system had a direct effect on the immune system. And, you know, for this one the in vivo study of pregnant mice, tube, or group were treated with up to 50 mg/kg THC by IP injection. And THC had a profound effect on the fetus as evidenced by the decrease in thymic cellularity on gestation day -- GD 16 -- post-gestation day 16, 17, 18 and post-gestational day one with marked alterations in the T cell subpopulations.

But this was based on one study and one species. And so further studies probably will need to be conducted to validate these experiments due to a limited number of animals as well as the species.

The last is the effects on bone growth. As mentioned, the endocannabinoid system has been implicated in the regulation -- regulating the bone mass. A few studies were conducted to show that THC had an effect on both growth indirectly. And so -- and the one paper -- or one paper cited was Wasserman in 2015 that conducted several in vitro experiments and it also had in vivo component to the experiment, where double CB1 or CB2

knockout mice were utilized.

And so the mice were dosed with up to 5 mg/kg per day intra -- I.P. -- by I.P. between weeks five and 11, and showed that there was a -- and showed that THC slows the skeletal elongation of the females in the wild type and CB2-deficient mice, but not the CB1-deficient mice.

And so while this proposes an interesting mechanism on the effect of bone growth, the study was conducted in non-pregnant mice, and the number of animals was not noted. And this mechanism is not -- has not been evaluated in other species, and therefore the relevance to humans is unknown.

So similar to the human studies, it's like there is -- there seems to be a trend where there may be -- where THC may result in a decrease in birth weight. The -- there are limitations in the study designs, whether it's the -- you know, how -- the number of animals, whether maternal toxicity was evaluated or there was a limited number of species. So it's difficult to make a definitive conclusion as to whether THC has a clear effect on the developmental toxicity.

CHAIRPERSON LUDERER: Thank you very much for that discussion. Do we have any -- actually, why don't -- since I'm the secondary discussant, I'll briefly talk about my overview of these studies and then we'll have

time for panel comments and questions.

COMMITTEE MEMBER AUYEUNG-KIM: Okay.

CHAIRPERSON LUDERER: So I agree with the limitations that you noted. I agree that there were actually many limitations in terms of the studies -- the N per group, the way that data were analyzed, in terms of not adjusting for litter effects. And, you know -- and as well as other limitations that you noted. As well, that the earlier studies that really looked -- that looked at general pregnancy outcomes were -- suffered from those deficits I think in particular.

I think I maybe put some more -- was more convinced possibly by the two more recent studies, the study looking at immune system development, as well as the bone development. I think because those studies looked at very -- at more specific endpoints focusing on a particular system, and analyzed some very -- made some very interesting mechanistic observations that I think make sense in terms of what we know about the role of cannabinoids and the cannabinoid receptors in terms of immune development and bone development.

And in the Wasserman study, although I agree that bone -- that they were looking at postnatal exposures and not prenatal, I think that to me, I mean, development does not end at birth. So the animals were maybe peripubertal,

based on the edge when they started dosing. So I would still consider that a developmental study, although, it's not prenatal development.

And they did find significant effects on bone growth and were able to show the relationship with the C -- the CB -- the cannabinoid receptor knockouts that they were specifically due to effects on cannabinoid receptor binding.

So in that -- taking the -- that database as a whole, and, in particular, I think maybe those -- the two latter studies I was -- I think that the weight of the evidence supports that there is developmental toxicity in the -- you know, in the animal models, based on the weight of the evidence.

Do we have questions, comments from other members of the Board?

Then we can -- should we move on to the next set of discussants, which is going to be the neurodevelopmental epidemiological studies. So Dr. Hertz-Picciotto is the primary discussant for those.

CHIEF COUNSEL MONAHAN CUMMINGS: It needs to be really close to your mouth.

COMMITTEE MEMBER HERTZ-PICCIOTTO: Oh, it needs to be really close?

CHIEF COUNSEL MONAHAN CUMMINGS: Yeah.

COMMITTEE MEMBER HERTZ-PICCIOTTO: All right.

I hear an echo, but it's good for you. I'll do it.

Okay. It makes it a little harder to see my notes. Let me get my glasses, so...

Okay. So in my evaluation of studies, my approach is to really focus on where the really high quality studies, the ones that I want to -- that I would really utilize in any kind of decision making. And so I -- I tend to go through a lot of the studies, and I've gone through their approach to their analysis, their design, their exclusions, and kind of the logic of their conclusions when they do draw conclusions. And it actually narrows down 68 studies to a much smaller number.

So let me just talk a little bit about the issues. So -- and other people starting with Suzan and other people who've spoken have brought up some of these. But some of the major issues are the co-exposures and how do you disentangle cannabis use from tobacco use, cocaine, so many of these studies looked at four substances and sometimes even and others, which were tobacco, cannabis, alcohol, and cocaine.

And so some of these studies actually cocaine was their main -- the main thing they were looking at, at least one or maybe two studies of that type.

Then there's sort of their process for screening for confounders. And this is actually something where very few studies actually use correct epidemiologic approaches for deciding what factors to control for in the models. You know, I would say there wasn't more than a handful of studies that -- maybe not even that many, that actually looked at whether addition or removal of the confounder changes the main effect of interest.

Most of them just used statistical significance for the relationship between that confounder and the outcome. And you can -- particularly in the small study, you can miss true confounders that way, because they won't reach statistical significance. And yet, they could be -- they could actually by having them in the model, it actually alters your conclusions -- your results of your -- of what we're interested in here, the cannabis association with the outcomes.

And then -- let's see if I can read my handwriting.

Oh, and then some of the studies also on this topic of what you control for as a confounder, some of them adjusted for intermediate variables, but they weren't doing a mediation analysis. Now, there's some that actually did do mediation analyses, and that was kind of their -- their main point was looking for whether an

effect of cannabis on, let's say, an outcome at age 14 was mediated by say child depression or inattention. So that was another type of study, but if they were not specifically focusing on a mediation analysis, but they adjusted for something that could be an intermediate, like low birth weight, which is one of the reproductive outcomes that we've heard about, then that can introduce bias into what you're really interested in, which I would say in most cases is the total effect, not the direct effect that's not through the mediating -- the mediating variable.

So those were issues that I looked at on -- throughout the literature. And -- and so with regard to these major cohorts that have been mentioned -- and I'm going to add one. So there was the Ottawa prenatal -- I forgot what the PPS stands for, but the Ottawa study. There's the Pittsburgh study. There's the Gen R study, which was from the Netherlands. And then there was also a -- I think it was Boston. There weren't very many, but there were a number of papers -- a small number of papers from that cohort.

And there were a few things about these studies that I just want to say in -- on the positive side, the quantitative aspects, these studies did quantify the use of cannabis. And so, for instance, in the maternal health

practices study, the one from Pittsburgh, they actually interviewed the mother three times, at the end of each trimester to get her, and I believe also -- they also got the father's intake use of cannabis in each trimester.

So they were actually able to do these very nice trimester-specific analyses, which I think were very informative. And so that was really a great thing about the study.

The Ottawa study also had quantitative data, but I believe they didn't -- I think they did not have the timing issues. And I -- I forgot -- I get confused sometimes.

The Gen R study also had timing. And they also did, not just self-report, but they -- and, in fact, so did the Pittsburgh study. They did a biomarker. They did urine analysis. And one of them also did meconium, which actually has some issues, because meconium may be getting much earlier exposures because of the lipophilic nature of cannabis of some of the cannabinoids.

And so all of those were really strong positive things. I got very frustrated with the analysis that was done by the Ottawa team, so they -- many of their -- many of their papers did an analysis where they looked at the exposure to cannabis as the outcome and then they looked at how all the other factors could predict the exposure.

And that's a problematic analysis, because you've got on the same side of the equation the actual outcomes that you're interested in, and the covariates, but you really want the covariates. You're really interested in the covariates, looking at how they are operating independently of -- how cannabis is operating independently of the -- of those other factors. And that's not what you get.

You've really got the wrong structure to really look at this properly. And so everything about, you know, their conclusions I feel a little skeptical. Like, I don't really know. Would this -- would we get the same findings if we turned this around and did it the way we usually think of it? The predictors come before temporally, the outcome in your model.

So I tended to not put a lot -- as much, you know, weight and confidence in those studies. Although I will say, these people are -- they're from the neuropsych field. They really know their measures. They really thought -- they had very thoughtful ideas about interpretation of their findings. And then they sometimes did interesting follow-up analyses to -- to identify, for instance, these pathways that different factors could be operating through.

The other point about -- just about -- again,

about the studies in general. The Gen R study, it actually had very few cannabis users who were not using tobacco. Now, that wasn't true of the other three. The other three actually had a little bit more, I would say, ability to separate cannabis from tobacco. But that one really it was very difficult, because it was like 84 percent of cannabis users who also used tobacco.

And one way that some of these studies kind of got around that issue is that they looked at the effect of tobacco and then they looked at the impact of tobacco plus cannabis and their -- and I'll point out a couple of outcomes where that -- they really saw the difference among the tobacco users. And I -- I think it's interesting, because in general, most of these kinds of neurodevelopmental outcomes are not the result of one exposure. There's multiple exposures that tend to operate together whenever you get sometimes complex diseases.

And when we live in a world with tons of exposures that we don't have any control over, as well as some that we do have a certain amount of control over, we really have to think of it as a multifactorial process that leads to these outcomes.

A few other points here. Most of the studies did not address family mental health. And I bring that up because cannabis is sometimes used by people with mental

health distrubances. And, in particular, I know it's certainly true among people with actually psychoses that many of them feel they can control their symptoms better with cannabis than they can with the pharmaceuticals that they are getting prescribed by their physicians.

And so it's -- it becomes this situation that you see in the pharm -- when you're looking at pharmacologic agents, where it -- the indica -- the indication for use, in this case, may be the reason that people may use it versus the actual substance that they're taking.

And so that's -- that's a question I think -- and because some of these conditions do have a genetic component, knowing something about the family history of those conditions is important. And I would say that almost none of these studies had that information.

Actually, the Pittsburgh study did, and they sometimes controlled for some of the study -- some of the papers actually did control for certain aspects of the maternal mental health status. They had variables like depression and hostility and a few others.

So that's kind of the background to this. And then just -- I'm going to -- I'm not going to go through study by study. There's -- there's a lot. But I am going to kind of go through the outcome by outcome and just kind of give a few -- a few points about those.

So the way that this -- these were presented -- and I -- I think what you presented was pretty much the way it was in the booklet, right. So it starts with infancy and then we go through -- or no, the infant -- yeah, because the infancy ones are totally different from all the other ones, so -- okay.

So -- well, one of the issues with the infancy studies is that almost all of them looked at this Brazelton Neonatal Behavioral Assessment Scale, the BNBAS. And in the field of child development and neuropsych, that's actually not considered a particularly good -- it's a measure that you can do. And if there -- if there's any validity to it, it might be at 30 months. And so a lot of studies did it at like 48 hours or 72 hours, and that sort of thing.

But even at 30 days, there are many people -- many people in the field who say, you know, it doesn't predict anything. Like, it just doesn't -- the studies -- except for the people who designed it, nobody else finds it really helpful.

So I was -- I was a little harsh here, but I basically said that out of all of the studies that were done, there were sort of two that I felt had -- had some, you know, I kind of highlighted, because I felt -- I felt better about them. One was a particularly large study and

that was the -- that was -- that was the Pittsburgh one. And they -- they had like -- what's the number? I forget. So they have about 600 kids in that. And they -- this was -- they used a different scale at eight months.

And so they actually -- and it was a very clear study. The methods were very clearly put together. And basically they saw that in the people who used it in the third trimester at a high level of one or more joints per day - that was the metric they had - they actually saw no association.

Oh, no, I'm sorry. They actually did see a reduced mental developmental index on the Bailey Scales that was large, but they say nothing when they looked at any use at all during pregnancy. So this is one where the timing actually made a difference.

Sorry, I said it wrong the first time. But they -- they -- then they looked at any use, they saw nothing. But when they looked at that trimester-specific thing, they saw something.

And then the other -- the other study that I thought was interesting from this was actually a study that was done in Jamaica, where there's a way in which they smoke it called ganja. And they actually also found no association. They did not have timing of exposure, so they were looking at the overall. And they did not see

effect.

And the authors were suggesting that the home environment, which is connected to it as part of the culture, which is very -- kind of a very positive home environment, that people use it in a very social way, that that actually maybe might have countered any, if there were negative effects. And that was one of the conclusions they drew.

But the women themselves felt that use of it increased their appetite, and hence their food intake. It relieved their nausea and it permitted them to accomplish child care and household tasks better. So it's kind of an interesting perspective.

Okay. So that was the infancy. So now, I'm going to go through the different outcomes that are -- were looked at at different age groups. And I'm starting with cognition here. And this -- there were actually quite a few studies of cognition that were strong. And I would -- would put some weight to seven of them. This is the most I saw with any of these outcomes. So there were seven studies that seemed useful.

And some of them -- so -- and some of them saw no associations, some of them did see some associations. But again, the Pittsburgh study, which didn't see anything when they did it kind of overall, once they broke it down

by trimester, they actually found not much, but they found two sort of marginal associations with some subscales based on second trimester use. But one was short-term memory and the other was -- no, they both seem to be short-term memory. Sorry. Something different about these.

