

HYBRID MEETING
STATE OF CALIFORNIA
OFFICE OF ENVIRONMENTAL HEALTH HAZARD ASSESSMENT
PROPOSITION 65
DEVELOPMENTAL AND REPRODUCTIVE TOXICANT
IDENTIFICATION COMMITTEE

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PROCEEDINGS

1
2 DIRECTOR THAYER: Welcome to everybody joining
3 this meeting of the Developmental and Reproductive
4 Toxicant Identification Committee. This meeting is being
5 held virtually and in person. So my name is Dr. Kris
6 Thayer. I am the new Office of Environmental Health
7 Hazard Assessment Director as of May of this year. Before
8 joining OEHHA, I was in the federal government. I worked
9 at NIEHS. I actually directed a program, the Center for
10 the Evaluation of Risk to Human Reproduction. And then I
11 was at U.S. EPA. So I have a history of being an
12 authoritative body. So I've long appreciated this
13 Program. So I'm very honored to be here.

14 So as you are aware, OEHHA is a department within
15 the California Environmental Protection Agency and its the
16 lead State agency for assessing health risks posed by
17 chemicals an environmental stressors.

18 As we get started, there's a few housekeeping
19 items for those attending in the room here in Sacramento.
20 The emergency exits, there are two double doors directly
21 in the back when you enter the room at the front of the
22 room to the left under the lighted exit signs. You can
23 access the restrooms by going out the back double doors,
24 turning left, and then walking to the end of the hall.

25 Our main agenda item for today is consideration

1 of bisphenol S, or BPS, for listing as a developmental
2 toxicant under Prop 65. BPS is on the Proposition 65 list
3 for reproductive toxicity based on female reproductive and
4 male reproductive endpoints.

5 So next, OEHHA will present for Committee
6 discussion, a proposal for development of hazard
7 identification materials on para,para'-bisphenol chemicals
8 to support consideration for listing by the DARTIC in
9 2026. The Committee is being asked for input on the
10 proposal today.

11 After the proposal discussion, the Committee will
12 take up a consent item on the Section 2700[SIC] list of
13 chemicals for which testing has been required, but has
14 been inadequate. This is different from the Proposition
15 65 list.

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

19 We will take a 45-minute break for lunch around
20 noon and may take a short 15-minute break sometime in the
21 afternoon. This meeting is being recorded and
22 transcribed. The transcript will be posted on OEHHA's
23 website. There will be public comment during this
24 meeting.

25 Oral public comments on the BPS item and the

1 proposal for development of the hazard identification
2 materials for para,para'-bisphenols chemicals. And there
3 should be details being shared on how to register for the
4 Zoom webinar to provide public comment. Those I'm sure
5 will come up.

6 So individuals who are in person and wish to make
7 an oral comment at today's meeting are asked to fill out a
8 blue comment card and give them to OEHHA staff. The blue
9 comment cards are located in the back of the room.

10 NEXT SLIDE

11 DIRECTOR THAYER: If you wish to provide a
12 comment anonymously, you may still fill out the blue card,
13 but just leave the name and affiliation sections blank.
14 You know, please -- instead, please write a unique
15 identifier of your choice, nickname, alias, a number at
16 the top corner of the card. This will be used to call on
17 you without revealing your identity. When called by the
18 Chair, please approach the microphone. We encourage you
19 to state your name and affiliation and then provide your
20 comment. However, there's no obligation for you to
21 identify yourself if you wish to be anonymous.

22 For those who are joining us virtually and wish
23 to make an oral comment at today's meeting, you are asked
24 to join the Zoom webinar. Please make sure that you join
25 under the name that you would like to identified as when

1 commenting, including if you would like to remain
2 anonymous. Information on how to join the Zoom is shown
3 on this slide several bullets down, in registering for
4 today's webinar. You will receive a link to join the
5 webinar at the end of the registration process. And if
6 you provided a working email address, you will also
7 receive an email with a link to join the webinar. Zoom
8 users who also access closed captioning by clicking the
9 "CC" button on the bottom of the panel.

10 For those of you watching by CalEPA webcast,
11 you'll be watching the meeting, but you'll need to join
12 the meeting by Zoom to speak. When requested by the
13 Chair, individuals on Zoom may queue to provide oral
14 comments by using the "Raised Hand" function. When you
15 are called during the opportunity for public comment, you
16 will be prompted to unmute yourself. Please unmute
17 yourself, state your name and affiliation if you're
18 willing to provide that information and provide your
19 comment. Again, anonymous commenters are welcome.

20 If you would like to present slides during the
21 public comment and have not already sent them, please
22 email them to the email address on this slide, the one
23 that starts with "P65public".

24 Okay. Now, we're going to go ahead and introduce
25 the DARTIC members. So I think we'll start from this

1 side. I'm going to be introducing other members of the
2 Committee, but I do want to note that Drs. Allard, Ha, and
3 Dr. Hertz-Picciotto are not able to join us today. So, as
4 I introduce you, please state your name and affiliation.

5 So, Dr. Diane Auyeung-Kim.

6 COMMITTEE MEMBER AUYEUNG-KIM: It's Diana
7 Auyeung-Kim with Genentech.

8 DIRECTOR THAYER: Okay. Dr. Pessah.

9 COMMITTEE MEMBER PESSAH: Dr. Isaac Pessah,
10 Professor Emeritus, UC Davis.

11 DIRECTOR THAYER: Yeah. You just have to push
12 the button.

13 COMMITTEE MEMBER PLOPPER: Oh, I see. Okay. So
14 is it working?

15 DIRECTOR THAYER: Yeah, you have the green light
16 on, so it's active.

17 COMMITTEE MEMBER PLOPPER: Okay. Charles
18 Plopper, Professor Emeritus, UC Davis.

19 DIRECTOR THAYER: I've introduced myself.
20 And then I'll turn it over to your Committee
21 Chair, Dr. Ulrike Luderer

22 CHAIR LUDERER: Ulrike Luderer, UC Irvine.

23 COMMITTEE MEMBER HARLEY: Kim Harley, UC
24 Berkeley.

25 COMMITTEE MEMBER CULTY: Martine Culty,

1 University of Southern California.

2 COMMITTEE MEMBER BRETON: Carrie Breton,
3 University of Southern California.

4 COMMITTEE MEMBER BASKIN: Larry Baskin, UCSF.
5 I'm a pediatric urologist in the Department of Urology.

6 DIRECTOR THAYER: All right. Welcome. And thank
7 you so much for your service. We know that this is quite
8 a commitment.

9 All right. Now, I get to introduce the OEHHA
10 staff. And as I do this, I just want to give a shout-out
11 to all the preparation that I know you put into this
12 meeting. It's very much appreciated.

13 So what I'll do is I'll introduce OEHHA staff.
14 For those in the room, I invite them to raise their hand.
15 And for those joining via Zoom webinar, I invite them to
16 turn on their cameras, as I introduce them.

17 So, Dr. Kimberly Gettmann, who is Deputy Director
18 for Scientific Programs. And from the Reproductive and
19 Cancer Hazard Assessment Branch, Dr. Martha Sandy, Branch
20 Chief. Dr. Francisco Moran, Section Chief of the
21 Reproductive Toxicology and Epidemiology Section. And
22 then staff of the Reproductive Toxicology and Epidemiology
23 Section that are joining us today, Drs. Faye Andrews, Erin
24 Delker, Sarah Park, Sarah Saucier, and Gabriel Tukeman.

25 Okay. And then, we have Office of External and

1 Legislative Affairs, Proposition 65 Implementation team.
2 Amy Gilson, who is Deputy Director of External And
3 Legislative Affairs. Okay. Tina Cox, Senior
4 Environmental Scientist, Section Chief of the Proposition
5 65 Implementation team. Esther Barajas-Ochoa, Analyst,
6 Proposition 65 Implementation team. Okay. And then Julia
7 Dolloff, who is our Senior Environmental Scientist, Prop
8 65 Ombudsperson.

9 Okay. All right. Now, I'm going to ask Kristi
10 for some introductory remarks about the Bagley-Keene and
11 other legal issues related to today's meeting.

12 KRISTI MORIOKA: Thanks so much Kris. I'm Kristi
13 Morioka. I'm from OEHHA Legal. This is my colleague
14 Corey Friedman, also from OEHHA Legal.

15 So today -- good morning. Thanks, everybody, for
16 being here. So I just have a few points to make. First
17 is feel free to ask us any questions today. We will be
18 here the whole time.

19 Next is reminder that the Bagley-Keene Open
20 Meeting Act applies to this meeting. The goal of
21 Bagley-Keene is to promote transparency, so for the
22 Committee members that means that the discussions and
23 deliberations about the agenda items need to be conducted
24 during the open meeting, not on the breaks or at lunch,
25 time, or with individual members of the Committee on- or

1 offline, including via phone, email, chats, or text
2 messages.

3 And second, all experts serving on this
4 Committee, that's you all, have participated in mandatory
5 ethics training, and have disclosed any potential or
6 actual conflicts of interest, including any relevant ex
7 parte communication about the subject matter. And we
8 really appreciate you all taking the time to do the
9 training. I know it is long.

10 And last, at today's meeting, you will be
11 considering adding an additional reproductive toxicity
12 endpoint to the listing of bisphenol S. OEHHA takes no
13 position regarding whether a chemical or additional
14 endpoints should be listed, though all of our staff are
15 here and available to answer questions or locate
16 information, if you need it.