Oh, oh, yeah. It's one thing. It was use during the second trimester with short-term memory. It also turned out that current use was also associated with short-term memory. But that -- we weren't really concerned with the postnatal exposure, so...

And -- but they also, yeah, didn't give us confidence intervals. So that was a little bit frustrating about that study. So that one I had a kind of maybe.

The next one that was interesting was -- was again that another one coming out of the Pittsburgh study at eight months, and large sample size here. They had low correlations in that study between marijuana use and either alcohol or cigarettes. So this was a study that kind of allowed that disentanglement of the two. And they saw third trimester the high level exposure reduced the mental developmental index. So I guess two studies were both looking at the same outcome there. Maybe that's only one.

There was no association with global intelligence in the -- this is the Ottawa study. This is one where they didn't do their weird analysis -- or maybe they did a little bit. But still they -- there were enough other good things about the way they did it this time.

And they did see some results from executive function, which actually is in another one. But they also saw spatial and visual functioning, which -- sorry. Those are the ones that showed no -- sorry. I'm sorry. The ones that did show an association were the picture completion in the block design. So there were a couple that did and a couple that didn't in that one.

A few other studies did start to see things at a little bit -- as the kids started to get older. So when we start looking at six-year olds, there's several studies that are seeing various aspects of verbal reasoning, and -- trouble focusing my eyes -- verbal reasoning and quantitative scales.

And again, this was specific trimesters. So first trimester, heavy use with poor verbal reasoning. Second trimester heavy use with the short-term memory and the quantitative scale, and third trimester with actually -- yeah, with the quantitative scale as well.

They did not see evidence of a dose response. It was the heavy users. So it really was to a linear type of

relationship, but they did see that the heavy users were definitely at higher risk of deficits.

And then at ten years -- there were several studies at ten years that also saw similar kinds of findings. And again, this is a study where they actually did have more data about the home environment and the social factors that -- that some of the other studies didn't adjust for. So I tended to put a little more weight on those studies. And then again at 14 there's some similar kinds of findings. So it seems as if it was less in the early childhood period. It was more in the middle childhood and adolescents where these findings on cognition showed up.

For attention, there were only three studies that seemed really strong. And one of them was one of the Ottawa studies. And that was looking at the -- some of the McCarthy Scales. There was -- there was -- there was consistency across three different measures that they had that were getting at attention. And so I thought that because there were multiple measures -- they used the Conner Parent Rating Scale, and they used the McCarthy Scale, and they used Gordon Diagnostic Scale for vigilance. So that gave me a little more confidence that -- the three of the different instruments.

And then the best study, I thought, on attention

really was from the Magee-Womens Hospital, the Pittsburgh study. And this was looking at the errors of commission and omission on one of these tests -- these computerized automated tests of attention. And they adjusted for the maternal psychosocial factors. This is one of the studies where they did that, the depression, and hostility, and life events. They had actually minimal losses to follow up. So a lot of really good things.

I think the only issue is that this study -- this is a population of -- in general, high risk. This is a low income, largely African-American population. And so there's a probability that there were other vulnerability factors that were contributing, but it was very much the cannabis and not the other -- other substances that was -- that was linked.

There were two studies that -- of that same cohort also looking at some of the same outcomes, but doing their analysis in different ways and still came up with really strong results. So that was the attention part.

Behaviors, other than attention, two critical studies that I was particularly impressed with. And these were -- again, this is at ten years. And the ten year olds were tested for inattention, impulsivity, and hyperactivity. And that those were associated with first

and third trimester use. And the inattention, in particular, was robust no matter what confounders they put in.

They also looked at delinquency behaviors -- or delinquent behaviors. And they had parent reports and teacher reports. And those were consistent, which again strengthens those outcomes and trimester specific aspects.

And the other study was from the Gen R cohort. And it was -- it was interesting, because the -- they saw strong associations of cannabis during pregnancy with externalizing behaviors. And then they did an analysis of be -- of pre-pregnancy cannabis use. And then they looked at tobacco use throughout pregnancy. And they saw some similar effects as they saw for cannabis during pregnancy. And so they concluded that the maternal cannabis result was a pure artifact.

But I wasn't entirely convinced, partly because they -- they -- they had such a high proportion of cannabis users who were tobacco -- who were smoking tobacco. And the difference between -- they also -- they saw things for the -- for the teacher report and the child reporting their own behaviors, but they didn't see anything from maternal report. And I think it's kind of telling that the child's own report about their behaviors would seem to me to be more accurate that moms may not

know what teenagers are doing all of the time. So that, to me, seems an interesting example of who do you believe.

They also -- the paternal effect that they saw, that was another reason why they wanted to reject the idea, the maternal effect. But on the other hand, epigenetics is one possibility. And, of course, there's a high correlation between maternal and paternal cannabis use, which they didn't address and they didn't try to adjust for each other. So I think there's -- there's a kernel there, especially with the child report. So that's the behaviors.

Then we get to the psychiatric symptoms. And here, I found about four studies that I thought were compelling or interesting enough to put some weight on. There was one that found cannabis had no association with -- in girls. And the age of these girls -- I'm sorry, let me just check this -- is -- was -- oh. Okay. This is anxiety in 18-month olds, which I thought was kind of interesting, because it's kind of a young age.

So there was no association, regardless of the tobacco, with girls with their anxiety or depressive scores as toddlers, I guess you'd call them. But for boys, they did -- they saw kind of a borderline effect that was inverse. In other words, it -- they seemed less anxious and less depressed.

And it was a P of 0.06. And so the author said there's no association. But I think, you know, these sorts of things when you're kind of in that direction, it's worth taking note. And this magnitude effect was similar to the effect of tobacco alone, which they actually spent a lot of time talking about.

So anyway, that's -- that was one of them.

Then another one for psychiatric symptoms was -- the next one was in childhood at age ten years. And it's self-report of depression, and it's -- no, I'm sorry. It's depressive symptoms and it's kind of a measure of general distress. But it's not a clinical diagnosis of depression. It's something less than that most likely.

And so there was a strong association, particularly with first trimester prenatal marijuana use. And there was a dose response for those with no exposure, and then low, moderate, and high -- heavier exposures, there was a very strong trend of those scores for depressive symptoms. And there were two different instruments that were -- gave similar results.

Then the next one is similar. I'm not going to go through all of these. But there were basically four studies that seemed to suggest psychopathology as an outcome. Well, three of them I guess suggesting it and the other one not so -- oh, I'm sorry, no, two of them.

So this is very mixed, in fact. This was a very mixed set of outcomes.

And then there's -- you know, there's one study that suggested head circumference. Moving now to -- actually before I talk about CNS and motor, there were also these -- a bunch of studies that had to do with substance use by the offspring, the children. And I -- I really have trouble considering that a neuro -- a neurodevelopmental outcome, because substance use has so many social factors that are going to contribute to substance use, you know, especially in teenagers, that the idea that the prenatal exposure of -- to the substance is somehow the reason for why a child would pick up drugs.

It seems likely to be swamped by all of the social factors that are going on. They could be in the home as well. But I -- I think that we're interested in biological effects when we're talking about listing things and not the social aspects of how children might respond to their parents' behaviors in the home. So I kind of dismiss that as an outcome that I would not consider part of my decision making for neurodevelopmental toxicity in humans.

And then the last two things were motor and central nervous system. And there's a study in each of those that's -- that, to me, had like no obvious biases

where they were looking at -- head circumference is for use of substances. And there was a trend towards smaller head circumference that did not reach statistical significance. Head circumference is actually a very good measure of brain volume, because there's not a lot else in head. So that's the rationale on that study.

And then the motor studies, there's several motor studies. But most of them -- or there's only three actually. And gross motor was not associated. And there's no association with the -- at 19-month olds -- 9 months and 19-month olds. So out of a few studies, there's -- that's not a particularly compelling outcome as far as does the evidence support an association.

So all in all, I think the -- you know, it's a mixed literature. I think the strongest data is in the area of cognition, and attention, and the psychiatric symptoms that seem to be maybe a little bit on the -- and maybe it's very hard in a way to actually kind of look at that at really young kids, but definitely by mid to late childhood and adolescence that seems to -- seems to be showing up.

And one of the questions I think is worth thinking about is that because medical marijuana, one of its uses is to curb nausea, you know, particularly in people who are undergoing chemotherapy, and nausea is one

of the phenomena that you have in pregnancy -- many women experience during pregnancy, that it's very -- it's really -- this -- that makes this very important. Because if there are consequences for the child, and that's what some of this use might be -- and none of these studies talked about why are you using marijuana? Is it purely recreational? Do you have any kind of medical condition that you're using it for, which I thought was interesting.

But, of course, many of these studies started quite a long time ago, maybe before even medical marijuana became a thing.

So I -- I think it's really important to -- for messaging for -- you know, for clinicians and for the public health community with regard to use during pregnancy, which might seem like a good idea if you're having a really bad case of nausea. And, of course, nausea varies among women, but there is a subset of women who tend to have nausea all the way through their pregnancy from the practically day of conception till delivery.

And I had a friend who sat around with a box of saltines. And that's all she ate her whole pregnancy, it seemed like. Her child came out pretty good for -- considering the nutritional aspect of that. But it was striking to me to see that, you know, actually one of my

friends had that experience. So nausea in pregnancy is a -- is a serious thing that people have to deal with. So I think that is all that I have to say.

CHAIRPERSON LUDERER: Okay. Thank you very much, Dr. Hertz-Picciotto.

Our -- the secondary discussant for this topic is Dr. Nazmi. So why don't we hear from him and then we can have further discussion as a panel.

COMMITTEE MEMBER NAZMI: Thanks very much.

In the -- in the interest of time and not being redundant, I won't comment on individual studies. I think our colleagues have done a pretty good job of covering much of the literature. So let me just remark on a few of my notes regarding kind of the totality of the literature that we were provided and that we reviewed related to the neurodevelopmental outcomes associated with THC exposure. And I will stick to the context of kind of the conventional criteria for causation as at least one of our colleagues has done maybe in a little bit more detail.

But one point drawing from Dr. Hertz-Picciotto's comments regarding the multifactorial nature of this exposure is really important to keep in mind, because it can be really challenging to disambiguate all of the variables in a lot of the larger studies, especially in their statistical models and in their kind of just

conceptual modeling. It's -- it's I think worth keeping in mind that it's not always easy to kind of dissect and look at those -- look at those exposures very well.

A few -- let me start with a couple of the caveats of reviewing this literature that I just kind of noted. One, as a few others have mentioned, related to study design, there were a few large studies in those three or -- those three main cohorts that we've been looking at. Many of the studies were a little bit -- were quite small, and some of the studies populations were quite homogenous.

The study statistical models varied quite a bit from, you know, some studies that basically didn't do almost any statistical modeling and statistical analysis to some, you know, robust models that took into account a lot of confounding factors, some ideation analysis, and so on.

The second caveat I'd like to mention is the assessment of THC use or THC ingestion. As others have also mentioned, there are some problems with validity and reproducibility of some of the methods related to frequency of use, reporting issues, potential bias, especially given that many of the populations seem to have a very low prevalence of use.

Also concentrations. Concentrations in some of

the studies, the assessment of it seemed relatively ambiguous, and especially in some of the newer studies, where perhaps the cannabis market was a little bit larger than in the older seventies and eighties studies. I think the routes of administration, there are so many different methods of ingesting THC. I think some of that is worth bearing in mind in the research, especially moving forward. As we all know, the cannabis market has totally exploded, so the routes of ingestion from here on going forward are probably only going to increase.

And then also a final caveat, regarding psychological, social, and cultural factors that are really difficult to measure. And not only difficult to measure and not only difficult to report on, but also really difficult to quantify. We know that there are pretty significant differences in use according to geography, socioeconomic status, and other factors, but it's not really clear how these differences could impact -- could impact outcomes.

So with those kind of general caveats, let me start with a couple of these criteria for causation that I'd like to kind of comment on just broadly. First, being -- the first two being biological plausibility and temporality of THC and the neurodevelopmental outcomes.

We know the fundamental mechanisms. They were

summarized by the OEHHA staff and some of our colleagues pretty thoroughly. We know that there are a number of known and some hypothesized pathways through which THC acts on neurodevelopmental endpoints.

And just transitioning into the literature, the consistency between the studies. Even though I took a similar approach to Dr. Hertz-Picciotto in that, if you look at the number of studies, there were dozens of studies, I think 68 studies. But when you start to look at the quality of the individual studies, you see really different study designs, different ways of approaching the research question.

Taken together, if I can just be general, to me, the results largely indicate significant effects of THC on neurodevelopmental outcomes. Nearly all studies showed significant effects. And, you know, given a -- given a relatively broad array of neurodevelopmental outcomes, attention, intelligence, achievement, mat -- CNS maturation, neuroimaging, function and processing, some behavior studies, mood studies, the findings, the way I read it at least, seem to suggest that there is the greatest -- there is a great -- there's a greater risk during exposure during the first trimester.