17 The Governor appointed you all because of your
18 scientific expertise to be the State's qualified experts
19 on the reproductive toxicity of chemicals. There is no
20 need for you to feel compelled to go outside that charge.
21 For example, you need not consider whether a warning will
22 be required for an exposure or any other consequence of
23 your listing decision today.

24 This Committee has maximum flexibility in
25 evaluating all pertinent scientific information in making

1 a determination and can consider human, animal,
2 mechanistic, or other data in deciding whether a chemical
3 has been clearly shown through scientifically valid
4 testing, according to generally accepted principles to
5 cause reproductive toxicity. If you need more information
6 or need more time to consider the evidence or discuss it
7 further before you vote on a listing, there is no
8 requirement that you make a decision today. For example,
9 you may table the decision and take it up again at a
10 future meeting.

11 Feel free to ask any other clarifying questions
12 of me or any other OEHHA staff. During the meeting. And
13 if we don't know the answer to your question, we will do
14 our best to find it out and report it back to you.

15 Do you all have any other questions?

16 Thank you so much.

17 DIRECTOR THAYER: All right. Thank you. And
18 then now I'm going to pass the meeting over to our Chair.

19 CHAIR LUDERER: All right. Thank you, Kris and
20 Kristi. Good morning and welcome to the Committee members
21 and members of the public who are joining today.

22 We're now going to move on to the main agenda
23 item, which is the consideration of bisphenol S, that
24 we'll refer to as BPS, for the developmental toxicity
25 endpoint under Proposition 65. So, I'd like to turn the

1 Chair over now to Dr. Francisco Moran, Chief of the
2 Reproductive Toxicology and Epidemiology section to begin.

3 (Slide presentation).

4 DR. FRANCISCO MORAN: Thank you, Dr. Ulrike.

5 Good morning. Relevant information has been
6 reviewed and considered by OEHHA for this year hazard
7 identification document, or HID, that is on the evidence
8 of developmental toxicity of bisphenol S or BPS. In the
9 last two meetings, BPS was considered for female and male
10 reproductive toxicity and it was added to the Proposition
11 65 list for both endpoints. This document was released
12 for public comments and no comments were received.

13 The HID and the references cited were provided to
14 the DARTIC for consideration for today's meeting.

15 NEXT SLIDE

16 DR. FRANCISCO MORAN: Today's presentation is a
17 brief overview and it will not cover every finding
18 discussed in the HID. I will start with a brief
19 background information and then we will present results
20 from animal and mechanistic studies, and then the
21 epidemiological evidence to finish with an integrative
22 summary all -- I'll try -- we'll try -- in less than 40
23 minutes. So bear with us, please.

24 I would like to acknowledge that this work was a
25 group effort from the staff in the Reproductive Toxicology

1 and Epidemiology Section.

2 NEXT SLIDE

3 DR. FRANCISCO MORAN: Here is the chemical
4 structure of BPS and its structural analog BPA.

5 NEXT SLIDE

6 DR. FRANCISCO MORAN: Here is a summary of what
7 was presented to you previously on BPS use, production and
8 exposure. Some increases in BPS production are associated
9 with regulations on BPA by California in 2011 and FDA in
10 2013. Since that time, manufacturers have been gradually
11 replacing BPA with BPS and consumer product -- in consumer
12 products. BPS reaches a production of up to 10 million
13 pounds per year. As such, exposure to BPS has increased
14 and studies from Biomonitoring California show detection
15 frequencies up to 77 percent in California residents.

16 NEXT SLIDE

17 DR. FRANCISCO MORAN: Using a systematic
18 approach, we conducted literature searches on the
19 developmental toxicity of BPS. We used HAWC as a tool for
20 multi-level screening of literature search results. For
21 this document, we focused on literature relevant to
22 developmental toxicity where the last comprehensive search
23 was in October 2024 and additional studies that came to
24 OEHHHA's attention after the last comprehensive search were
25 also included.

1 NEXT SLIDE

2 DR. FRANCISCO MORAN: Following oral exposure,
3 BPS is rapidly absorbed. It is distributed throughout the
4 body and likely undergoes enterohepatic circulation. This
5 has been detected in human, including umbilical cord,
6 amniotic fluid, and placenta. BPS undergoes metabolism by
7 conjugation and hydroxylation in human and rodents. It is
8 excreted in urine, bile, feces, and breast milk.

9 The half-life in humans has been reported to be
10 between seven and nine hours and in rodents from three to
11 eight hours. In addition to the body weight, several
12 maternal physiological changes occur during pregnancy that
13 affect developmentally-relevant exposure, including
14 increased blood volume, metabolic changes, and increased
15 renal function, among others.

16 NEXT SLIDE

17 DR. FRANCISCO MORAN: The studies on the
18 developmental toxicity of BPS evaluated potential adverse
19 effect of prenatal exposure on the developing offspring.
20 Some animal studies that combined prenatal and postnatal
21 exposure were also reviewed.

22 There was a wide range of BPS exposure doses used
23 in the study of animal models. For example, doses in
24 rodents were from micrograms to milligrams per kilogram
25 body weight, while BPS concentration in zebrafish model

1 was from micrograms to milligrams per liter.

2 As mentioned earlier, our presentation today does
3 not cover the entirety of the data of the developmental
4 effects of BPS, but will highlight the most important and
5 informative findings. For a comprehensive overview,
6 please see our published hazard identification document.

7 The results that we are presenting today are all
8 statistically significant, unless otherwise indicated, and
9 we include the effective dose and the time of exposure for
10 each study included in this presentation.

11 NEXT SLIDE

12 DR. FRANCISCO MORAN: Now, Dr. Sarah Saucier will
13 start presenting the evidence of BPS exposure on early
14 development from studies in animals.

15 Thank you very much.

16 NEXT SLIDE

17 DR. SARAH SAUCIER: Thank you, Dr. Moran.

18 Before we begin our presentation on the hazard
19 identification findings, we wanted to provide this graphic
20 as a brief overview of the stages of development in humans
21 by trimester, rats by days, and zebrafish by hours from
22 fertilized egg through neurogenesis. This side-by-side
23 comparison demonstrates the parallel stages of development
24 that are relevant as we review the findings that result
25 from a specific window of exposure. This information will

1 help guide some of the data presented today.

2 NEXT SLIDE

3 DR. SARAH SAUCIER: The following developmental
4 toxicity findings in animal systems will be presented with
5 relevant mechanistic evidence when possible. But please
6 note that not all mechanistic evidence will be presented
7 here today.

8 As Dr. Moran said, our presentation today will
9 highlight the most important findings, including
10 implantation and early embryonic development, placental
11 effects, fetal malformations and variations, litter
12 outcomes, growth, neurodevelopmental toxicity,
13 reproductive effects, metabolic effects, and circulatory
14 system effects.

15 I will begin by reviewing the effects of BPS on
16 implantation and early embryonic development.

17 NEXT SLIDE

18 DR. SARAH SAUCIER: Successful implantation and
19 embryonic development depend on tightly coordinated
20 molecular signaling. Disruption to these processes can
21 have detrimental effects on early developmental events,
22 including implantation and establishment of the placenta
23 and other extraembryonic tissues.

24 BPS diminished implantation and early embryonic
25 development. Embryo development was inhibited in mice and

1 sheep, as indicated by arrested development of
2 preimplantation embryos, and altered number and/or rate of
3 embryos and blastocysts, and/or a decreased IVF rate.
4 Implantation effects in rats included decreased
5 implantation sites and increased post-implantation loss.
6 And in a chick embryo study, growth, mass, and size were
7 decreased with delayed development.

8 NEXT SLIDE

9 DR. SARAH SAUCIER: Mechanistic evidence supports
10 these effects, including altered pluripotency markers in
11 human amniotic and fetal stem cells, a decreased
12 blastocyst attachment rate in a human implantation model,
13 and decreased gastrulation markers in a human embryoid
14 model, and accelerated embryo development in bovine
15 blastocysts.

16 NEXT SLIDE

17 DR. SARAH SAUCIER: Next, I will present on the
18 effects of BPS on the placenta.

19 NEXT SLIDE

20 DR. SARAH SAUCIER: Proper placental formation
21 and function are critical for embryonic and fetal
22 development. Toxicant-mediated responses could arise from
23 either direct effects on the placenta, conceptus, mother,
24 paternal epigenome, or some combination. Trophoblasts,
25 the major placental cells, are key in establishing

1 placental networks. Disruption to any component of
2 placental function can adversely impact embryo/fetal
3 development and maternal health. BPS induced adverse
4 effects on placental tissue.

5 Placenta weight was increased in rats with a
6 non-significant effect in sheep. There were
7 histopathology findings in the sheep study as well as in a
8 mouse study, including a decreased ratio of the
9 spongiotrophoblast zone to giant cell area, as seen in
10 this cross-sectional image, as well as quantitatively.

11 NEXT SLIDE

12 DR. SARAH SAUCIER: Several studies provide
13 mech -- supportive mechanistic evidence of placental
14 disruption in animal and cellular models. In animal
15 studies, there were decreases in fatty acids in mouse
16 placenta, placenta-related proteins in sheep serum, and
17 placental DNA methylation in rats, and altered
18 trophoblasts and placenta-related genes in rats and sheep.

19 In cellular studies, there was increased
20 apoptosis, altered gonadotropin and progesterone levels,
21 and evidence of immunotoxicity in a human
22 placenta-on-a-chip model, as well as evidence of altered
23 trophoblast signaling, including altered neurotransmitter
24 levels in mouse trophoblasts, decreased markers of EGF
25 signaling in human primary trophoblasts, and decreased

1 EGF-receptor binding in a competitive binding assay.

2 NEXT SLIDE

3 DR. SARAH SAUCIER: Next, I will discuss the
4 effects of BPS on fetal malformations and variations.

5 NEXT SLIDE

6 DR. SARAH SAUCIER: In our hazard
7 identification, fetal variation is defined as a change
8 that is unlikely to negatively impact the survival or
9 health of the animal and may or may not also occur in
10 control animals, and fetal malformation as a permanent
11 structural change that is likely to negatively impact the
12 survival or health of the animal.

13 NEXT SLIDE

14 DR. SARAH SAUCIER: Malformations, variations,
15 and physiological abnormalities were increased in
16 BPS-treated animals. There was a dose-dependent increase
17 in total skeletal malformations in rats and none observed
18 in the control animals. Also, in rats, there was an
19 increase in the incidence of individual visceral
20 variations with a non-significant increase in the
21 incidence of total visceral variations, and in sheep,
22 there was an increased incidence of decreased biparietal
23 diameter, a skeletal variation, in male fetuses. There
24 were increased malformation rates in zebrafish and
25 non-significantly increased defect rates in Chinese medaka

1 fish.

2 Several morphological abnormalities were reported
3 in fish and chick embryos, including craniofacial, spinal,
4 yolk sac, heart, and gonadal, among others. There were
5 also abnormalities of the zebrafish swim bladder, a
6 lung-like organ, including decreased inflation.

7 NEXT SLIDE

8 DR. SARAH SAUCIER: Next, I will present on the
9 effects of BPS on litter outcomes.

10 NEXT SLIDE

11 DR. SARAH SAUCIER: Litter outcomes were
12 considered due to the potential developmental contribution
13 to these effects. Several litter outcomes were affected
14 in BPS-treated maternal animals. There were increases in
15 total litter loss and stillbirth and decreases in litter
16 size and number of liveborn pups in rodents. Parturition
17 distress and nursing problems were reported in mice and
18 mortality was increased in rat pups during the first
19 postnatal week, with a higher mortality in males.

20 Hatching is the development of an embryo or egg
21 into larva. In fish, *C. elegans*, and *drosophila*, hatching
22 rates and/or times were generally decreased. There was a
23 decrease in *drosophila* pupae formed and *C. elegans* brood
24 size with an increase in embryonic lethality.

25 NEXT SLIDE

1 DR. SARAH SAUCIER: Finally, I will discuss the
2 effects of BPS on growth.

3 NEXT SLIDE

4 DR. SARAH SAUCIER: BPS altered the growth of
5 developing organisms, with most evidence found in
6 non-mammalian species. birth weight and body length were
7 altered in rodents, with direction depending on dose. In
8 zebrafish and C. elegans, body length was generally
9 decreased, with one research group finding an increase in
10 body length and weight in zebrafish.

11 NEXT SLIDE

12 DR. SARAH SAUCIER: Thank you for your time. Dr.
13 Tukeman will now present on the neurodevelopmental effects
14 of BPS

15 NEXT SLIDE

16 DR. GABRIEL TUKEMAN: Thank you.
17 Neurodevelopment during the pre-, peri-, and
18 post-natal periods is especially sensitive to chemical
19 exposures. Effects of BPS on neurodevelopment have been
20 observed in several studies and have manifested as
21 alterations in movement, cognitive function, neurogenesis,
22 and social and maternal behaviors.

23 NEXT SLIDE

24 DR. GABRIEL TUKEMAN: Altered neurodevelopment
25 can be observed in physical movements. In zebrafish,

1 movement was assessed using motion tracking and demarcated
2 plates. There was an effect on movement in seven of 14
3 zebrafish studies with alterations in the number of
4 spontaneous movements depending on assessment time,
5 decreased touch-evoked swim response and swirl escape
6 rate, altered swimming speed and distance traveled with
7 directionality dependent on assessment time, and increased
8 activity frequency.

9 NEXT SLIDE

10 DR. GABRIEL TUKEMAN: Four of four C. elegans
11 studies observed effects on movement, with decreased body
12 bend frequency in L4 larvae and adults, decreased
13 pharyngeal pumping in adults, and altered head thrashing
14 behavior in L4 larvae and adults with directionality
15 dependent on assessment time. One- to two-day old
16 drosophila, there was an increased distance traveled and
17 decreased vertical climbing time, indicative of
18 hyperactivity.

19 NEXT SLIDE

20 DR. GABRIEL TUKEMAN: BPS developmental exposure
21 may negatively impact cognitive function in mice, rats, C.
22 elegans, and drosophila. In one of two mouse studies, BPS
23 exposure decreased working and short-term memory in female
24 offspring. In one of two rat studies, BPS exposure
25 decreased learning and memory function in juvenile

1 offspring. BPS also increased the number of touches
2 needed for habituation in C. elegans and decreased
3 associative learning via aversive stimulus in drosophila.

4 NEXT SLIDE

5 DR. GABRIEL TUKEMAN: Images of juvenile rat
6 hippocampi taken in conjunction with learning and memory
7 tests showed BPS had the following effects: decreased
8 proliferation in the granular cell layer and hilus.

9 NEXT SLIDE

10 DR. GABRIEL TUKEMAN: Decreased stemness and
11 self-renewal in neural stem cells.

12 NEXT SLIDE

13 DR. GABRIEL TUKEMAN: Decreased neural stem cell
14 differentiation into neurons.

15 NEXT SLIDE

16 DR. GABRIEL TUKEMAN: And increased myelin sheath
17 decompaction and loosening and increased percentages of
18 damaged synapses in hippocampal neurons.

19 NEXT SLIDE

20 DR. GABRIEL TUKEMAN: BPS-mediated effects on
21 developmental neurogenesis were reported in five zebrafish
22 studies. Several of these studies utilized transgenic
23 lines to visualize neuronal processes using fluorescent
24 reporters. There was an increased number of gonadotropin
25 releasing hormone 3 or GnH -- GnRH3 positive neurons in

1 the hypothalamus, with a downstream effect of increased
2 expression of reproductive neuroendocrine-related genes.
3 There was increased neurogenesis and proliferation in
4 rostral and caudal regions of the hypothalamus,
5 respectively.

6 NEXT SLIDE

7 DR. GABRIEL TUKEMAN: Decreased central nervous
8 system neurogenesis with decreased motor neuron axon
9 length

10 NEXT SLIDE

11 DR. GABRIEL TUKEMAN: And increased and
12 accelerated neurogenesis as indicated by the ratio of
13 newborn to mature neurons and the number of proliferating
14 neuronal stem cells.

15 NEXT SLIDE

16 DR. GABRIEL TUKEMAN: Zebrafish studies with BPS
17 developmental exposure observed alterations in the
18 expressions of genes relevant to neurodevelopment. These
19 changes were in genes encoding neuron-specific RNA binding
20 proteins; proteins related to axon growth, pathfinding,
21 and regeneration; myelin formation, structure and
22 stability; TGF Beta superfamily members; neuronal
23 development, growth and differentiation; and early
24 development.

25 NEXT SLIDE

1 DR. GABRIEL TUKEMAN: Altered social behaviors
2 were observed in mice, zebrafish, and drosophila. Four of
3 four studies found BPS-induced social and maternal
4 behavioral effects in mice, with decreased social novelty
5 preferences in juvenile offspring, increased anxiety and
6 depression in adult male offspring, and decreased interest
7 in social interaction in adult offspring. One study
8 reported alterations in F1 maternal behavior with
9 increased incidence of infanticide and pup neglect,
10 decreased latency to interact with and retrieve pups, and
11 changed time spent on the nest

12 In zebrafish, there was increased novel tank
13 stress in adult male offspring and decreased shoal
14 cohesion in both larvae and adult male offspring, as
15 determined through nearest neighbor distance and increased
16 interindividual distance. In one- to two-day old F1
17 drosophila, there were decreased social interactions
18 between flies of the same sex and an increased number of
19 male combats.

20 NEXT SLIDE

21 DR. GABRIEL TUKEMAN: There were also observed
22 alterations in neurotransmitter-related gene expression in
23 rats and zebrafish following BPS exposure during
24 development with changes in genes encoding proteins
25 related to the acetylcholine system, dopamine system, and

1 serotonin system, as well as genes involving
2 neurotransmitter regulation in the form of
3 neurotransmitter breakdown and release at synapses.

4 NEXT SLIDE

5 DR. GABRIEL TUKEMAN: Dr. Park will now present
6 on developmental reproductive effects.

7 NEXT SLIDE

8 DR. SARAH PARK: Thank you, Dr. Tukiman.

9 NEXT SLIDE

10 DR. SARAH PARK: OEHHA previously presented
11 animal evidence on BPS-mediated effects on developmental
12 reproductive toxicity. This included altered ovarian
13 development, mammary gland development, and reproductive
14 function in females, and altered spermatogenesis, and
15 decreased sperm count, motility, and daily sperm
16 production in males. Altered hormone levels and molecular
17 markers were reported in both females and males.

18 In this document, four additional studies in
19 females and one additional study in males are included and
20 are overall consistent with the previous observations.

21 NEXT SLIDE

22 DR. SARAH PARK: In female mouse offspring, BPS
23 altered folliculogenesis, accelerated pubertal onset and
24 time to first estrus, and increased estrous cycle length.
25 Decreased litter size and fertility were also observed.