Moving on to strength of association. In general, I might say that the strengths of association

suggested small to some studies maybe moderate effects of exposure on neurodevelopmental outcomes. Some number -- some studies -- a smaller number studies showed no detectable impact of THC. Some of them -- some of the smaller studies showed significant effects, which is complicated with smaller studies, because it -- it can lead to a lot of imprecision, as we suggested before with the confidence intervals.

But most studies, and many with robust models for adjustment, and appropriate analysis, taking into account a lot of confounders in different ways granted, did show detectable risks -- detectable levels of risk difference between THC exposed and unexposed, even given that many of them were kind of dichotomous use or not use outcomes.

That's not to say that there were a few -- a few studies that looked at dose response. And a small number of studies that did look at dose response, there seemed to be a suggestive dose response effect. Although, I'd say that was -- that was a bit limited.

So in terms of the criteria for causation, those -- those -- what, those four or five that are reviewed, six, to me stood out as relatively consistent things you could actually put your finger on, given the large number of studies, even if you were to pare down the studies and look at the ones that were a little bit higher

quality.

I also agree with Dr. Hertz-Picciotto about the factors that we don't study, the reasons, the psychological and the social, the home life as to -- as to why these -- why these exposures occur, right? And the multi-factorial nature in which they occur makes it a really difficult thing to -- it's a behavioral -- it's a behavioral exposure, which is inherently really difficult to study.

So that's really all I have in terms of my notes. I noted a large amount of consistency, which I found to be -- in the evidence, which I found to be convincing for neurodevelopmental outcomes.

CHAIRPERSON LUDERER: Thank you, Dr. Nazmi.

Dr. Woodruff.

COMMITTEE MEMBER WOODRUFF: Yeah. Thank you both for doing that great summary of the epidemiological literature. I just wanted to add to the point you were saying. I really like that you brought up the issue about the biological mechanisms by which this might occur. And I just would note that there's also, given the pharmacokinetics, and that THC is lipophilic, and the brain is very fatty, particularly during the prenatal period, that there's likelihood -- and I think there was some -- some evidence of this, that there would be

accumulation in the brain where there are these cannabinoid receptors. So those both sort of add strength to this -- the science around that this is a developmentally sensitive period, particularly for neurodevelopment.

So -- and I just really appreciate you talking about that -- the issue about we -- the general trend of the relationships. And we would anticipate that there would be some inconsistencies in the findings, because these are humans, so the findings -- and the different methods and every -- and different aspects of study design. So looking across them as a whole, I think is -- it was very informative.

CHAIRPERSON LUDERER: Thank you. Any other comments from other panel members?

No.

All right. Then we will move on to the discussing the animal studies of neurodevelopmental outcomes. So

COMMITTEE MEMBER WOODRUFF: Do you want me to go first?

CHAIRPERSON LUDERER: No, I'm happy to go first.

So the -- so I'll be the primary discussant on this. So I think overall, just quickly again summarizing the database on the experimental animal studies of

neurodevelopment effects of exposure to cannabis or THC, it's relatively extensive, with one study in monkeys, three in mice, and 39 in rats, and four in zebrafish.

So the exposure routes included very few inhalation exposure studies. Mostly oral, which are obviously both routes that are relevant to humans, and then a number of parenteral exposures, intravenous, intraperitoneal, subcutaneous, which some of the authors argued was more relevant to inhalation exposure in humans than oral dosing would be. Of course, they did not talk about inhalation -- why they did not do inhalation however.

The -- most of these studies used the delta-9-THC. Only a few of them, three studies, and that was by the same group, exposed to cigarette smoke. And there were whole body exposures, which, as has already been discussed, may not be the best model. On the other hand, I would argue that oral exposure is quite relevant. And as many of the other panel members have already been discussing is maybe becoming more relevant with the explosion of cannabis products that we're having right now.

And then couple -- one used hashish extract and one cannabis extract. So really most of what I'm going to be saying has to do with the THC exposure, just because

that's what most of the studies utilized. So there's already been a lot said about study quality with the -- the pregnancy outcome, the developmental, non-neurodevelopmental outcomes.

And so in terms of the neurodevelopmental studies, strength of them is -- nearly all of them that you would think that this would be obvious, but of the pregnancy studies, utilized timed matings, I think I found one where they did not apparently do that, even though then they established a gestational day one.

Many studies controlled for litter size by culling, so standardizing litter size, soon after birth, which is a strength. Fewer of the prenatal exposure studies controlled for effects of the THC on maternal behavior by fostering pups to unexposed dams, but some of them did do that.

None of -- almost none of the studies, or very few of them, commented on randomization or blinding. And the N per group, in general, was small for most of these studies. This has already been commented on. Most of the studies unfortunately that were -- did not use litter as the unit of analysis or adjust for litter when exposures occurred during gestation, lactation, or even preconception.

Some studies didn't apparently adjust for

offspring, sex, or analyze male and female offspring separately. So these are broadly just some of the problems. And some studies actually only analyzed offspring of one sex.

Finally, when adult female offspring were analyzed, some of the studies utilized ovariectomy to eliminate estrous cycle related changes that would potentially confound the results.

Others tested on estrous -- the day of estrous -- of the estrous cycle, which I thought was the strongest approach, and others on random estrous cycles stages, or did not specify, which obviously those would be the weaker approaches.

So I'm going to try to focus my comments on studies that I thought were -- as others have done, that were stronger. So generally compared male and female differences, adjusted for litter, et cetera, some of the other things that I've been talking about.

And I'm going to group them I think somewhat similarly to how they were grouped in the document. So starting out with activity, locomotor activity. So multiple studies investigated motor activity, as well as exploratory behaviors. And I'm going to focus on kind of two groups of studies that came -- both came from -- appeared to be the same department and Universidad

Complutense in Madrid.

The first set of studies was those by Rubio, Navarro, and co-workers. So that was from 19 -- Rubio 1995 and '98 and Navarro '94, where pregnant Wistar rats were exposed to THC at doses of 0, 1, 5, or 20 milligram per kilogram by the oral route.

And then another one where they used hashish extract, also by the oral route. And all of these were in the same dosing interval from gestational day five to postnatal day 24.

So two of these studies do appear to be the same animals, but some -- one study only reported on postnatal day 70, where the other ones reported on earlier ages as well. In both -- in all of these studies, or most of them, they mentioned that the investigators were blinded to experimental group, and that the females were tested in the estrous stage of the estrous cycle. And they also analyzed -- did two sets of analyses at least for several of their studies, where they used pup as the unit of analysis, and then they compared the results to using litter as the unit of analysis. And they stated that the results were similar, which I thought was a strength. Although, they did not present as much detail about the litter results.

They observed effects at the 1 and 5 milligram

per kilogram doses on locomotor activity, but not the highest 20 milligram per kilogram dose. They found increased locomotor activity in both sexes at postnatal day 15 with those two doses, and in females, but not in males at postnatal day 70, and in neither sex of the intermediate ages of days 20, 30, and 40.

They also observed another behavior, which was increased rearing in males at postnatal day 20 and in both sexes at postnatal day 70.

They also did -- tested the animals in the elevated plus maze and found that males had increased exploration activity in that. And they tested emer -- used the defensive withdrawal test and found that there was decreased emergence latency in the defensive withdrawal test in that study as -- in -- as well, in Rubio et al. '98. And in contrast, the study that looked at the Hashish extract did not find effects on locomotor activity.

The same group then did another kind of group of studies that had similar strengths. And these were using lower doses of THC, so 0.1, 0.5, and 2 milligrams per kilogram, where the other study the lowest dose was one that I just talked about, those studies. And it's the same exposure window of gestational day five to postnatal day 24.

However, in this group of studies, instead of testing the females on estrous, they ovariectomized them prior to testing, which I -- and they did not state at what age or for -- how long before testing they did the ovariectomies.

In these -- in this set of studies, which was Moreno et al., 2003 and 2005 - I guess just two studies - immobility was increased and locomotion was decreased. So in contrast to the increased locomotor activity that was observed with those higher doses, they saw decreased locomotion in both sexes. And exploration was also decreased in females at postnatal day 70 with greater -- as I said, greater effects at the lower doses.

They also in this study -- these studies challenged with dopamine D2 receptor agonist apomorphine and quinpirole, and observed increased immobility in the males with that, but not in the females that were exposed to THC developmentally. And they also treated with a CB1 inhibitor, and found decreased immobility in both sexes with that treatment, but not the other -- no effects on the other endpoints.

Finally, some of these studies looked at effects on hypothalamic-pituitary-adrenal axis. And there were -- several of the studies found increased serum corticosterone concentrations in females and either

reduced or unchanged corticosterone concentrations in males. Corticotropin-releasing factor content was increased in both sexes and one -- it was measured in one of the studies, while some other pituitary hormones were not affected.

So -- and they suggested that this affect on the HPA access could be an explanation for the sex differences that they observed in these locomotor activity endpoints. So taken together, I think the results by this group seem to point to a -- potentially point to non-monotonic dose response, where we're seeing that lower -- the lower doses, less than one milligram, decreased locomotor activity during the same dosing interval, while the moderate doses increased activity. And then at the highest dose, there was no affect.

Then I just wanted to -- since that was the gestational and lactational exposure, I wanted to talk about a couple of studies that looked at other exposure windows for those same endpoints.

So there was another rat study by Silva et al. where they used and I.V. exposure to 0.15 milligrams per kilogram per day THC in Sprague-Dawley rats just during gestation, so gestation day 1 to 21, and found no effect of locomotor activity -- on locomotor activity in either male or female offspring.

In this study, they did use the analysis by litter -- the litter was the unit of analysis. And then another study that was a more recent study, where they examined the treatment of both parents during adolescence with again a parenteral route, zero or one and a half milligrams per kilogram THC during the adolescence of the parents. And then they examined the F1 offspring and it found decreased locomotor activity again. And this -- these Long Evans rats, but in the females only, kind of similar to what we saw in some of the other studies I mentioned. But they did not describe whether the litter or the offspring was the unit of analysis.

Then finally with the activity, I wanted to finish up with the three studies in zebrafish that support neurodevelopmental effects of THC, where they -- that was Ahmed 2018, Carty 2018, and Achenbach et al., 2018. And they found altered locomotor activity in all three studies. Two of them were using different loco -- assessing locomotor responses to visual stimuli. And ones -- and one study in addition also observed changes in motor neuron morphology, synaptic activity at the neuromuscular junction and different -- effects on locomotor responses to sound. So I think that those are supportive of the mammalian studies.

So then moving on to tests of cognitive function.

There were several cognitive function domains that have been studied. In general, there are not a lot of studies that use the same tests. So it's a bit difficult to compare the database that way. Kind of grouping them on what they were looking at, I'll first talk about some studies that looked at visual attention, which we've already been talking about - effects on attention in the neurodevelopmental epidemiologic data as well.

So the single primate study in the database, which was the Golub et al. study from 1981, exposed female rhesus monkeys 2.4 milligrams per kilogram per day delta-9-THC in food treats for two years before mating and then through lactation.

And they then tested the offspring at one and two years of age. And at both ages, the offspring had increased visual attention to novel images, but there was no difference based on the developmental THC exposure for familiar images compared to controls. But they did use two different tests at the two time points, and they didn't really say why they chose to do that. Maybe someone else can shed light on that.

Studies -- then there were also some studies of visual attention in rodents, also found effects. A study by Silva et al. found that offspring of both sexes exposed during gestation only to THC took more trials to complete

an attention task and completed the various phases of this task at lower rates.

And another study by Levin at al. from 2019 found that preconception exposure just to the father of -- with THC decreased both male and female offspring performance on an operant visual attention task in adulthood. So those were the attention studies.

Then there was some studies of memory. And I'm focusing on the -- on two of them, O'Shea and Mallet 2005 found that juvenile males that were exposed from postnatal day four to 14, subcutaneously to THC, had no deficits in spatial discrimination in a food-motivated double Y maze at postnatal day 56. But when the task -- the more complex task of this maze, they had decreased correct choice on the delayed alternation task, which is a test of working memory.

Similarly, in a study by Campolongo et al. from 2007, male rats were exposed to THC gestational day 15 through postnatal day nine via the mother. And they were able to learn to avoid an aversive stimulus, which was a foot shock during the training period. But then 24 hours later, they had decreased ability to remember that foot shock and therefore to avoid it.

And moreover, their short-term social memory was also impaired. And this was the -- tested by the ability

to distinguish a novel from a familiar juvenile that they had been exposed to for a five-minute training period 30 minutes later.

The next set of studies also -- these are also endpoints that were examined in the -- in the epidemiological neurobehave -- neurodevelopmental studies is increased sensitivity to drugs of abuse. And really the ones that I'm going to focus on, most of them, were on opiate self-administration. Some -- there were several studies that examined morphine self-administration and a couple that examined heroin self-administration.

So that same group from the Universidad Complutense that I had spoken about earlier found that gestational and lactational exposure during that same exposure window from gestational day five through postnatal day 24 to THC increased morphine self-administration rate when it was on a fixed ratio schedule in females only. And that means that for every push of the lever, they got the same amount of morphine. They didn't have to keep increasing their lever pushes.

But when they used a progressive ratio schedule, where they had to do more basically to get the same amount of morphine, there were no effects observed in either sex. And with the fixed ratio, it was observed in females only.

There was also an effect on conditioned place

preference testing, where -- which revealed that there was increased sensitivity to the reinforcing effects of morphine versus saline in both prenatally exposed males and females. And those were Rubio et al. 1995 and 1998. The other one was -- Vela '98 and Gonzalez 2003 were the other two studies.

And two other groups observed similar effects of exposure to THC during late gestation through adulthood. And that was Spano et al., 2007, or during the juvenile period Singh et al., 2006 on latency to heroin administration in the Spano et al. study self-administration or on heroin-induced place preference, similar to what was observed in the other studies with morphine. And that was in -- those were in male rats.

And in the Singh et al. study, they also looked at the effect of the juvenile exposure to THC on immunoreactivity of Fos in the nucleus accumbens, the amygdala, the medial caudate-putamen, and the periaqueductal gray. And they found that this was increased with the pre -- the juvenile exposure to THC. And then heroin -- the heroin self-treatment further increased Fos immunoreactivity in most of those regions as well.

And now I'm going to turn - this is kind of a segue - into effects on neuronal -- neurotransmitter

systems in different brain regions that were examined in a number of -- some of the studies that I've already talked about, as well as additional studies.

So looking at catecholaminergic systems. Two -- a study by Bonin et al. in 1996 studied the effects of five milligrams per kilogram per day THC from gestational day five until the time of euthanasia, which was done at multiple different time points. And they found that tyrosine hydroxylase expression and enzymatic activities, so rate-limiting enzyme in dopamine synthesis, were increased in female brains, gestational day 14 and gestational day 21, but not during the intervening time points or postnatal time points.

While the expression and activity were decreased in males in late gestation, gestational day 21 and postnatal day 1. They didn't observe any effects on whole brain or forebrain dopamine or norepinephrine content, which you might expect, given that there was decrease in tyrosine hydroxylase activity.

Gestational and lactational exposure to THC decreased the ratio of dopamine metabolite to dopamine in females in the nucleus accumbens and ventral tegmental area but in the basal ganglia in another study by Gonzalez et al. And gestational and lactational exposure to hashish extract also decreased the content of that same

metabolite DOPAC in the limbic forebrain in males only. And there were no effects on -- however, on limbic dopamine, tyrosine hydroxylase activity or dopamine D1 receptor binding sites in a study by Navarro et al.

Finally, there were also no effects noted on striatal dopamine recept -- D2 receptors or on tyrosine hydroxylase activity with preconception through postnatal day 21 exposure to the mother in rats, in another study Walters and Carr, 1988.

The -- there were a couple of studies that looked at the -- that also looked at the D2 dopamine receptors. So Szutorisz et al. who did peri -- periconception exposures found decreased concentrations of those -- or decreased receptor content in the dorsal striatum in adult males that were exposed pre -- periconcept -- preconceptionally, I'm sorry. And DiNieri et al, with a perinatal exposure found similar also effects on the DDR2 content in the nucleus accumbens.

There were a couple of studies that looked at norepinephrine or adrenergic signaling related endpoints. So basal levels of cortical norepinephrine were decreased in perinatally THC exposed rats in the Campolongo study, et al. that I mentioned earlier. And there was an increased binding of cortical alpha 1 adrenergic receptors, so the Bmax was increased in PND 20 -- on PND

20 in rats exposed during premating through postnatal day 20, so on the last day of dosing in that study.

So then turning to glutaminergic neurotransmitter system. So in perinatally, THC exposed male rats - this was the Campolongo study again - basal levels of cortical glutamate were decreased. And in rats that were exposed gestationally and lactationally to THC, the protein expression of glutamate transporter GLT1 and glutamate/aspartate transporter, GLAST, in synaptosomes from hippocampal slices were decreased. That was Castaldo et al., 2010. And in another study, the GLAST, the glutamate/aspartate transporter, was decreased also in cerebellum. And this was also in gestational lactational exposure. And that was Suarez et al., 2004. And that same study also found that another glutamate transporter was decreased in cerebellum and that was the EAAC1 transporter.

The Castaldo et al. study also then looked at hippo -- cultures of hippocampal slices taken from those perinatally THC exposed male rats. And they observed decreased basal and potassium evoked glutamate outflow, decreased glutamate uptake, and loss of stimulatory effect of THC on the glutamate release.

And some additional studies that also found evidence of effects of the developmental THC exposure on

the glutaminergic systems were the Szutorisz et al., 2014 study that found increased glutamate -- glutamine receptors in the nucleus accumbens on postnatal day 32 within decreases subsequently on postnatal day 62 in the dorsal striatum. And this was the preconception exposure. And they were looking at the AMPA as well as NM -- NDMA expression of those -- the genes related to those -- those receptors.

Then I'm going to spend -- say a little bit about GABAergic effects. So in postnatal day 90 hippocampal slice culture that was again similar to the Campolongo study, perinatally exposed male rats. There was decreased basal and potassium-evoked GABA outflow, as well as decreased GABA uptake, and decreased CB1 receptor Bmax.

There was also decreased potassium evoked GABA outflow in response to a THC challenge in the culture. And that was blocked by CB1 receptor antagonist showing that it was mediated by that CB1 receptor. And that was the Beggiato et al., 2017 study.

So there was then a study that tied together the -- I think was an interesting study that looked at the glutaminergic and GABAergic effects was the study of de Salas and Quiroga et al. from 2015 that investigated the roles of CB1 receptor expression in glutaminergic and GABAergic cortical neurons on the effects of a -- of three

milligram per kilogram per day exposure to THC during a window of exposure that they defined as being the active period for glutaminergic neuron generation. That was gestational day 12 and half to 16 and a half - this is in mice - on development of corticospinal motor neurons.

They found that THC exposed heterozygous CB1 receptor, heterozygous offspring - unfortunately, in this study they did not specify the sexes of the offspring they studied - had decreased cortical projection neuron development, and as well as impaired function on several skilled motor tests.

So again, kind of going back to those earlier studies of locomotor activity that we talked about per -- and decreased seizure latency, as well as increased seizure induction by exposure to a drug PTZ, while those mice that were null for the CB1 receptor had impairments, whether they were exposed to vehicle or THC during that gestational day period that looked similar to what was observed in the THC exposed heterozygous offspring, which did have the -- that CB1 receptor expression.

They also observed decreased CB1 receptor protein in the brains on gestational day 17 and a half in the THC-exposed animals, not on postnatal day 2.5. And those were the ones obviously that were not the CB1 receptor null.

They were able to rescue the effect of THC on the corticospinal motor function by expressing CB1 receptor selectively in glutaminergic cortical neurons, but not by expressing it selectively in the forebrain GABAergic neurons. So -- and that was for the motor function, the behavioral test.

But for the seizure activities, so the increased seizure activity with THC, they -- the expression of CB1 receptor in glutaminergic or GABAergic neurons, each of those partially rescued the increased THC-induced seizure sensitivity. So there was a role for both of those systems in the THC-induced seizure sensitivity. But it looked like just the glutaminergic was involved in the motor.

So I'm almost done here.

Opioidergic system. So we've already heard some things about opioid self-administration. And there were some kind of neuro -- chemical and neuroanatomic data supporting that. So in the study that I already mentioned by Spano et al. from 2007, they found that in the nucleus accumbens' shell and substantia nigra there was increased mu opioid receptor agonist-stimulated G-protein coupling, while this -- while treatment with the CB1 receptor agonist had no effect on G-protein coupling. And that was in animals that were -- again, that were exposed

gestational day five to postnatal day 62.

On postnatal day 62, they also found increased expression of proenkephalin in the nucleus accumbens and the amygdala, but in contrast to decreased expression of those in -- at post -- of proenkephalin in postnatal day two in animals exposed from gestational day five to postnatal day 62, so during exposure.

So overall, the developmental THC exposure impacts, multiple different neuronal -- neurotransmitter systems that are involved in many of the behavioral endpoints that have been measured after prenatal THC exposure. And examples include the changes in gene expression in the nucleus accumbens, which is -- which are associated with the addiction vulnerability, compulsive behaviors and reward sensitivity, as well as changes in the hippocampus that are associated with memory and learning.

So I think overall there's -- it's a broad database that has both neurochemical and neuroanatomical -- that demonstrates neurochemical and neuroanatomical effects on brain regions and neurotransmitter systems that are known to be involved in some of those behavioral endpoints that were looked at, including the -- some of the cognitive function endpoints, the increased drug sensitivity, as well as activity.

And I'll stop there.

All right. Tracy Woodruff. Dr. Woodruff.

COMMITTEE MEMBER WOODRUFF: Okay. Thank you.

That was good. You covered a lot. And so I am going to, in the interest of the thorough explanation you gave, and I just want to say I've -- I'm going to give some summary remarks and just add on to some of the things that you've said. And I, too, have read these studies.

I just want to note there were -- that you guys have identified 47 studies. So there were a lot of animal studies. And I wanted to note that the advantage of the animal studies is that they have a controlled experimental design. So this helps us look at the animal data in conjunction with the human data, which we don't have controlled experimental design.

So we have -- don't have the same issues like there may be with what was discussed about potential confounding by tobacco or other confounders. So I think that that means that the animal studies have significant advantages in that way.

I also note that we -- you talked about the experimental design of the studies. I also went through and looked at the methodological quality of the studies and evaluated them based on bias domains. And I think we looked at pretty much the same ones, two of them related

to blinding, and then reporting of data, and then one on randomization.

And I would say, because I've been on this Committee for a few years, that the quality of these studies was a little bit higher than some of the animal studies we saw. And I, in particular, want to point out that the -- I -- the lab that was in Madrid, the Navarro -- I call them the Navarro studies, because this person appeared to be -- the senior author or author on all the studies.

What I liked about them was that actually they did mention that they randomize. They also noted that they were blinded in the experimental design to -- the people who did the assessment of the behaviors were blinded and they used not a subjective measure, but they used these photocell cages for an objective measure of motor behaviors. So they didn't do a visual exam, but they actually used essentially an objective look, almost like a mechanical way to examine the outcomes. So that cluster of studies I thought I had a lot more confidence in, because of the nature of the study design.

And they did look at multiple different endpoints, but -- which you went over, and I agree with you that, in general, they saw effects of the exposure to THC.

There was something else I was going to say about them.

That was it. So -- and you covered all the outcomes.

The other thing I wanted to note was -- and this I think would be helpful in the future is that there were studies that were coded in different areas that looked at this passive avoidance test that was covered in six of the animal studies. And the passive avoidance is -- is essentially -- it sounds so much nicer when I say passive avoidance. But what they have is two rooms and they -- the animal goes into another room and they shock it. And then they go back and then they either see whether they learn to remember the shock that they got when they went into that room. That's a general layperson's discussion of that outcome, because I've not done the test myself, but I read about it.

But it's -- it was interesting, because it's a cog -- a measure of cognitive performance in learning and memory. And one of the things that's been noted is that it declines -- the latency declines with increasing latency between acquisition and retrieval. And that basically, it gets worse as animals get older. So it gets worse as -- if -- as a -- could be a measure of effects of THC.

And I will note that the -- there were these six studies that looked at this, albeit in many different situations and at different time points. Some of the studies -- I just want to say some -- it's interesting, because some of these studies are quite old and some of them are newer. And so that sometimes affects the qualities of -- quality of the studies.

So the studies were Vardaris. It was a 1976 study. And what was -- I thought was interesting was that they saw an effect on this cross-over. And actually, I didn't really -- the write-up in the tables didn't seem to reflect the -- actually going back to the paper, which was that they found a significant effect on the time difference between the THC and the placebo-exposed animals.

There was then the Silva study, which you mentioned, which has exposures by IV during gestation. They evaluated the animals at postnatal day 50. And they saw a decline in the number of entries between the THC and the vehicles again for the shock avoidance test.

I thought the most probably compelling one was the Campolongo, which you talked about as well. I think you talked more about the neurochemical findings in that study. But they also looked at this shock avoidance test. And again, the avoidance latency went down in the animals

that were exposed prenatally to THC, indicating that they probably didn't learn that there was a shock in the room. And so again is an indication of development of cognition.

The other two studies that looked at this were the Abel studies. I don't think you mentioned these. I didn't think -- these were done in 1990, and they had exposures at gestational day six. But their measurements of the -- of the shock avoidance test were at postnatal day 16 to 17. So it was a little bit earlier than the other ones, which tended to be around 50, 70, or postnatal day 80.

And they did, in one study, see a relationship, meaning the shorter time period, for the animals that were exposed to THC compared to the non-exposed. But in the other study they didn't appear to see an effect.

But I thought that the -- essentially looking at those endpoints together was very helpful, because I was -- you're able to see that you could compare this endpoint that was the same type of measurement across multiple studies, which I think added, because they were seeing a similar effect across different labs and study design -- not study designs, but different experimental locations added more strength to the finding that THC developmental exposures was affecting neurodevelopment in the animals.

And I don't think I have anything else.

No, you went over all the other studies -- the relevance of the other studies, so that's it.

CHAIRPERSON LUDERER: Thank you, Dr. Woodruff.

Do we have any questions or comments from other Panel members on those sets of studies?

No. All right. Then we will continue with our -- the mechanistic studies. And the primary discussant for those is Dr. Allard.