1 In the ovaries, there were decreases in antioxidant and
2 ovarian markers and increased ROS and apoptosis.

3 NEXT SLIDE

4 DR. SARAH PARK: In female rat offspring, there
5 was a non-significant delay in pubertal onset and
6 non-significant increase in cycle regularity. In two of
7 nine BPS-treated chick embryos, thinner ovaries were
8 reported. In zebrafish, BPS altered ovarian and
9 reproductive function, and ovarian gene expression of
10 reproductive hormones in the untreated offspring and/or
11 grandoffspring of treated F0 parents.

12 NEXT SLIDE

13 DR. SARAH PARK: In male rat offspring, there
14 were no effects on pubertal onset. In the untreated
15 offspring and grand-offspring of treated F0 zebrafish, BPS
16 decreased sperm concentration. Effects including altered
17 spermatogenesis and decreased testosterone were previously
18 reported for zebrafish in the hazard identification
19 document on male reproductive toxicity.

20 NEXT SLIDE

21 DR. SARAH PARK: In C. elegans, the primary
22 method of reproduction is the self-fertilization of
23 hermaphrodites. BPS decreased the number of egg laying
24 days and eggs laid, decreased brood size, and altered
25 vulval morphogenesis.

1 NEXT SLIDE

2 DR. SARAH PARK: BPS-mediated effects on
3 metabolic function were observed across multiple species.

4 NEXT SLIDE

5 DR. SARAH PARK: All right. Overall, gestational
6 BPS exposure altered adiposity in male mice and rats
7 including altered adipose tissue weights and adipocyte
8 hypertrophy. There was also increased lipid accumulation
9 in cultured mouse adipocytes and decreased adipocyte size
10 in fetal male sheep.

11 NEXT SLIDE

12 DR. SARAH PARK: The effects of developmental BPS
13 exposure on glucose and lipid levels varied. In male
14 mice, BPS decreased glucose and increased triglyceride
15 levels. And in larval zebrafish, BPS decreased brain
16 glucose uptake, increased glucose, or decreased lipid
17 levels.

18 NEXT SLIDE

19 DR. SARAH PARK: BPS altered the expression of
20 genes related to hepatic and/or lipid metabolism across
21 multiple species and cells or tissues.

22 NEXT SLIDE

23 DR. SARAH PARK: Gestational BPS exposure altered
24 fatty acid levels. One epidemiologic study reported
25 associations between increased maternal urinary BPS and

1 altered cord blood fatty acid metabolite concentrations.

2 BPS altered fatty acid levels in both mice and
3 rats. Proteomics analysis of treated mouse adipocytes
4 identified enrichment of pathways related to fatty acid
5 synthesis and metabolism.

6 In zebrafish, BPS decreased long chain fatty acid
7 levels and the expression of genes related to their
8 metabolism. Transcriptomic analysis identified enrichment
9 of pathways related to fatty acid, amino acid, and glucose
10 metabolism.

11 NEXT SLIDE

12 DR. SARAH PARK: BPS-mediated effects on the
13 circulatory system were also reported.

14 NEXT SLIDE

15 DR. SARAH PARK: In fish, BPS induced cardiac
16 edema and altered heart rate in some studies, while other
17 studies reported no effects.

18 NEXT SLIDE

19 DR. SARAH PARK: In zebrafish vessels, BPS
20 decreased endothelial cell numbers, distance between the
21 inflow and outflow tracts of the heart, and blood flow
22 velocity, and increased common cardinal vein area, ectopic
23 sprouting, red blood cell numbers, and lipid accumulation.

24 NEXT SLIDE

25 DR. SARAH PARK: BPS altered molecular markers

1 related to the circulatory system, including increased ROS
2 and apoptotic cells and expression of apoptosis-related
3 proteins in human umbilical vein endothelial cells and rat
4 embryonic heart cells, and enrichment of pathways related
5 to the cardiovascular system in BPS-treated zebrafish and
6 human embryonic stem cells.

7 NEXT SLIDE

8 DR. SARAH PARK: Nitric oxide plays a key role in
9 implantation, placentation, embryo development, and
10 vascular function. In zebrafish and human umbilical vein
11 endothelial cells, BPS increased nitric oxide levels and
12 nitric oxide synthase activity and the expression of its
13 encoding gene.

14 NEXT SLIDE

15 DR. SARAH PARK: Dr. Delker will now present on
16 the human epidemiologic evidence.

17 DR. ERIN DELKER: Thank you, Dr. Park.

18 NEXT SLIDE

19 DR. ERIN DELKER: Differences in the measurement
20 of BPS exposure should be considered when discussing
21 results from epidemiologic studies. Most studies measured
22 BPS levels in urine spot samples. The limits of detection
23 for BPS varied widely across studies, and therefore, the
24 percentage of participants with BPS detected in each study
25 were similarly varied, ranging from 14 to 99 percent of

1 the participants.

2 NEXT SLIDE

3 DR. ERIN DELKER: Study samples for the included
4 studies represented different settings. The birth years
5 of participants ranged from 1998 to 2023. Most studies
6 analyzed data from China or the United States. And of the
7 US studies, nine unique cohort studies were represented.

8 NEXT SLIDE

9 DR. ERIN DELKER: Studies measured associations
10 between prenatal BPS exposure and a variety of
11 developmental outcomes.

12 NEXT SLIDE

13 DR. ERIN DELKER: We'll start by discussing
14 findings from the papers examining birth outcomes, namely
15 length of gestation, fetal size, and birth size.

16 NEXT SLIDE

17 DR. ERIN DELKER: Most studies calculated
18 gestational length based on dating by the first
19 ultrasound. This variable was analyzed as a binary
20 variable for preterm birth, indicating births before 37
21 weeks gestation, and as a continuous variable, measured in
22 days or weeks.

23 NEXT SLIDE

24 DR. ERIN DELKER: We present the reported
25 estimates on the association between BPS and preterm birth

1 by timing of exposure assessment from preconception
2 through the third trimester.

3 When comparing the magnitude of associations
4 across studies, keep in mind that there were differences
5 in how the BPS exposure variable was operationalized. For
6 example, some analyzed BPS as a continuous variable and
7 reported associations per unit increase and others used
8 binary or three-level versions of this variable. This
9 heterogeneity makes it difficult to draw comparisons.

10 Plotted on the x-axis are the odds ratios or risk
11 ratios with 95 percent confidence intervals, and those
12 highlighted in blue are statistically significant.

13 Analyzing data from people attending a US fertility
14 clinic, per unit increases in preconception urinary BPS
15 were associated with over three times higher risk of
16 preterm birth.

17 Analyzing data from a birth cohort in China,
18 trimester one serum BPS in the highest tertile was
19 associated with about a twofold higher odds of preterm
20 birth compared to the lowest tertile.

21 And in a US-based case-control study of preterm
22 birth, detected urinary BPS measured in the third
23 trimester was associated with a twofold higher odds of
24 preterm birth.

25 Looking at the full picture, estimates tended to

1 be to the right of the null with BPS measured in trimester
2 one and two, and to the left of the null with BPS measured
3 in trimester three, though most confidence intervals were
4 wide and included the null value.

5 NEXT SLIDE

6 DR. ERIN DELKER: Other studies reported
7 associations between BPS and gestational length measured
8 as a continuous variable. The plotted effect estimates
9 here correspond to the estimated difference in days per
10 unit change in the BPS exposure variable.

11 Again, estimates of the association with BPS
12 measured in trimester one or two were to the left of the
13 null, indicating an association with shorter gestational
14 length, though the confidence intervals included the null
15 value, and these findings were not statistically
16 significant.

17 The two studies that reported significant
18 associations observed effects in opposite directions. Of
19 note is that both these studies used a cross-sectional
20 design with BPS measured at the delivery encounter.

21 NEXT SLIDE

22 DR. ERIN DELKER: Three of the studies on the
23 previous slide that reported no significant associations
24 in the full sample, reported associations between BPS and
25 shorter gestation duration among specific subgroups only.

1 These included an association with shorter gestation among
2 women reporting negative life events, an indicator of
3 psychosocial stress, among non-Hispanic white women, but
4 not women of other race/ethnicities, and among only
5 pregnancies with female fetuses in one study and male
6 fetuses in another.

7 NEXT SLIDE

8 DR. ERIN DELKER: Now, I'll present data for
9 fetal size and birth size, each which were measured by a
10 series of different indicators measured in utero between
11 16 and 35 weeks, and at birth, respectively. Most of the
12 studies on size at birth examined associations with birth
13 weight. And so these are the data for size measured at
14 birth that I'll focus on later in this presentation.

15 NEXT SLIDE

16 DR. ERIN DELKER: Two of the four studies
17 reported significant associations with fetal weight, one
18 reported associations with lower fetal weight among
19 pregnancies with male fetuses only, and one reported
20 associations with larger fetal weight. Two of six studies
21 reported significant associations with larger head
22 circumference, one of which observed significant
23 associations in female fetuses only. Two of five studies
24 reported associations with longer femur length, one of
25 which observed associations again in female fetuses only,

1 and one study reported associations with shorter femur
2 length. And there were no statistically significant
3 associations between BPS and abdominal circumference or
4 biparietal diameter.

5 NEXT SLIDE

6 DR. ERIN DELKER: Many studies reported
7 associations between BPS and birth weight analyzed as an
8 expected change in grams per unit change in the BPS
9 variable. The estimates from these studies are again
10 plotted by timing of BPS exposure measurement.