COMMITTEE MEMBER ALLARD: All right. Thank you very much.

So I just want to start by saying how I approached looking at the mechanistic studies. The way I looked at them was to really provide a foundation and really biological plausibility to what has been observed in human studies or not observed in human studies, and also, to some extent, in animal studies.

So what that meant is that I actually mechanistically did not consider, although I did read all the information the changes in bone length, for example, or the very nice series of experiments that looked at early embryonic effects, meaning like -- rate of blastocyst formation, oviductal transport, or implantation. There was a beautiful series of experiments in animal studies. But these were either not examined in

human studies or not replicated.

I also -- although, I am an epigeneticist, I did find all these results -- epigenetic results very compelling. And I am actually glad that this is included now as important pieces of information. But those were mostly associations and not -- there was no causation established, at least that I could find. So I did think that this was something to keep in mind, especially when we think about long-term effects, but not something that could be innocently informative.

So what I thought was compelling the results that were on the neurodevelopmental side, both on the human side and animal side, where from my reading of the literature seemed to actually align very well. And this is where really I thought there was also compelling mechanistic data that provided biological plausibility.

So I think Dr. Luderer actually already alluded to quite a bit of what I was going to say. So what we already heard was that actually many different types of neurotransmitters are affected by the endocannabinoid system that we knew. And also -- through the studies, we also know that delta-9-THC also affects the production of those neurotransmitters.

So we -- I'm going to try to summarize -- I had longer remarks, but I'm going to try to summarize a little

bit.

So we know that delta-9-THC acts through CB1R, in particular in the nervous system. That it does to add -- act - sorry - presynaptically, both at inhibitory and excitatory synapses. So either affecting the GABAergic system or the glutamatergic system. And that, in general, just, because this was already alluded to, seems to decrease the production or signaling of glutamate. So the -- one of the major mode of neuronal excitation or the production or signaling of GABA, so one of the main mode of inhibition.

We know that the endocannabinoids fulfill that function, and that delta-9-THC -- and there's a series of studies that show that also can have the similar effects. So one study in particular, Beggiato et al. from 2017 shows that there -- for example, the effect of delta-9-THC on the reduction of GABA is actually indeed mediated by CB1R.

And so it's important to think that it's not just these two neurotransmitters. We also know of the effect on the dopaminergic system. Although that literature is a bit more -- I would say it's dense, because, we -- the literature, in general, as reviewed by Bloomfield in 2016 tends to show that there's increased dopaminergic signaling going on. But this seems to be exposure dose

and location dependent, because early on during life, so including during gestation, you can actually see downregulation of some of the components of dopaminergic signaling, such as, for example, in a DiNieri at al. paper in 2011, a downregulation of DRD2 in human ventral striatum in people who've taken cannabis. So the effect on the dopaminergic system can go in either direction.

I think it's also really important to think about -- mechanistically speaking, about the fact that chronic exposure to a ligand to -- to those cannabinoid receptors can actually ultimately lead to the downregulation of those receptors. That's pretty well established.

This has been shown in human, ... et al. in 2012, for example, showed that -- and this is really, I think, critical to think about, because that will obviously perturb the normal action of endocannabinoids, which they won't be able to fulfill the -- as I just said, their normal course of action.

So I guess I did not necessarily say that it's also interesting to think that delta-9-THC is a partial agonist of cannabinoid receptors, so it's not -- it's not a full agonist. And that in itself can have interesting distinctions from either synthetic cannabinoids or endogenous cannabinoids, but it still seems to have pretty

high affinity for the C1BR receptor.

So why is this all important to think about? Why is this really lending support to biological plausibility for these neurodevelopmental effects that we've been hearing about?

Well, that's because we know that the -- of course, we all know that the development of the nervous system is highly dynamic, that it goes through critical phases of development. And it's significant, because alteration of several of the signalings that we're talking about, whether it is glutamatergic or GABAergic is very important, because, for example, with GABAergic system, we know that GABAergic signaling regulates not just the function and inhibition specifically of neurons, but also many effects of those neurons biology from -- from their differentiation to function, and ultimately all affect plasticity, and therefore memory.

So I've not necessarily -- have a long explanation about the formation of memory here, and long-term potentiation, for example, but all these systems that I've described are critical for memory for -- and for neuronal plasticity. And the effects of delta-9-THC on the systems is highly concerning from that perspective.

So this is where I'm going to stop at this time.

CHAIRPERSON LUDERER: Thank you very much, Dr.

Allard. And our secondary discussant on this topic is Dr. Baskin.

COMMITTEE MEMBER BASKIN: Thank you, Patrick, for that excellent summary and also the scientists who put together an incredible packet.

I'll be reasonably brief. I think the question that Patrick and I were kind of asked to address is does any of these epidemiologic, as well as animal studies, make sense in terms of the basic science? And it seems pretty clear from the papers that I read that I would react in the positive.

The endocannabinoid system, of course, is a system that exists in our bodies. It's -- and it's very well defined. I'll quote our scientist in that they labeled it the gateway of neuronal development. And I think one of the key points is that the receptors are basically all over the brain, in particular, as well as in the nervous system. So without the receptor, you really can't have any type of significant reaction. They're expressed both in the fetal and the adult brain. And one of the big breakthroughs was this idea of retrograde signaling defined in 2001, which really allowed the study of the direct effect of the ligand on the receptor, which seems to modulate not only cell proliferation, differentiation, migration of the cell, cell death, that

there is an impact directly on neuronal structure, which relates obviously to memory and motor function.

The receptors that were influenced are the ones that at least I've heard of. So that was kind of good news, dopamine, serotonin, norepinephrine, acetylcholine. And all of these can be regulated by endogenous action, as well, of course, marijuana or synthetic marijuana.

So taken as a whole, it seemed quite plausible that there was good basic science or relevance to what we're seeing specifically in the papers related to neurologic issues. And I would point your attention in our nice packet to the Figure 11 by Andersen in 2013, which nicely highlights the stages of development, the stages of the different windows of vulnerability -- I forget the page number, but I think we've all kind of seen this -- showing exposures to the cannabinoid agonist really can directly impact neurologic function, such as memory and learning, which is consistent with some of the prospective studies that we saw.

There were three papers in particular that I thought were especially noteworthy. The Keimpema paper -- I'm not pronouncing their name right -- in 2011, the Kano paper in 2009, and the Andersen paper in 2003.

So taken as a whole, I would just reiterate that there's quite relevant basic science behind some of the

things that we appear to be seeing clinically in humans, as well as in the animal studies.

CHAIRPERSON LUDERER: Thank you very much. Do we have any comments or questions related to those last two presentations? And I know we do need to take a break for our transcriptionist, which I'm sorry that we have forced you to do this for so long without a break.

Yes. Dr. Hertz-Piccioto.

COMMITTEE MEMBER HERTZ-PICCIOTTO: Yeah. I was just wondering in one of the epidemiological studies there was mention of the -- and maybe somebody said this and I missed it today, but -- that fetus -- that the fetus and infant actually may have far more of the endocannabinoid receptors in their brain, their nervous system than the adults.

It was sort of mentioned in the discussion. I didn't see any citations with it, but I just wondered if that's -- if there appears to be data on that, or is that -- was that speculation, just curious?

COMMITTEE MEMBER BASKIN: I think Tracey had mentioned that there was more fat in the fetal brain.

COMMITTEE MEMBER WOODRUFF: Right, more lipid. That's what I -- but I don't know if there's more -- I don't know.

COMMITTEE MEMBER HERTZ-PICCIOTTO: Yeah, but

that's -- that's -- that's about retaining --

COMMITTEE MEMBER WOODRUFF: Right.

COMMITTEE MEMBER HERTZ-PICCIOTTO: The lipids are about retaining the actual compounds.

COMMITTEE MEMBER WOODRUFF: Right, it's about the exposure. Right.

COMMITTEE MEMBER HERTZ-PICCIOTTO: But I was -- I was thinking in terms of the developmental aspect of the brain.

COMMITTEE MEMBER BASKIN: I don't recall -- recall the quantitation between the fetus and the brain, other than -- the fetus and the adult other than that it was ubiquitously expressed.

COMMITTEE MEMBER ALLARD: No. What -- the same deal, I do not recall a question of quantitation of the amount of receptors. What really permeated through the animal studies and some human studies -- although the human studies that I remember are not fetal. But anyway, it's highly stage-specific and region-specific expression. So it's very, very dynamic expression of the receptors that tend to change quite a bit as you progress through development.

COMMITTEE MEMBER WOODRUFF: I think, right, this is what you were -- somebody -- I can't remember who said this, said that it was very important that this -- there's

something unique about the CB1Rs in brain development, not necessarily that there are more or less of them, right?

COMMITTEE MEMBER ALLARD: So CB1R is highly expressed in the brain. Although, the other receptors tend to also be expressed in the brain but at slightly lower levels. Correct me if I'm wrong with that, but --

COMMITTEE MEMBER WOODRUFF: That's what --

COMMITTEE MEMBER ALLARD: Right.

COMMITTEE MEMBER WOODRUFF: Maybe you said that in your presentation, I think.

COMMITTEE MEMBER ALLARD: And THC -- delta-9-THC has a higher affinity for CB1R. I'm trying to remember the levels now, but I think it's double the affinity than for CB2R.

COMMITTEE MEMBER WOODRUFF: Right. So it might not be amount, but it's more around -- related to activity, right, is that what -- I think was it you that said this?

DR. NIKNAM: Yes.

COMMITTEE MEMBER WOODRUFF: I'm sorry, I can't -- I can't see, because these are not the right glasses.

DR. NIKNAM: During development, there tends to be a switch from the CB2 receptor to CB1R receptor expression. And that's very different than the adult.

COMMITTEE MEMBER WOODRUFF: Right. Thank you.

CHAIRPERSON LUDERER: All right. Thank you. Now, we will take our ten minute break. So we'll reconvene at about, oh, I guess, we can say ten after 3:00.

(Off record: 2:57 p.m.)

(Thereupon a recess was taken.)

(On record: 3:13 p.m.)

CHAIRPERSON LUDERER: All right. Okay. Is this on?

Yes, it is.

All right. I'd like to reconvene.

The -- we next -- next item on our agenda is we have time now for some public comments. And we've received requests for public comments from two people. I don't think there have been any additional ones that came in. The first person is Ellen Komp from California NORML.

MS. KOMP: Hello. Yeah.

Hi. My name is Ellen Komp. I'm Deputy Director of California NORML, the State Chapter of the National Organization for the Reform of Marijuana Laws.

Cal NORML has advocated for consumer safety and science-based regulations for cannabis since 1972. And I have a degree in biochemistry from Penn State. So although you might think I'm just a crazy zealot, I actually have great respect for science. And I appreciate

all the effort the Committee and the staff has put into today's hearing.

It is NORML's position that existing scientific evidence on the reproductive risks of prenatal cannabis use is insufficient to warrant a Prop 65 warning. To date, the only human studies that have been conducted involve women who smoked cannabis during pregnancy, meaning we have data on cannabis smoke, but not on THC or any other cannabinoid or terpene in humans, nor do we have studies on cannabis that is vaporized or taken orally, topically, et cetera during pregnancy in women.

Studies that have looked at cannabis smoking and pregnancy have, as we have seen today, produced conflicting results. One thing that I haven't seen mentioned as a -- very much as a conflicting -- or, you know, a -- sorry, it's been a long day for me too -- as a, you know, concomitant factor is socioeconomic factors.

In the studies I've look at, they all talk about this at great length and sometimes they try to match mothers and things. But this is something that I think should be looked at more carefully. It's funny that the 1994 March of Dimes funded study in Jamaica was mentioned. That is often always misreported as finding no difference between babies born to women who use cannabis and those who didn't.

Actually, at 30 days, when the Brazelton method is probably more useful, it found that babies born to mothers who use marijuana had superior scores in some of Brazelton measures. And, in fact, the women who used the most cannabis, their children had the highest scores. And this was related to perhaps some of the socioeconomic factors around this.

Also, the mothers didn't have other polydrug use. They found that it helped their eating and there was less societal sanction against it.

As far as the animal studies -- oh, and what I wanted to say about that Jamaican study is there was a five-year follow-up, which found again no change or positive results, but NIDA would not fund a further follow-up study. And this points out a factor that's been going on. NIDA is always ready to fund studies that look for negative effects of marijuana and positive effects are hardly ever reported or studied. And this could be one reason why a lot of the early animal studies have concentrations maybe 300 times the adult dose of cannabis, which we figure is about maybe 0.4 milligrams per kilogram.

So I heard studies talked about -- the animal studies -- none of the studies on the zebrafish, on cognitive function, on visual attention, on memory, on

opiate self-administration, on immunoreactivity, I didn't hear anything about the dosage of cannabis in that. And I ask you to look very carefully at the animal studies and the dosage.

Some of the later studies maybe -- there was one that came in at the right Moreno et al. from 2003. But some of the earlier ones, like Rubin et cetera, were way off base. And so I think those really need to be re-examined.

Also not mentioned was the 2017 NAS comprehensive report, which concluded that -- you know, National Academy of Science reviewed all existing evidence. They concluded smoking cannabis during pregnancy is linked to lower birth weight in offspring. I would look at how much lower. The relationship between smoking cannabis during pregnancy and other pregnancy and childhood outcomes is unclear, the NAS concluded in 2017.