11 The two studies that reported associations with
12 larger birth weight were different from the rest in key
13 ways. The first was the only study that measured BPS
14 during preconception, reporting that per unit increases in
15 preconception BPS were associated with larger birth
16 weight. The second study was the only study sample to
17 include twins. When examining between-twin pair
18 differences, high versus low levels of BPS measured in the
19 second trimester were associated with heavier babies at
20 birth.

21 A study from China measured BPS in all three
22 trimesters. It reported that IQR increases in trimester
23 one and trimester two BPS were associated with lower birth
24 weight by 32 and 38 grams respectively. The association
25 with trimester three BPS was in a similar direction but

1 not significant.

2 A U.S.-based study observed that one-unit
3 increases in trimester one BPS exposure were associated
4 with lower birth weight by about 150 grams, though the
5 sample size here was small and the estimate was imprecise.

6 Findings from the other studies were mixed, with
7 many estimates near or around the null value.

8 NEXT SLIDE

9 DR. ERIN DELKER: Now, I will present data from
10 studies on the association between BPS and infant growth.

11 NEXT SLIDE

12 DR. ERIN DELKER: Five studies measured infant
13 growth trajectories. Two of those reported significant
14 associations with prenatal BPS exposure. One reported
15 that BPS measured in trimester three was associated with
16 more rapid growth from birth to six months in females, and
17 a second reported that BPS measured in trimester one was
18 associated with having a low-increasing trajectory, shown
19 in the figure as a red line, versus a moderate-stable
20 growth trajectory, shown in blue, from birth to 24 months.

21 NEXT SLIDE

22 DR. ERIN DELKER: Seven studies measured infant
23 size at other points after birth. Five of the seven
24 studies reported statistically significant associations
25 with prenatal BPS exposure. One of the studies reported

1 associations with smaller subscapular skinfold from birth
2 to four years. And four studies reported associations
3 with different indicators of larger child adiposity at
4 multiple points of assessment ranging from three months to
5 three years of age.

6 NEXT SLIDE

7 DR. ERIN DELKER: Now, I'll hand it over to Dr.
8 Andrews for a review of the rest of the developmental
9 outcomes.

10 DR. FAYE ANDREWS: Thank you, Dr. Delker. I'll
11 start by going into neurodevelopment outcomes.

12 NEXT SLIDE

13 DR. FAYE ANDREWS: For cognitive function
14 outcomes, two out of six studies observed statistically
15 significant associations.

16 First, those in the highest socioeconomic status
17 with higher second trimester BPS had worse cognitive
18 development at age two than those with lower levels of
19 BPS. Second, authors observed worse psychomotor
20 development at age two with higher gestational BPS
21 exposure. Higher first trimester BPS levels were
22 associated with better mental development compared to
23 those with lower BPS levels, although this association
24 varied by timing of exposure.

25 Four out of four studies report statistically

1 significant findings on socioemotional development between
2 two to four years. First, authors measured eye tracking
3 performance at age two and found reduced eye tracking
4 reaction time with higher second trimester BPS exposure.
5 Authors report that negative associations with reaction
6 time can be predictive of higher IQ scores and are shown
7 to be shorter in children with autism spectrum disorder.

8 Among females age 26-28 months, there were worse
9 scores for internalizing behavior and emotional reactive
10 problems with pooled BPS exposure over pregnancy.

11 Third, authors found -- oops sorry. Lost my
12 spot.

13 Lastly, a study observed higher odds of emotional
14 problems at age four from higher first trimester BPS
15 exposure.

16 NEXT SLIDE

17 DR. FAYE ANDREWS: Next, I will discuss immune
18 function and related outcomes.

19 NEXT SLIDE

20 DR. FAYE ANDREWS: Three out of six studies
21 reported statistically significant associations between
22 prenatal BPS exposure and asthma. One study observed
23 higher odds of asthma for children at age three, while
24 another observed only for males at age five. The next
25 study observed varying directions of associations between

1 girls and boys at age 13, where higher odds of asthma for
2 girls and a lower -- and a borderline lower odds of asthma
3 for boys with prenatal BPS exposure. Three studies found
4 no associations.

5 Within the same studies as the asthma ones, two
6 out of three studies reported reduced lung function at age
7 13, while another study observed better lung function at
8 age two months with higher BPS exposure.

9 For wheezing outcome, one out of three studies
10 report lower odds of late and persistent wheezes -- wheeze
11 patterns for -- after four years of age with detectable
12 BPS levels, while two other studies did not find
13 associations with wheezing at age three or six. One study
14 reported higher odds of bronchiolitis at age three. And
15 lastly, one study reported reduced odds of atopic
16 dermatitis at ages five to nine years for girls only with
17 average prenatal BPS exposure.

18 NEXT SLIDE

19 DR. FAYE ANDREWS: Next, I will go over endocrine
20 and metabolic outcomes.

21 NEXT SLIDE

22 DR. FAYE ANDREWS: Two out of three studies
23 reported statistically significant associations between
24 prenatal BPS exposure and thyroid stimulating hormone, or
25 TSH, with mixed results. One study reported that for

1 newborn boys, BPS was associated with lower TSH levels
2 while another study reported greater TSH levels per
3 doubling of BPS exposure for newborns, consistently
4 stronger for female newborns, while the last study did not
5 find any associations.

6 One study observed for boys age nine to ten years
7 there was lower insulin and glucose associated with first
8 trimester BPS exposure and lower odds of high LDL with
9 second trimester BPS exposure. One study reported that
10 follicle-stimulating hormone FSH was lowered in newborns
11 with higher BPS exposure for those whose birth parent had
12 normal pre-pregnancy BMI and separately for those whose
13 birth parent had a cesarean delivery.

14 Lastly, one study observed higher kisspeptin
15 levels at age six, and it was shorter -- it was shorter.
16 Excuse me. It was stronger for males for the highest BPS
17 exposure group. Kisspeptin is a family of peptides
18 involved in a number of reproductive processes, including
19 the secretion of gonadotropins and the regulation of
20 fertility and puberty onset.

21 NEXT SLIDE

22 DR. FAYE ANDREWS: Lastly, I'll go over other
23 outcomes within the developmental toxicity endpoint.

24 NEXT SLIDE

25 DR. FAYE ANDREWS: One study observed higher odds

1 of rapid AGD and lengthened anus-clitoris and anus
2 fourchette distance at 48 months in girls with detected
3 BPS exposure in the third trimester. One study observed
4 delayed first menstruation in girls at 10 to 13 years with
5 BPS exposure averaged across gestation. Lastly, two out
6 of two studies showed lower bone mineral density, one
7 observed only in males, while the other observed in the
8 whole population at age 10.

9 NEXT SLIDE

10 DR. FAYE ANDREWS: In the next several slides, we
11 provide a brief summary across evidence streams
12 highlighting BPS-mediated effects on the developmental
13 toxicity endpoint.

14 NEXT SLIDE

15 DR. FAYE ANDREWS: In this presentation, we
16 summarized data linking BPS exposure to many different
17 developmental outcomes in animals, mechanistic evidence,
18 and human epidemiologic data. Now, we'd like to highlight
19 for those outcomes with the most consistent findings
20 within and across evidence streams. These outcomes
21 include neurodevelopmental, developmental reproductive,
22 and metabolic effects.

23 NEXT SLIDE

24 DR. FAYE ANDREWS: BPS was associated with
25 neurodevelopmental effects in animals and humans. Animal

1 evidence included altered locomotion, decreased cognitive
2 function, increased anxiety and depression-like behavior,
3 and altered social behavior. In support of these
4 findings, BPS was associated with more emotional and
5 social behavioral problems in humans. In animal and in
6 vitro systems with these effects, mechanistic evidence
7 included altered neurogenesis and neurodevelopmental and
8 neurotransmitter related genes.

9 NEXT SLIDE

10 DR. FAYE ANDREWS: BPS was associated with
11 developmental reproductive effects. Animal evidence
12 included alterations to ovarian function, female pubertal
13 onset, estrous cycle, and reproductive function in females
14 and males. There was abundant evidence of endocrine
15 disruption in vivo and in vitro. This was supported by
16 female evidence of associations with delayed pubertal
17 onset and increased AGD.

18 NEXT SLIDE

19 DR. FAYE ANDREWS: Lastly, BPS altered metabolic
20 function in animals and was associated with related
21 indicators in humans. Animal evidence included increased
22 adipose weight and lipid accumulation. In support of
23 these findings, BPS was associated with greater postnatal
24 adiposity and rapid post-natal growth. Within animal
25 systems with these findings, there was supportive

1 mechanistic evidence including altered glucose, lipid, and
2 fatty acid levels, and altered expression of hepatic and
3 lipid metabolism markers.

4 This concludes our presentation. Thank you for
5 your time and attention.

6 CHAIR LUDERER: Thanks very much for your
7 presentations. That was a wonderful overview. Very
8 complicated set of studies that we have here.

9 So now, I'd like to ask if there are any
10 clarifying questions from any of the members of the panel.

11 Yes Isaac.

12 COMMITTEE MEMBER PESSAH: The one thing that I
13 didn't hear that I think would be very helpful to the
14 Committee, especially reviewing animal and mechanistic
15 studies, what were the levels, geometric means, in urine,
16 or cord blood, or serum. I know those are out there, but
17 I didn't hear anything about those levels.

18 DR. FRANCISCO MORAN: Yeah. Unfortunately, I
19 don't have the data in my mind, but I can figure out
20 easily, if you give me some time during the break. It
21 wasn't measured in many studies. Yeah, internal dose.
22 You're asking for that, right, internal dose? Yeah.