Also not mentioned was a 2018 Population Study CO that found marijuana use during pregnancy was not independently associated with infant birth weight or gestational age. That's on your list of excluded studies. I don't know why.

In any case, Prop 65 warnings are unnecessary, because warnings are already required by current Department of Public Health regulations. All licensed

cannabis products in California, whether intended to be smoked, vaporized, or taken orally are currently neighbor -- labeled quote, "Cannabis use while pregnant or breastfeeding may be harmful".

These CDPH warnings are similar to the Surgeon General warnings on packages of cigarettes or alcohol, which do not contain extra and potentially repetitive confusing Prop 65 warnings.

Marinol which is approved by FDA, it's an oral THC. Sorry, I thought I had that here. What Marinol says is in the patient pamphlet -- sorry, I've lost that. But it does not say that -- it does say don't use it while pregnant, but It does not say that there is any connection between reproductive effects. And in fact, it mentions several of the -- three of the rat studies -- or rodent studies that were mentioned here today as proving that it does not necessarily have those effects. So that's a federal agency, the FDA. I would look at that as well.

I think the Committee really needs to look harder at this right now. We're in situation with the cannabis industry where overregulation and the cost of that is causing people to go to black market for unlicensed untested products. And we have a current public health crisis on our hands with unlicensed vapes causing lung injury and death.

And we really need to look hard at where we're going with this. I know you're only supposed to look at the science and not even think about the labeling, but I think you need to do it with that in mind, as well as the fact that marijuana policy at times even separates children from their mothers unnecessarily, because of bad science.

So thanks a lot for your time. I'm always available for any questions.

Thanks.

CHAIRPERSON LUDERER: Thank you very much for those comments.

Our second commenter is Mr. Dale Gieringer. I can't --

DR. GIERINGER: I'm just following up on Ellen's comments a little bit. I just did want to emphasize, first of all, that cannabis smoke and THC are different things. Cannabis smoke has hundreds even thousands of chemicals in it. THC is a single chemical. All of our epidemiological evidence in human beings comes from cannabis smoking.

There have never been any epidemiological studies on reproductive effects or most any other effects from oral THC, or topicals, or other vari -- other cannabinoids that sometimes get in cannabis and so forth. So I think

that distinction needs to be noted clearly here.

But in any case, the epidemiological evidence that we do have from the women who smoke marijuana seems to go two different ways. We've got different studies with different results. I just want to quote from Prop 65 itself the voters intent where it says, "A chemical is known to the State to cause cancer or reproductive toxicity within the meaning of this chapter if, in the opinion of the State's qualified experts, it has been clearly shown through scientifically valid testing, according to generally accepted principles to cause cancer or reproductive toxicity". I don't think there's any clear showing of anything here.

As Ellen pointed out, the industry already is required under State law to give a warning about possible -- a warning to pregnant women about possible reproductive risks. Another warning out there is just going to complicate and confuse things further. I would urge the Committee to defer and wait for further evidence to accumulate on this.

Thank you.

CHAIRPERSON LUDERER: All right.

Thank you very much for those comments.

Did we get any additional requests for public comments?

No. All right. Thank you.

We did have a few clarifying questions that -- one that I raised and -- where I was asking about the rhesus monkey study as to whether -- why two different tests were chosen at the two different ages. And Dr. Golub, the author of that study, is here to actually answer that question.

So, Dr. Golub.

DR. GOLUB: Yes. I'm Mari Golub. And I'm currently working as a retiree here at OEHHA. This study was done in the 1970s. And, of course, I don't remember. So I looked it up while we -- while you were talking. And we began assessing the animals when they were very young with the puzzle solving test and a response to visual and auditory stimulation. That's when we noticed that they had the prolonged attention.

So on the second study, we used a technique that provided more detailed data, as far as visual attention in a structured situation that was devoted specifically to that. So that was basically the reasoning.

CHAIRPERSON LUDERER: Thank you.

COMMITTEE MEMBER WOODRUFF: That was the study that was in the packet?

CHAIRPERSON LUDERER: Yes.

COMMITTEE MEMBER WOODRUFF: Right. Could you

talk about the findings in the study that was sent to us in email that we found that was referenced in that study, the behavioral mother-in -- mother-infant interaction from the THC treatment?

DR. GOLUB: Right, that was the same infants.

COMMITTEE MEMBER WOODRUFF: The same infants. But you found a difference in the mother behavior interactions, is that right?

DR. GOLUB: Right. So at a certain age in monkeys, the infants start leaving the mothers. And so that's sort of a critical period in the mother-infant interaction. And we found some differences at that time period. I don't recall right away what the endpoint was. Do you have that in front of you?

COMMITTEE MEMBER WOODRUFF: Percent of non-social behaviors initiated by the mother. Percent of total time. Number of behaviors initiated per hour in terms of mother and infants social and negative behaviors.

DR. GOLUB: Right. So one of the questions at that separation period is whether it's initiated most by the mother or by the infant. And I think those measures were reflecting that who initiated the separations during that time period when they being separated.

COMMITTEE MEMBER WOODRUFF: All right. Thank you.

DR. GOLUB: So that's all the information that we have. It's just -- just, you know, a dip into mother-infant interaction. And I didn't see any human information on that. So difficult to know what the relevance would be.

CHAIRPERSON LUDERER: Thank you.

It's not often that the author can provide answers --

(Laughter.)

CHAIRPERSON LUDERER: -- immediately like that.

So the other question was regarding the timing of bone development in humans versus rodents. We had a bit of a discussion about whether the five -- I think it was postnatal week five to ten in that -- the rodent study that was presented, whether that exposure would be relevant to in utero exposure in a human pregnancy, which is what Prop 65 is intended to address.

DR. CAMPBELL: I don't know that -- we don't have the information to just say that yes or no. We -- you know, what I did find was that they say sometimes you start to see the epiphyseal plates, the secondary centers of ossification that are going to be the epiphyses starting to develop prenatally in humans. But I got the impression it wasn't always. And I don't even have quantitative information on that. In mice, you don't.

So it is indirect evidence that there could be effect prenatally, because we know the process carries on. You know, it does -- it's not going to really change, but we don't have any direct evidence that that happens.

We don't have anything where they even measured bone length or even crown-rump length in, you know, the animal fetuses when they evaluated them.

So that's all I can tell you really.

CHAIRPERSON LUDERER: Okay. So it may be relevant, but we're not really sure.

DR. CAMPBELL: Yeah. They picked -- they picked the period of most rapid bone growth, so if there was an effect, they would be sure to see it.

CHAIRPERSON LUDERER: Did have a follow-up question?

COMMITTEE MEMBER AUYEUNG-KIM: No.

CHAIRPERSON LUDERER: Okay.

All right. We have time for additional panel discussion. Are there any other -- Dr. Nazmi.

COMMITTEE MEMBER NAZMI: You know, I think it -- I think it came up during the presentations at least twice. But the folks from NORML also bring up the issue of the component that we're looking at THC in isolation versus THC as ingested especially in the human studies that I reviewed. Many of them, as you all indicated,

were -- the exposure was I believe in all of the studies for the humans, marijuana, in other words, THC smoke, which maybe I'd like to bring back to the Committee to see if anybody has any comments on how that might impact our interpretation of the findings that THC, you know, delta-9 in isolation versus THC smoke as ingested, you know, conventionally is the -- is the outcome that we have been -- that we have been discussing, if that's -- is that clear what I'm saying?

CHAIRPERSON LUDERER: Yes. And I just -- I don't think I mentioned this earlier, but we are going to be vote -- have to vote separately on cannabis smoke and delta-9-THC. So we don't have to come to the same conclusion about those two.

COMMITTEE MEMBER NAZMI: Okay. Okay. I did not know that.

CHAIRPERSON LUDERER: I should have mentioned that at the beginning.

COMMITTEE MEMBER HERTZ-PICCIOTTO: Is that true? I'm sorry. I didn't have the wording in front of me, but it says cannabis smoke or it just says cannabis?

CHIEF COUNSEL MONAHAN CUMMINGS: It's cannabis smoke.

CHAIRPERSON LUDERER: Yeah, but cannabis and -- but we vote separately on cannabis versus delta-9-THC.

COMMITTEE MEMBER HERTZ-PICCIOTTO: Right.

DR. SANDY: Cannabis smoke.

CHAIRPERSON LUDERER: Oh, it is cannabis smoke. Okay. Then I was correct.

COMMITTEE MEMBER HERTZ-PICCIOTTO: Okay. Okay.

Well, I'm just -- in terms of the actual wording in our charge, I just want to make sure the charge is about the cannabis smoke, if -- and where -- I want -- where does it say that? Oh, it does say smoke on the front of the document.

CHAIRPERSON LUDERER: The title.

COMMITTEE MEMBER HERTZ-PICCIOTTO: Yes. Okay. All right. It is important. I mean, this is a legal document. And so you have to kind of pretend you're a lawyer when you --

DR. SANDY: If I may --

CHAIRPERSON LUDERER: Yes.

DR. SANDY: -- say it says it's the name -- it's the title of the document. It's also in the preface saying that you were bringing cannabis smoke and delta-9-THC and in my introductory remarks this morning.

CHAIRPERSON LUDERER: Any additional discussion comments from panel members?

Patrick

COMMITTEE MEMBER ALLARD: Yeah. I have been

thinking also about this, the distinction between the smoke, especially when you hear, you know, about the number of chemicals, non-cannabinoids and cannabinoids, there's a high number of chemicals, right. So you can think about synergistic effects or inhibitory effects between the different ones.

But purely from the part -- the job that I had today from the biological plausibility perspective, both aspects independently have been sort of well described in the literature. And, I mean, definitely from the delta-9-THC perspective, there's quite a bit of literature that specifically mechanistically looked at that in isolation. But there's also some studies that have looked at, through inhalation, that we -- you know, we -- Dr. Luderer discussed as well that have looked at that.

So from a biological plausibility perspective, not thinking about the human epidemiological studies, from that perspective, the weight of evidence would look at those two things going in the same directions.

COMMITTEE MEMBER HERTZ-PICCIOTTO: What do you mean by going in the same directions? That seems vague to me.

COMMITTEE MEMBER ALLARD: Right. So meaning that they both seem to be showing a reduction in GABAergic and glutamatergic signaling.

CHAIRPERSON LUDERER: Dr. Woodruff.

COMMITTEE MEMBER WOODRUFF: Yeah, I wanted to follow up on that, because one of the comments that I was going to make that I didn't make was that there are -- in the smoking, there's a list in this document of all the different chemicals that are in the smoke. And many of them are already known by the State -- and -- by the State of California to be developmental reproductive toxicants and carcinogens. So I think that is an important element that adds to the combination with the THC and exposure.

Also, there is a discussion in the document about the pharmacokinetic studies that have been done in humans showing that the THC is absorbed through the lungs after the smoking occurs. So to me that indicates that there -- similar to what Dr. Allard is saying is that the effects that we see are going to be similar, whether they're directly exposed animal studies, we can infer that the humans will be getting that exposure to THC when they are smoking. Well, actually, the data show that that is to be true.

CHAIRPERSON LUDERER: And kind of a related comment that we know that in the cannabis compared to when most of these human epidemiological studies were done that we reviewed the con -- THC content of cannabis has gone up quite several-fold, I believe.

MS. KOMP: Can I say something about that?

CHIEF COUNSEL MONAHAN CUMMINGS: Excuse me, there was already a public comment period.

MS. KOMP: You wore me down, but if you -- if it's strong, you just smoke less.

CHIEF COUNSEL MONAHAN CUMMINGS: Excuse me. Excuse me, the public comment period is over.

CHAIRPERSON LUDERER: All right. Any other comments, thoughts from the panel?

COMMITTEE MEMBER HERTZ-PICCIOTTO: Does anybody want to clarify on the issue of the doses in the animal studies. And, I mean, I would love to see a comparison of that with doses that are today's kinds of doses that people --

COMMITTEE MEMBER WOODRUFF: Well --

COMMITTEE MEMBER HERTZ-PICCIOTTO: If there are any -- just even -- or there are -- obviously --

COMMITTEE MEMBER WOODRUFF: No. I mean, there were comments in the papers -- I don't know if you want to comment on this, Ulrike. But there were -- and I'm -- was trying to go through and find, because I made notes on this. But there were a number of the studies that actually designed their dosage to be similar to moderate use of THC. And these are older studies, so it probably doesn't reflect more current exposures or current THC

contents that we have reviewed. So I'd have to go back and find -- but there were the animal studies.

And I think the Navarro studies in particular were paying attention to making sure that --

CHAIRPERSON LUDERER: Right.

COMMITTEE MEMBER WOODRUFF: -- their doses were similar to moderate use of cannabis.

CHIEF COUNSEL MONAHAN CUMMINGS: Excuse me. This is --

COMMITTEE MEMBER HERTZ-PICCIOTTO: When were the Navarro studies?

COMMITTEE MEMBER WOODRUFF: Those studies were started in the -- 1995 and went all the way up to Moreno, which went to 2005. So they had a series of studies. That's one -- I think there were six. One, two, three, four, five, six studies.

CHAIRPERSON LUDERER: Other comments, thoughts?

If not, then I -- Yes, Dr. Nazmi.

COMMITTEE MEMBER NAZMI: I wonder if Dr. Zeise might just be explicit in exactly what -- what the points are that we're going to vote on, just to kind of try to disambiguate the smoke versus the THC, et cetera.

DIRECTOR ZEISE: So the two agents are cannabis(marijuana) smoke is the first one. And the second one is delta-9-tetrahydrocannabinol(delta-9-THC).

So those are the two.

COMMITTEE MEMBER NAZMI: My question was whether that's going to be stratified by human versus -- there's one endpoint that we're voting on today, right, only?

DIRECTOR ZEISE: Correct. There is one -- it would be on each substance you would vote whether or not it has been clearly shown --

COMMITTEE MEMBER NAZMI: Got it.

DIRECTOR ZEISE: -- taking into account the evidence -- the spectrum of evidence that you have looked at.

CHIEF COUNSEL MONAHAN CUMMINGS: Excuse me. This is Carol. Two -- two comments on that. The one being that under Prop 65, you don't have to find that there's human evidence of the effect of a chemical. It's just evidence. And so that could be, you know, exclusively on animal data, although you've got human data here that you can consider certainly.

And then the question about dose, generally, we don't consider whether or not the current exposures are high enough to cause the effects. What you're looking for is a scientific decision on whether or not the chemical causes the effect. And then we deal with the dose level later, you know, say when we're setting a safe harbor level, or looking at safe use determination, or something,

we can look at dose then.

COMMITTEE MEMBER ALLARD: Right.

COMMITTEE MEMBER HERTZ-PICCIOTTO: This is equivalent to a half --

COMMITTEE MEMBER ALLARD: It's hazard versus risk, right? That's what --

COMMITTEE MEMBER HERTZ-PICCIOTTO: Hazard, yeah, right.

CHIEF COUNSEL MONAHAN CUMMINGS: Correct.

CHAIRPERSON LUDERER: All right. Then are we all ready to vote?

COMMITTEE MEMBER WOODRUFF: Can I ask one more question?

CHAIRPERSON LUDERER: Yes.

COMMITTEE MEMBER WOODRUFF: We're going to do -- can you just -- the endpoints -- are we going to do the endpoints different or are we just going to do it as a whole?

CHAIRPERSON LUDERER: Just as a whole.

COMMITTEE MEMBER WOODRUFF: Okay. Thank you. Sorry. Right. I knew that. Sorry. I just was -- I was -- I forgot we didn't do the male and female reproductive endpoints.

COMMITTEE MEMBER BASKIN: Correct.

COMMITTEE MEMBER WOODRUFF: Thanks.

CHAIRPERSON LUDERER: We -- it might be useful for the -- either as we're voting to state what your reasons were or we could discuss that beforehand. It was just suggested.

COMMITTEE MEMBER WOODRUFF: Who suggested that?

CHAIRPERSON LUDERER: Panel member by panel member.

COMMITTEE MEMBER WOODRUFF: Was that Lauren's suggestion?

COMMITTEE MEMBER BASKIN: That's -- I mean, I thought the reasons were we felt there was scientific evidence.

(Laughter.)

COMMITTEE MEMBER WOODRUFF: That is my reason.

CHAIRPERSON LUDERER: For a summary of what our speech about the scientific evidence was.

COMMITTEE MEMBER HERTZ-PICCIOTTO: Talk about which evidence we found compelling, is that --

CHAIRPERSON LUDERER: Yeah.

COMMITTEE MEMBER WOODRUFF: I'm sorry. Can you -- didn't we -- I mean, it seems like everyone summarized what their thinking was on it. So just for clarity, is this --

CHAIRPERSON LUDERER: I agree, yes.

COMMITTEE MEMBER WOODRUFF: Is this Lauren who

wants this? I'll do it for you Lauren. That's fine, but...

(Laughter.)

DIRECTOR ZEISE: You know, it's up to you as you're voting, if you want to say something or not. It's entirely up to you.

COMMITTEE MEMBER WOODRUFF: Okay. Okay. Okay. Thank you for clarifying that.

CHAIRPERSON LUDERER: All right then, as was discussed, there are two separate votes that we have to take. I will start with the first one, which is we have to decide to vote yes or no to this question: Has cannabis(marijuana) smoke been clearly shown through scientific valid testing, according to generally accepted principles to cause developmental toxicity?

All right. So starting with Dr. Woodruff?

COMMITTEE MEMBER WOODRUFF: Okay. So which one are we doing first, the smoke?

CHAIRPERSON LUDERER: Cannabis smoke.

COMMITTEE MEMBER WOODRUFF: Okay. Well, I'm -- I am going to vote yes, because of the biological mechanistic data that has been presented. The human evidence I agree is un -- has some variability, but it is consistent with the animal evidence that was presented, particularly for neurodevelopmental effects. And I found

the bone -- the discussion about the effects on bone growth particularly compelling.

COMMITTEE MEMBER BASKIN: Yes.

CHAIRPERSON LUDERER: Dr. Hertz-Piccioto.

COMMITTEE MEMBER HERTZ-PICCIOTTO: I'm undecided. I think I'm going to abstain at the moment.

CHAIRPERSON LUDERER: All right. Abstain.

COMMITTEE MEMBER HERTZ-PICCIOTTO: By the end I might change my mind.

COMMITTEE MEMBER CARMICHAEL: I'm saying yes for similar reasons as Dr. Woodruff, plus the analogy with tobacco smoke.

CHAIRPERSON LUDERER: I say yes for those same reasons.

COMMITTEE MEMBER NAZMI: I would agree yes for cannabis smoke.

COMMITTEE MEMBER BRETON: I'll just use the same one.

Yes.

COMMITTEE MEMBER AUYEUNG-KIM: Yes, based on the smoke.

COMMITTEE MEMBER ALLARD: Yes, as well, based on the alignment of biological plausibility data, mechanistic -- also mechanistic data, animal data, and human data for the neurodevelopmental endpoints.

COMMITTEE MEMBER HERTZ-PICCIOTTO: Actually, I realized that it's not logical, given that there's already compounds within smoke that are already listed that you have to basically -- the hazard is there. That's -- that's evidence in that -- under this mechanism and...

CHAIRPERSON LUDERER: So yes.

COMMITTEE MEMBER HERTZ-PICCIOTTO: So it's a yes. I've changed my vote to a yes.

CHAIRPERSON LUDERER: All right. So that was unanimous yes vote.

So then we'll be moving on to the next question is has delta-9-tetrahydrocannabinol, Delta-9-THC been clearly shown through scientifically valid testing, according to generally accepted principles to cause developmental toxicity?

We'll start with Dr. Allard.

COMMITTEE MEMBER ALLARD: Yes, and for the same reasons as mentioned before. But those apply to delta-9-THC as well.

COMMITTEE MEMBER AUYEUNG-KIM: I vote yes as well for the same reasons.

COMMITTEE MEMBER BRETON: Yes.

COMMITTEE MEMBER NAZMI: I would vote no for -- citing lack of evidence on specificity of THC, delta-9.

CHAIRPERSON LUDERER: I vote yes for the reasons

that were already discussed.

COMMITTEE MEMBER CARMICHAEL: Yes.

COMMITTEE MEMBER HERTZ-PICCIOTTO: Yes.

COMMITTEE MEMBER BASKIN: Yes.

COMMITTEE MEMBER WOODRUFF: Yes.

CHAIRPERSON LUDERER: Okay. So one no and eight yes votes.

All right. So that concludes our discussion of cannabis smoke and delta-9-THC.

And we have some staff updates next.

CHIEF COUNSEL MONAHAN CUMMINGS: Actually, I'm sorry, but we have the Section 2700[SIC]item. It's just a consent item.

CHAIRPERSON LUDERER: Oh. Okay. Sorry. Yeah, I skipped the consent item. Pardon me. There's a consent item, which is update of Section 27000 regulations that list chemicals requiring testing by federal and State. And Carol Monahan Cummings will be presenting that. Sorry about that.

(Thereupon an overhead presentation was presented as follows.)

CHIEF COUNSEL MONAHAN CUMMINGS: That's okay.

This is quick. So this a consent item for the Committee. We provided you with a staff report and recommendation on November the 22nd. I hope all of you

have had a chance to look at it. The report summarizes information received from other relevant entities. The staff report we sent you looks like this.

--o0o--

CHIEF COUNSEL MONAHAN CUMMINGS: So you can see it in your materials, if you need to. Section 27000 list is a list of chemicals that under State or federal law require additional testing for cancer or reproductive toxicity endpoints. It's not the same list as the more well known Prop 65 list. And it doesn't have any particular effect, other than to highlight the fact that there's still studies that need to be done.

For this list, we rely on U.S. EPA and the Department of Pesticide Regulation within CalEPA to give us information about mandatory chemical testing.

--o0o--

CHIEF COUNSEL MONAHAN CUMMINGS: So you can see on this slide the information provided by the Department of Pesticide Regulation recommends removal from the list, these five chemicals, because they've had sufficient testing to satisfy Department of Pesticide Regulation requirements.

--o0o--

CHIEF COUNSEL MONAHAN CUMMINGS: On this slide, the Department of Pesticide Regulation is recommending an

update, saying that there's a need for a tera rat study, for sodium chlorate.

--o0o--

CHIEF COUNSEL MONAHAN CUMMINGS: And on this slide, there's a suggestion from U.S. EPA that they have sufficient information reported to them on MITC.

So what we're asking the Committee to do is consent for our office to add, or delete, or update the list based on the information that I just showed you provided by U.S. EPA and DPR that is also described in the staff report.

Do you have any questions before you vote on that?

COMMITTEE MEMBER WOODRUFF: Can I ask a question?

CHIEF COUNSEL MONAHAN CUMMINGS: Sure.

COMMITTEE MEMBER WOODRUFF: So the Methyl isocyanate, does that mean there are now new data on this chemical?

CHIEF COUNSEL MONAHAN CUMMINGS: That's possible, because they're reporting now that they -- they've already received the information.

COMMITTEE MEMBER WOODRUFF: Okay.

CHAIRPERSON LUDERER: No other questions. Do we need to vote or just --

CHIEF COUNSEL MONAHAN CUMMINGS: Yeah, you need

to vote, but it can just be a hand vote. That's fine.

CHAIRPERSON LUDERER: Does anyone have any additional questions before we vote?

COMMITTEE MEMBER HERTZ-PICCIOTTO: So we're voting to remove it from the current Prop 65 list?

CHIEF COUNSEL MONAHAN CUMMINGS: (Shakes head.)

COMMITTEE MEMBER HERTZ-PICCIOTTO: No we're -- this is a separate list.

CHIEF COUNSEL MONAHAN CUMMINGS: Yeah, it's a separate list and it was required in the original statute. It's not entirely clear the purpose of it, but I think it was just to point out that there were chemicals that needed additional testing. And so we check with these two agencies to find out whether that has been received or not. And so we'll take the chemical off, once they've received the data they requested. So sometimes we add an additional test that they're asking for or we'll make another update to add a chemical that needs additional testing. But it's really -- it's completely separate from the Prop 65 list.

COMMITTEE MEMBER HERTZ-PICCIOTTO: And I don't know. Yeah. Okay. So this is just saying because EPA did it, we believe that we trust their authority in this?

CHIEF COUNSEL MONAHAN CUMMINGS: Right. We're just relying on their statement that the requirements that

they've put on these chemicals have been satisfied and the same thing for DPR.

CHAIRPERSON LUDERER: Any other questions?

Okay. I guess we're ready to vote then. Do we -- can we -- we can vote on them all together.

CHIEF COUNSEL MONAHAN CUMMINGS: (Nods head.)

CHAIRPERSON LUDERER: We don't have to vote on them separately. All right.

CHIEF COUNSEL MONAHAN CUMMINGS: Right, it's just consent to go ahead and make the changes.

CHAIRPERSON LUDERER: Okay. So the text is based upon the recommendations in the OEHHA staff report, should section 27000 of Title 27 in the California Code of Regulations be amended as indicated in Section 6 of the staff report?

So who votes yes, raise your hands.

(Hands raised.)

COMMITTEE MEMBER HERTZ-PICCIOTTO: Wait a second. We're going them all at once?

CHAIRPERSON LUDERER: Yes.

COMMITTEE MEMBER HERTZ-PICCIOTTO: So if I disagree on one of the compounds?

COMMITTEE MEMBER WOODRUFF: Which one?

CHAIRPERSON LUDERER: Vote no.

COMMITTEE MEMBER HERTZ-PICCIOTTO: Well, I

disagree a methyl isocyanate.

DR. IYER: Did you --

CHIEF COUNSEL MONAHAN CUMMINGS: I can't go back. Can you --

I don't know how to go back.

So just as a reminder, this list doesn't affect the Prop 65 list. These chemicals may or may not be already listed, but this is just basically saying that we're going to make these changes based on the information we received from U.S. EPA and DPR. And it's fine if you vote no, either way.

CHAIRPERSON LUDERER: All right. Let's -- shall we try again. Who -- raised your hand if vote yes?