23 COMMITTEE MEMBER PESSAH: Yeah. It's very
24 important in putting animal --

25 DR. FRANCISCO MORAN: Right.

1 COMMITTEE MEMBER PESSAH: -- and cellular studies
2 in perspective in terms of biological plausibility,
3 because --

4 DR. FRANCISCO MORAN: Right.

5 COMMITTEE MEMBER PESSAH: -- I think the levels
6 are in the 0.25 range micrograms per milliliter I think it
7 is or liter.

8 DR. FRANCISCO MORAN: Yes. The range is huge
9 from micrograms to milligrams per kilogram in mammals and
10 micrograms to milligram per liter in non-mammals. I
11 understand your concern, but we -- unfortunately most of
12 the publications don't report and they compare control
13 versus treated. And that -- what we assume that something
14 is happening with the treatment, you know, having the
15 right control. That's the limitation problem of the
16 systems that we don't have much data.

17 COMMITTEE MEMBER PESSAH: Right. But there are
18 measurements --

19 DR. FRANCISCO MORAN: There are some
20 measurements, yeah.

21 COMMITTEE MEMBER PESSAH: -- in serum, urine --

22 DR. FRANCISCO MORAN: Yeah.

23 COMMITTEE MEMBER PESSAH: -- and cord blood that
24 are perhaps studies that didn't look at neurodevelopmental
25 outcomes --

1 DR. FRANCISCO MORAN: Right. Right.

2 COMMITTEE MEMBER PESSAH: -- at least as -- I
3 don't know if NHANES has some of those.

4 DR. FRANCISCO MORAN: Right, but yes.

5 DR. SARAH SAUCIER: In the cellar studies we
6 highlighted, we did provide the range -- the dose range.

7 COMMITTEE MEMBER PESSAH: Yeah, and I really
8 appreciate that.

9 CHAIR LUDERER: Any clarifying questions from
10 other members of the Panel?

11 All right. Not seeing any raised hands then, we
12 will -- oh, we do.

13 COMMITTEE MEMBER PLOPPER: In trying to assess --

14 COURT REPORTER: Microphone.

15 COMMITTEE MEMBER PLOPPER: -- the toxicity
16 here --

17 COURT REPORTER: Microphone.

18 CHAIR LUDERER: Turn on your microphone.

19 COMMITTEE MEMBER PLOPPER: Yeah. In trying to
20 assess the toxicity, you did a thorough job of explaining
21 what the dose ranges were for each study, but they vary.
22 Some of them are in nanograms, some of them are in
23 micrograms, some of them are milligrams, some are in
24 molar, micromolar. And the problem for -- at least for me
25 trying to go over those 88 studies was trying to come up

1 with some method for establishing what the relationship is
2 between the concentrations that they're exposed to and the
3 response, because as you are well aware almost everyone of
4 the studies you outlined here for a specific function or
5 activity found both effect -- high effects, low effects,
6 and no effects.

7 And I think it would be very helpful to have
8 known what those -- what all -- if they were all in the
9 same concentration range and the same time frame range, if
10 that's -- just -- I know you can't do anything about it
11 now, but I just wanted to emphasize that this is such a
12 complicated set of studies, that it would really help to
13 have some kind of a way. I know it's a tremendous amount
14 of work, but to get some way to get, so that we could see
15 what the concentration, exposure, and dose was for each
16 one of these. Particularly, it makes -- when you're
17 sitting and you're looking at the animal studies, and you
18 say, well, I wonder if this level was this -- like this in
19 the human studies. Well then, quite frankly, I just
20 didn't have time to go back and recalculate to figure out
21 how they relate to each other.

22 So I just -- from following up on what Isaac
23 said, that was one of the challenges that I found with
24 trying to make some relationships out of these studies was
25 making sure I had some perspective on what the time frame

1 and the concentrations were of the exposures, so I just --

2 CHAIR LUDERER: All right. Thank you very much.

3 Do we have any -- Martine.

4 COMMITTEE MEMBER CULTY: I just wanted to say
5 that it was also very complicated for me, but there was
6 some indication in -- at least in the urine levels of a
7 woman, like from a California study. So I know it's not
8 the cord blood or the amnio -- amniotic fluid, but there
9 was likely in a study in Californian in women, you -- the
10 Table 1-1 mentioned open 38 microgram per liter, which
11 is within the range of solve of animal studies in -- so I
12 know it's from the urine from the metabolite, but it still
13 sort of indicates some type of similar range for some of
14 the animal studies, but yeah, it's also like not
15 absolutely clear maybe when they put in the drinking water
16 similar level how much was really absorbed and, you know,
17 went for a DME and was really basically reaching the
18 target tissue.

19 But I think some of the -- of the woman
20 measurement at least suggests that some of the animal
21 studies tried to be in the range of what was measured in
22 human, not all of them. As you say, it's -- you know, it
23 goes from thousand range difference depending on the
24 experiment. But there is some experiment that sort of
25 matched. I think, you know, some of the exposure level

1 measured in human. I don't know if it helps or not.

2 COMMITTEE MEMBER AUYEUNG-KIM: Yeah. This is
3 unfortunately where -- I know that we tend to look more at
4 the peer-reviewed papers and that's where a lot of the
5 times, the measurement, the plasma levels and stuff aren't
6 measured. However, this is the case where the industry
7 reports from like the BASF, that they do show what the
8 concentrations are. But again, a lot of it is much higher
9 than what we would see in human exposure.

10 COMMITTEE MEMBER PESSAH: Again, when I -- when I
11 was trying to find by logical plausibility, because there
12 are many in vitro studies, the vast majority saw effects
13 above a micromolar. And I back-calculated what
14 information I could get out of the human literature for
15 urine levels, serum levels, and cord blood levels, and
16 they typically -- if you're over a micromolar in terms of
17 dosing cells or whatever, you're about 30,000 to 60,000
18 times higher than human relevance. And so, I use that as
19 a guide for which studies I highlight in the mechanistic
20 studies.

21 CHAIR LUDERER: All right. Thank you.

22 Do we have any other clarifying questions before
23 we move on -- oh, Dr. Sandy.

24 DR. MARTHA SANDY: Thank you. I just wanted to
25 say a few things. We don't have any human experimental

1 obser -- you know, studies, where they gave a known dose
2 of BPS and then measured levels in urine or in blood. We
3 have estimates of the half-life, which is fairly short.
4 The epidemiology studies may have taken a few different
5 time points for urine samples to measure, but it's a
6 snapshot in time, keep that in mind, and also that humans
7 are exposed to BPS through different, you know,
8 mechanisms, touching different things. And so they may
9 have increased levels for a short period of time during a
10 critical window, and we don't -- so we don't have the data
11 we'd like to have on that.

12 And the animal studies, they're experimental
13 studies with controls that were untreated, and then we
14 know how much was administered to the animals. Many of
15 these studies reviewed did not also measure the levels of
16 the BPS in the blood or the urine.

17 CHAIR LUDERER: Thank you very much for the
18 clarification and that discussion. I don't think I see
19 any additional questions.

20 So, then what I'd like to -- I'd like to move on
21 to hearing from the initial discussants. So, we will hear
22 first from Dr. Carrie Breton and then from Dr. Kim Harley
23 on the human studies. And then we'll hear from Dr.
24 Plopper, Dr. Auyeung-Kim, and Larry Baskin on the animal
25 studies. And finally, Dr. Isaac Pessah and Martine Culty

1 on the mechanistic studies.

2 So, then we will start with Carrie.

3 COMMITTEE MEMBER BRETON: Okay. Let's see, can
4 you guys hear me okay?

5 All right. So I thank you very much for the nice
6 presentation and summary. I always love seeing how you
7 guys put things together actually. It's great.

8 So, I guess my job is to start in thinking about
9 and sort of providing my take on the human studies for
10 BPS. So, I guess I'll just start by saying that, you
11 know, in total there are -- were, as you reported, 65
12 human epidemiological studies that have been conducted.
13 And so that's a decent amount of human research. So --
14 and as I think has been acknowledged unfortunately, there
15 are -- there are concerns that I think just are good to
16 keep in mind as we talk about the human studies. One of
17 them, as you mentioned, is definitely the sort of low
18 detection rates of BPS in a lot of these studies, which
19 just limit what you can do from an analytical point of
20 view, right, with human studies, and looking at detect
21 versus non-detect, not necessarily being able to look at
22 dose response at all, which I think is something that we
23 would like to be able to do.

24 And then the primary, I think, relevant
25 endpoints, for which there is some set of evidence,

1 include fetal -- altered fetal growth, changes in
2 gestational age at delivery or a preterm birth, and the
3 neurobehavioral outcomes. So I'll touch a little bit on
4 those and spend a little bit more time where I think there
5 is some suggestion of evidence versus where there -- I
6 think really the literature is just too sparse or there
7 really isn't much evidence so far.

8 So gestational length, there were seven studies
9 that showed either a risk of preterm birth or shorter
10 gestational age. Some of these though, and I think this
11 was mentioned, were in the same cohort. So even though we
12 have multiple studies, maybe the cohorts that are
13 represented for any one outcome are actually smaller in
14 number.

15 One of these studies includes a larger nationwide
16 pooled analysis. That's from the ECHA Program. And then
17 there was one that showed the op -- a direction of effect
18 that was sort of the opposite of what we would
19 hypothesize. And four of the seven were null results. So
20 really there's sort of a mixed bag of results for looking
21 at preterm birth and gestational age.

22 So I think, you know, in summary from these
23 studies, there's a trend toward a risk for preterm birth
24 and shorter gestation, specifically from looking at
25 trimester one exposures or preconception exposures. So

1 definitely the preponderance of the evidence looks --
2 seemed to suggest to me that if there is an association,
3 it really is in the early pregnancy period where the
4 exposures seems to be relevant. And then -- and there was
5 some suggestion of evidence that it might -- there may be
6 stronger effects in male infants.

7 So I think -- let's see. I thought it was
8 interesting one of the stronger studies is this ECHA
9 analysis that's really a pooled analysis that brings
10 together a lot of cohorts across the U.S. And what I
11 found, I think, interesting, but also highlights the
12 complexity of this -- the potential associations are that
13 they did not -- while they didn't see an overall
14 statistically significant effect, they did find a subgroup
15 effects, and the suggestion that there's a U-shaped
16 response curve, which I think is worth mentioning and
17 keeping in mind.

18 Again, most of the studies don't even have the
19 ability to try and look at a U-shape or a dose-response
20 curve that may not be linear, especially when we're
21 running up against the boundaries of detection limits.
22 And with a lot of these studies having 75 -- or 60 to 75
23 percent of their -- the samples being below the limit of
24 detection, you really are limited in what you can do
25 there.

1 And, if there truly is a U-shaped dose response
2 curve, then I think that's going to heavily influence why
3 we have such a mixed bag of responses in these studies,
4 especially when you're looking just at not detect and
5 non-detect as the exposure.

6 So, let's see, I do want to point out though that
7 even for the null findings, a lot of the times the -- if
8 you looked at the coefficient, it was suggestive and
9 trending in the right direction. For this -- these seven
10 studies, the one study by Wang et al. that was -- that
11 found an opposite direction, I think it's important to
12 note that that was one of the only studies that actually
13 measured the exposure at delivery. And so it's making
14 this huge assumption that what you see at delivery is that
15 representative of my -- of the exposure windows perhaps in
16 the first trimester that might be most relevant. So it
17 was cross-sectional in nature.

18 I think -- let's see I want to be able to move
19 on, so -- but I think two of -- three of the strongest
20 studies that all showed increased risk for preterm birth
21 or a lower gestational age are the Liang 2021 paper, the
22 Trasande paper, the ECHA paper, which I already mentioned,
23 and the Yang 2021 paper. And these, generally speaking, I
24 felt were strongest in the sense that they had some of the
25 largest sample sizes. And so the great -- and the

1 greatest statistical power, as well as relatively greater
2 proportions of exposures that were above the LOD.

3 I also want to talk about birth weights. I'll
4 move on to birth weight. I think of all the human
5 studies, there are probably the most studies looking at
6 birth weight. So, by my count, there were 18 in total
7 looking at birth weight or fetal weight. I think I lumped
8 fetal weight into this grouping. But even looking at that
9 and birth weight as a really common outcome in humans
10 studies, only five of these publications were, you know,
11 supportive in terms of a statistically significant
12 association with risk for low birth weight. Two were in
13 the opposite direction and 11 of these were null.

14 Although, as I mentioned with the other ones, a
15 lot of the null results are trending toward the inverse
16 association. So, in many cases, I think we're dealing
17 with a situation in which we're simply underpowered or
18 have low power to really detect the magnitude of
19 associations that we are seeing.

20 What else do I want to say about this?

21 So, I guess I really felt that the results for
22 birth weight were mixed, when looking at the total of the
23 18 studies. Although, I think there are definitely some
24 papers and some studies that are stronger methodologically
25 than others. And I think when you look at some of -- some

1 of -- some of the papers with larger sample size that had
2 the ability to look at subgroup analyses, there are some
3 questions raised about seeing different effects in
4 different subgroups. And, I mean, this remains a
5 question, I think, in my mind too.

6 And then, let's see, in terms of fetal size and
7 sort of other fetal measurements, I really found that
8 there were typically less than half of the studies showed
9 some sort of association. So I thought there was pretty
10 limited evidence for some of the other fetal measurements
11 that have been evaluated so far.

12 So I would say the same for infant growth with
13 looking actually at growth trajectories, that the results
14 were mixed, as was shown before. So some showed support
15 and some showed null results for looking at growth, but
16 looking at infant size at various ages, usually between
17 two, and three, and four years of age, I think the
18 strongest evidence actually in the human studies was
19 look -- was for infant size in childhood, where there were
20 a total of seven studies, most observing associations with
21 higher weight, or higher BMI, or a larger skinfold
22 measurements at this sort of range of around two to three
23 years of old. So I think to me, some of those studies and
24 that body of work is some of the strongest work in the
25 human studies looking at size -- at infant size, as well

1 as neurodevelopment.

2 So that would be the other outcome I think for
3 which there -- the human studies had some of the greatest
4 suggestion of evidence, and specifically for the
5 socioemotional behavior -- behavioral development
6 outcomes. And that is -- you know, it's still a limited
7 body of work. It was, I think, four studies in total that
8 looked at prenatal BPS, and specifically some of
9 socioemotional outcomes, but they all found negative
10 associations. So when -- you know, consistency I think is
11 a good thing at -- a good thing in terms of evidence for
12 the associations that we're trying to understand and
13 evaluate.

14 And let's see, immune function and endocrine and
15 metabolic effects, and then some of -- and what was -- the
16 other one was bone mass and mineral density. All of these
17 I thought had sort of weaker levels of evidence. Immune
18 function in particular looked mostly at asthma risk and
19 lung function. And those were the primary outcomes under
20 this category. I think there -- you know, some studies
21 had a little bit of evidence for risk of asthma. But the
22 two largest studies that looked at multiple cohorts, one
23 was in the U.S. and one was in Europe, largely found no
24 associations or even protective associations. And so I
25 think one has to really take that with a grain of salt at

1 this point, in terms of just the preponderance of the
2 evidence.

3 And, I mean, let's see. So I think I'll just end
4 there. I think the -- there's limited evidence for the
5 effects of preterm birth on bone mineral density, but --
6 and immune development, but some suggested evidence. I
7 think the strongest evidence among the humans -- human
8 studies being for low birth weight, sort of a lower
9 gestational age, and the socioemotional behavioral
10 development outcomes.

11 CHAIR LUDERER: Thank you very much, Carrie, for
12 that summary of very many studies.

13 (Laughter).

14 CHAIR LUDERER: And Kim, would you like to
15 continue?

16 COMMITTEE MEMBER HARLEY: Sure. Yeah, I agreed
17 with a lot of what Dr. Breton said. As she mentioned,
18 there were 65 different papers, but those were from 27
19 different pop -- study populations. And to do this
20 research requires -- generally requires a large ongoing
21 longitudinal cohort study. So what we have is a much
22 smaller number of cohort studies that we're getting the
23 information from. I wanted to take a step back and just
24 kind of talk about the quality of the studies and some of
25 the problems that were going to encounter with this kind

1 of research.

2 We talked about this last time we talked about
3 BPS. BPS is a nonpersistent chemical. It stays in our
4 bodies. The half-life is about seven to nine hours. It's
5 probably out of our body in -- you know, within a day. If
6 you take a measurement in urine in the afternoon, you're
7 probably getting a measure of what that person had for
8 lunch. And if they had something different for lunch, you
9 know, yesterday, you would have gotten a different
10 measure.

11 So we have a very noisy measure here. And many
12 of our studies -- for me, the biggest weakness in these
13 studies is the exposure assessment. And I mean, it's just
14 such a glaring difficulty in studying this chemical.

15 There was -- I want to call out one study, the
16 French study, Sapage study, which there were, I think,
17 maybe seven or eight different papers. They were the only
18 study that took daily -- they took three urine samples a
19 day for a week. In the second trimester, they took three
20 urine samples a day for a week. In the second trimester,
21 they pooled those and got one measure, and that was the
22 only study that I felt like really tried to get a good
23 measure of what that person -- that pregnant person's
24 exposure was in the -- you know, during one week of the
25 second trimester, one week of the third trimester. I wish

1 that it had worked out better for them, because their
2 limit of detection was a little high and their levels -- I
3 think their levels of BPS were actually fairly low. And
4 what happened in that study is they ended up with a lot of
5 people below the limit of detection, and all they could
6 look at was are you detected or are you not detected.

7 And so, it was a really good effort, but
8 unfortunately, they didn't end up with a great measure of
9 exposure. Then we had several other studies that took
10 three measures or maybe two measures during pregnancy.
11 Often they took one measure, one urine sample in each
12 trimester, which is good because you can average those
13 three and you can start to get, you know, an idea of what
14 your exposures over the course of pregnancy. But most of
15 those studies, I mean, they did do that, but often they
16 were looking at one trimester at a time.

17 So, it's great that on one hand we can look at
18 the timing of exposure, but we have to remember that when
19 we're talking about exposure in the first trimester, we're
20 basing that on one urine sample, similarly with the second
21 and the third trimester. So, those are sort of the second
22 best studies. And they're good -- a lot of these studies
23 are very well done, and yet we're still running up against
24 the limitations of these measures.

25 And then we have a bunch of studies that only

1 took one measurement. We have a bunch of studies that had
2 a lot of people below the limit of detection, so we're
3 only, you know, 25 percent of people or 40 percent of
4 people were even detected. So again, that's a difficulty.
5 And then, we did have a couple of -- a few studies that
6 measured in serum rather than in urine. And urine is
7 really, I think, the most approved metrics for us to look
8 at.