(Hands raised.)

CHAIRPERSON LUDERER: Okay. Eight yes.

And raise your hands for those voting no.

(Hand raised.)

CHAIRPERSON LUDERER: One. All right. Thank you.

Now, we can move on to the staff updates. This is going to be on chemical listings via the administrative listing mechanisms and safe harbor level development. And Julian Leichty, Special Assistant, will be talking about that.

MR. LEICHTY: All right. So since the

Committee's last meeting we have administratively added eight chemicals to the Proposition 65 list.

Okay. Since the Committee's last meeting, we have administratively added eight chemicals to the Proposition 65 list. You'll see on this first -- you'll see on this first slide, Bevacizumab was added for developmental toxicity and female reproductive toxicity.

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

Okay.

--o0o--

MR. LEICHTY: And since the last meeting, these three safe harbor levels were adopted in regulation. A no significant risk level of 0.7 micrograms per day was adopted for bromochloroacetic acid effective April 1st 2019; a no significant risk level of 0.95 micrograms per day was adopted for bromodichloroacetic acid effective April 1, 2019; and a maximum allowable dose level of 28,000 micrograms per day oral and 20,000 micrograms per day inhalation was adopted for n-hexane effective July 1, 2019.

--o0o--

MR. LEICHTY: And on this last slide you'll see we have also proposed safe harbor levels for two chemicals. We're still in the regulatory process for maximum allowable dose levels by the oral, inhalation, and dermal route for chlorpyrifos; and a no significant risk level for p-chloro-alpha,alpha,alpha-trifluorotoluene.

I'll now turn things over to Carol.

CHIEF COUNSEL MONAHAN CUMMINGS: Hi. Back again. Sorry.

(Laughter.)

CHIEF COUNSEL MONAHAN CUMMINGS: So I just usually give a litigation update. And so I was just going to skip through these cases rather quickly, because most them are not related to this Committee directly. We do have two cases that are in the federal courts right now. One dealing with the warnings for glyphosate, which was listed in 2017. Those are first amendment challenges. There's also a similar challenge that was recently filed against the warnings for acrylamide in food. Both of those are still at the trial level in the federal courts.

We have a -- we continue to have a case in the court of appeal on the listing of BPA as a developmental toxicant. As you may recall, it's on the list for female reproductive toxicity, but the court required us to delist it some time ago. The case has been waiting since about

2015 for hearing. And we don't have a date for hearing yet.

There -- and similarly, there's a case pending on the listing of DINP, which has been briefed, but there's no hearing date set for that one.

We were successful in defending a case that was filed by Syngenta Crop Protection regarding our listing of three triazine pesticides and three breakdown products. The court of appeal agreed with the trial court that the listing was within our authority to do. The Syngenta Crop has asked the California Supreme Court to review that decision. They're not required to. And we're waiting for a decision from the court about whether they will hear it.

And our other cases are probably not of any interest to you.

So. Any questions on those?

Okay. Thanks.

CHAIRPERSON LUDERER: Thank you both of you.

We -- the final -- well, we were discussing whether we wanted to revisit the questions that had been brought up by Dr. Woodruff regarding kind of the format by which the data summaries are presented in the document that's provided to the Committee by the staff or also -- or possibly other -- another question that was bought up was regarding the search strategy and how that's

presented.

So do we want to have any further panel discussion about that this afternoon?

Dr. Allard.

COMMITTEE MEMBER ALLARD: No. I just want to agree. I think a flowchart of the -- that gives you an idea of the number of studies and also the inclusion exclusion critera. So Basically a visual for this. And then I'm -- I apologize if it's in there, but I -- I thought the graph that was presented earlier with the odds ratio across the different studies was extremely useful. Was that in the HID?

Okay. So that's what -- thank you.

All right. So I thought this -- that kind of visual is extremely informative. Of course, there's more to each study than just that. But, you know, in order for us to really get a quick glance at the wealth of studies, especially for chemicals like what we had to evaluate. I thought that was extremely informative to have like those kind of graphs.

COMMITTEE MEMBER WOODRUFF: Yeah. I -- man, talk about this at 4:00 not so enticing. But I want to say that there's a couple of things that -- just to follow up on what Dr. Allard was saying is that he -- I and -- I'm trying to think of who else has been on here. Larry. I

think we're the ones with the longest tenure on this Committee.

So -- or maybe -- no, I think we were before Ulrike, weren't we? Yeah, probably.

So just over time, there's been a lot more developed around systematically searching the literature and search strategies and also tools to report to document searches, as well as upload them and make them publicly available and -- I'll send this to you, but there was a nice -- there's been some work on systematic evidence mapping. So developing a protocol and then using Tableau, which is a publicly-available software, to document the evidence for the different health effects.

So it would allow us to see more clearly, a little bit like what you had for the epidemiology studies, where the evidence you have in terms of certain outcomes for the -- whatever the chemical is that is under consideration. And this was done recently in a paper in an online, available, interactive, graphical database for perfluorinated chemicals, which I think would be quite useful if the State of California did it, because its -- it also creates a living document record of what studies there are out there. And then you can add to it later and then people -- it's much easier visually for people to see.

Plus, if you have a protocol about how you did your systematic review, people will have more confidence and be able to trace from the beginning to the end how the study happen -- how you included the studies, in the review and I think that's important, because I think studies came up today that weren't included or people found outside, and it wasn't always clear. And I think if we have something to point to that has more clarity around it, it will make your job a lot easier and it will make it more clear for the public and ourselves for looking at the studies.

So -- and I just think that we can display the animal and the human evidence in a similar way. I think there's some opportunities to do them graphically that would help bring more clarity to what we see in the studies. I thought it was helpful with the human studies, like Patrick said.

CHAIRPERSON LUDERER: I just wanted to add that I thought that the data that were provide in the tables on the animal studies, that was very -- they were very thorough and it was actually very useful and helpful in reviewing those papers.

COMMITTEE MEMBER WOODRUFF: Yes. I will say right -- Larry said that it -- definitely, we've gotten -- the tables have gotten so much better since when we

started. I can't even remember what we had when we started, but I'm sure you guys have a record of it. So, yeah, and I think we -- there's -- as people are doing -- there's more of these automated tools out there. You guys you Swift for some of your -- your review searching that we can continue to improve them, so that they have -- they're more easier to see the key elements of the studies.

CHAIRPERSON LUDERER: Dr. Zeise.

DIRECTOR ZEISE: Yeah, I just -- maybe to get a little more clarification, so that we understand what maybe you mean by the evidence map. So this is where you would display the study counts for each outcome, is that right? When I'm thinking about the Tableau table, what you're talking about --

COMMITTEE MEMBER WOODRUFF: Right.

DIRECTOR ZEISE: -- is looking at --

COMMITTEE MEMBER WOODRUFF: Right.

DIRECTOR ZEISE: -- endpoint by endpoint and having the study count. So some of the material that was presented in the presentations would then be put in a tabular form.

COMMITTEE MEMBER WOODRUFF: Right. And so I think you had that with the epi studies, there was a table that said, okay, for this -- whatever this endpoint --

cognitive, and they had this Many studies for the cognitive endpoint. And then we had this many studies for the -- okay, the motor endpoint.

First of all, doing that for the animal studies, because like I said, there was all these -- there were a number of tests that were the same across the studies, and being able to look at them together, because one of the things that's challenging when reviewing this is we want to look at people who've looked at the same endpoint but from different study designs or different study conditions.

And having that at least in a place where we could -- you could see them -- the value of having it on the internet and accessible is that then it's easy for you -- for everyone to see it or access it.

DIRECTOR ZEISE: I think we can explore -- we can explore that. In terms of a State government, we'll see what we can do and what's possible.

COMMITTEE MEMBER WOODRUFF: Of course, you can't make this -- the study themselves, but we could see the abstracts in the titles.

DIRECTOR ZEISE: So anyway, we'll explore that.

COMMITTEE MEMBER WOODRUFF: I totally get the copyright issue.

DIRECTOR ZEISE: Martha, do you have --

DR. SANDY: Just to follow up on that. We also are usually doing this in a year or less, as opposed to some other agencies at the federal level and other organizations that may have more time.

COMMITTEE MEMBER WOODRUFF: Yeah, that PFAS one was done by a non-profit, so...

DR. SANDY: Yeah.

COMMITTEE MEMBER WOODRUFF: That one, I agree that you guys -- I was actually wondering when you started. And you said it was March, so -- and this is -- what is this? I think this is November. Or, no, we're in December. So, yeah, so that's -- but I think if you also use the same method -- if you develop a method and then use it the same as you move through your studies, I think the -- your initial investment will be high, but over time it will be more efficient. You look skeptical, but --

DR. SANDY: We will -- we will explore --

COMMITTEE MEMBER WOODRUFF: We will test it. You could actually test that.

DR. SANDY: -- what we can do, yes.

COMMITTEE MEMBER WOODRUFF: Yeah.

DIRECTOR ZEISE: And I just wanted to clarify with respect to the missing study. I think what we did say was that it was actually in the document one of the excluded ones, because it was cross-sectional, so just

wanted to clarify for the record.

COMMITTEE MEMBER WOODRUFF: That wasn't -- that wasn't the one only, but that's fine. In the end, we had a lot of studies, so I think that -- where we're going to be challenged is when we're talking about chemicals that don't have a lot of studies, we want to make sure we capture everything. So in this case, it probably didn't really influence what we were looking at.

DR. KAUFMAN: This is Dr. Kaufman.

It has been our policy in the past to include as many studies as we identify. And in this case -- and that would include cross-sectional studies. In this case, the volume of studies was so great, that we felt it was -- would be a burden, first of all, to -- on the Committee to go through even more studies, and felt that classifying the studies as higher quality, better quality, and of not so good quality would have been more useful to the Committee. And so we did that and excluded all of the studies that were ecological, and, as I mentioned, cross-sectional.

If this -- if the Committee deems to choose a different way for us to approach this, we would definitely be open to it.

COMMITTEE MEMBER WOODRUFF: Yeah, I'm not -- I agree that there can be ways, if you have a large

database, to winnow down your -- the study types, right? That is totally appropriate. And I think if you have a lot of prospective cohort studies, you're right, there's no reason to look at ecological studies. I think what would help in the document is that the language was a little bit vague around that in term -- I mean, I would be very crystal clear, we only looked -- we only included prospective cohort studies period.

Whereas, I think the language in the -- in the appendix is maybe not quite as clear. And then also I think it's important for us to know that that's like what that universe looks like. I mean, because you -- it's great that -- to have that decision, but we would probably want to review that also, right, as a Committee?

DR. KAUFMAN: Yes. It was our intent and we had a draft. The time constraints due to the volume and complexity of this data set precluded us from executing that and presenting it in the HID. But I totally agree with you, that is very useful and we will definitely strive to include all that in the future.

COMMITTEE MEMBER WOODRUFF: There was something else about that I wanted -- but anyway. Thanks.

CHAIRPERSON LUDERER: Thank you. If we have no further discussion, Dr. Zeise, would you --

DIRECTOR ZEISE: Let me -- thank you. Let me

summarize the Committee's actions. So the Committee voted unanimously to add cannabis(marijuana) smoke as being clearly shown through scientifically valid testing, according to generally accepted principles to cause developmental toxicity. So it would be added to the Proposition -- it will be added to the Proposition 65 list. It requires six votes or a quorum of this Committee is six votes and it received 9. So we're going to add that to the list.

And similarly, delta-9-tetrahydrocannabinol (delta-9-THC) was also voted with eight yes votes, one no vote. So six yes votes are required to add the chemical to the list. And again, for both of these, it will be added to the list of chemicals known to cause reproductive toxicity for the developmental endpoint.

So that's the Committee's actions on the substances that were considered.

And then in terms of the Section 2700[SIC], the Committee voted eight yes, one no to amend Section 6 of the staff -- based on Section 6 of the staff report to amend section 2700[SIC] of Title 27 California Code of Regulations. So since six yes votes were required to make changes to that list in that section, those changes will also be made.

So that is the summary of the Committee's

actions. And then I think just to close by thanking the Committee for the tremendous amount of work that went into preparing for this meeting. Always amazed at how well prepared the Committee is and the level of discussion underway. So we really appreciate the Committee for all the work done and for their -- providing their time and expertise to the State of California to address these important issues. And cannabis is a very important issue. So thank you to the Committee.

And I want to thank members of the public for taking the time to participate in the meeting and listen online. So much appreciate your participation as well.

And I want to thank the OEHHA staff for the tremendous amount of work that went into preparing the materials for the meeting, and all of the behind-the-scenes work that needs to be done. So I thank the RCHAB team, I thank our Executive Office staff, and I think the implementation staff for all the work that went into this meeting. So thank you all and have a very Happy Holidays and a very safe trip home.

CHAIRPERSON LUDERER: Thank you. And the meeting is now adjourned.

(Thereupon the Developmental and Reproductive Toxicant Identification Committee adjourned at 4:09 p.m.)

C E R T I F I C A T E O F R E P O R T E R

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, Developmental and Reproductive Toxicant 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 meeting nor in any way interested in the outcome of said meeting.

IN WITNESS WHEREOF, I have hereunto set my hand this 29th day of December, 2019.

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