9 So, we have a lot of studies of -- with a lot of
10 problems in exposure assessment. There's a lot of noise
11 in our exposure assessment, and a lot of this is sort of
12 like a blunt instrument. We're trying to find a signal in
13 a lot of noise. So, given that that's true, we're looking
14 for our bigger studies. We're looking for consistency
15 among studies. And, you know, that's kind of what we're
16 trying to get at here.

17 The other thing I did want to mention is Carrie
18 brought up the fact that people -- some studies found
19 associations in certain subgroups. And I think that's a
20 little bit of a double-edged sword, because remember,
21 we're making a lot of comparisons here already. So,
22 most -- almost all of these studies they're not just
23 looking at BPS. They're looking at BPA, BPF. So at the
24 minimum, they're looking at three chemicals. Most of them
25 throw in some other phenols. Some of them throw in some

1 phthalates. Some of them are looking at you know, 12, 15
2 different chemicals. Then they're looking at, I don't
3 how, many three, four, five, six endpoints, so you can see
4 we've got a lot of opportunity here for a Type I error and
5 finding associations just by chance.

6 And then you start saying, well, is it in boys
7 and not girls? It is low SES or high SES? Is it in
8 different racial groups? And I think it's important to be
9 able to try to tease apart these different subgroups, but
10 I also think you're really setting yourself up to find
11 things that aren't real, that are just, you know,
12 associations by chance. And for us, it's really hard to
13 tease those apart, which ones do we believe, and which
14 ones do we think are just by chance?

15 And then the last thing about these studies is I
16 mentioned there's many different chemicals, so they're
17 looking at mixtures of exposures. And some of our studies
18 did actually try to tease that apart and use different
19 mixture analysis measures to try and see like how much is
20 BPS actually contributing to this, but a lot of the
21 studies didn't do that. So, that's just another sort of
22 caveat to put out there.

23 Can I just say a little bit more about the
24 different -- so just -- Carrie went through and talked
25 about what she thought were sort of the stronger

1 associations in our studies. With the preterm birth and
2 the gestational age, I'm a little bit more on the fence, I
3 think, that there were, you know, five studies found
4 associations, but six didn't. And some of the ones
5 that -- you know, many of the ones that did find
6 associations, they found them only in subgroups and not in
7 the entire population. So, I'm not really convinced about
8 a pattern there. Similarly, with the birth weight and the
9 fetal growth, I was -- I felt like the evidence was
10 stronger with the child growth. And Carrie mentioned this
11 that we seem to see a trend towards heavier -- higher BMI
12 in young children. So I think there's a little bit more
13 consistency in that particular outcome.

14 Similarly, with the neurodevelopmental, I didn't
15 see -- there were three studies that looked at cognitive
16 development, looked at IG, didn't find any associations.
17 I think the jury is still totally out on that one. That's
18 a really hard analysis to find an association with, so
19 there's no evidence for it. It doesn't mean it doesn't
20 exist, but there's no evidence currently. But there were
21 those three or four studies that found associations with
22 behavior problems in two to four year olds occurring to
23 parental report, looking at internalizing -- seeing
24 internalizing problems, emotional, social, behavioral
25 problems. And I think that's interesting and I think we

1 should -- you know, we should take a look at that.

2 Asthma and immune function, I didn't think that
3 the associations were as strong.

4 Is that telling me to stop talking?

5 (Laughter).

6 COMMITTEE MEMBER HARLEY: I can -- I can leave it
7 that and we can have some conversation or conversation,
8 but -- or discussion, but yeah, the behave --
9 neurobehavior and the -- and the body size in young
10 children I thought were the strongest, where the evidence
11 was the strongest.

12 CHAIR LUDERER: Thank you, very much, Kim. We
13 could -- if we have maybe some time now for discussion
14 about the human data before we move on to the mechanistic
15 studies, more in the sense of clarifying questions.

16 COMMITTEE MEMBER PESSAH: I just want a
17 clarification here from the epidemiologists. Clearly,
18 there are going to be spikes in hour-by-hour exposures,
19 but over the period of time that the studies are
20 measuring, wouldn't you expect, if the exposure are
21 consistent over time, that there would be a steady state
22 level. And that's what the geometric means that are in
23 the documents suggest. Is that -- or am I way off here?

24 COMMITTEE MEMBER HARLEY: I think that the
25 sources of exposure vary. We know a lot of it's from

1 diet. And I think it can just change from day to day. So
2 I should look at -- I can look in the document in a few
3 minutes. I think there was something that was there.
4 Somewhere in there there was the ICCs between measures.
5 And they were okay. You know, like you guys can maybe
6 know the numbers better than me. I was remembering like
7 0.1 to 0.4 or something as the ICCs, which are not great.
8 They are correlated. I'll just say if you take three
9 measures during pregnancy, they're correlated. They're
10 not super correlated, but they are correlated. And it's
11 sort of like a matter of how regular are your behaviors,
12 how similar is your diet. You know, it's -- yeah, it's
13 hard to know.

14 COMMITTEE MEMBER BRETON: But certainly, that's
15 the assumption that we tend to make when we conduct the
16 studies and make the choice of taking one sample, right,
17 per -- I mean, there's all sorts of operational,
18 logistical reasons too, of course, but -- yeah.

19 CHAIR LUDERER: All right. Why we don't move on
20 then next to the discussion of the animal studies. And so
21 we'll start with Dr. Plopper.

22 COMMITTEE MEMBER PLOPPER: Okay. Thank you. I'd
23 like to recognize the quality of the work that the staff
24 did here. They've pretty much covered most of the issues
25 that I had on my list, so -- and those documents are

1 excellent as far as I'm concerned. I mentioned the things
2 that frustrated me, but basically, those were good.

3 What I like to do then is just provide an over --
4 my overview of how I would see these various studies. And
5 I would like to start with the early embryo development
6 and compare what's been found in mammals with what's been
7 found in chickens and then in the zebrafish. And just
8 to -- and we'll do the same thing with various -- with the
9 post -- first the -- what happens with the embryo and then
10 once the embryo has gotten itself matured into either a
11 fetus or in the -- in the case of zebrafish, a larva.
12 Then what happens to the next stage? Does it move on?
13 Does it become -- how it impacts the individual at birth,
14 in the case of the mammals, and cracking the egg with the
15 chick, and how do they survive?

16 And then finally, I'd just like to make a few
17 comments on our -- just rehash very shortly our detailed
18 work that this Committee and OEHHA has done on
19 reproductive systems for both females and males. And I
20 think as we emphasized the first time when we actually
21 reviewed those, about two-thirds of the changes that
22 occurred, occurred -- were associated with things that
23 were -- that happened while we were -- while we were
24 dealing with embryos and fetuses and these were the
25 outcomes, survivors. And I'd like to make a few comments

1 on neurodevelopment and then circulatory systems, but I'll
2 try to keep it short, but there's a lot there. And so,
3 I'm very impressed with how much data there is.

4 Well, let's start with the embryos and the fetus.
5 There were five studies in mice and seven studies in rats
6 that assessed what happens to the pup, what happens to the
7 embryo once it's been post-fertilization and you get the
8 two to four stage. And what I found very interesting is
9 that two of the studies -- rat studies -- or mouse studies
10 have -- showed decreases in the number of four-cell
11 embryos and an actual negative impact on the total embryo
12 development, but three of them didn't show any impact on
13 litter size, which I thought was quite interesting.

14 The same thing with the rat, five of the studies
15 showed impacts on failure, either of implantation or of
16 the pups per litter. In other words, the embryos were
17 all -- all the eggs were fertilized, but a large
18 percentage of them did not successfully move on through
19 embryo into a fetal stage and then into a neonate.

20 But again, two of those studies phone -- found no
21 implantation loss at all. The one study in the sheep
22 showed that embryo rate and the four-cell embryos were
23 done, and chicks all four of the studies that were done
24 with infiltrated or in -- where they took the eggs and
25 provide them. They all had decreased hatching rates and

1 decreased survival rates and increase in embryo. So in
2 other words once they were fertilized and then treated,
3 they -- all of them had negative success.

4 One of the things I thought was most interesting
5 and why I brought up the issue regarding the dose range in
6 studies is that in the zebrafish there were 19 studies
7 that looked at the hatchability rate, in other words what
8 they called it, which is the movement from the embryo to
9 the larva, and then the larva successfully be able to live
10 on its own essentially, and start feeding and doing other
11 things. And two of them showed increase in hatching rates
12 and seven of them showed a decrease in hatching rate, in
13 other words, their greater -- two had greater and seven
14 had less success compared to the controls. And then there
15 were two that were second generation and they found the
16 same -- these are exposed, and then they're -- they were
17 second. This is the next generation up and they had
18 decreased hatching rates.

19 The thing I thought was interesting is that eight
20 of these studies pursued a no effect on hatching rate at
21 all, so that it didn't -- exposure didn't affect the
22 embryo or the larva. And the thing that got me stirred up
23 about this, and that's why I bring up the dose and time
24 thing, is that if you sit down and you actually look at
25 what all of these studies did and calculate out exactly

1 what the doses were, most of these studies, the dose
2 ranges were at the lower end. You're talking micrograms
3 or nanograms, really tiny, and they were very short
4 exposure times.

5 The key thing here is that -- and it depended on
6 the study, but the time from an embryo to a functional
7 larva is five to six days, depending on a number of
8 factors, including concentration, light sources. There's
9 a number of things that make it irregular. Well, all of
10 these eight studies that had no effect were all the ones
11 that -- except for one, that they didn't even -- they
12 didn't even expose them past day four. So what it would
13 say to me is that what the no-effect studies here show you
14 is not that this is maybe not an effect at all, this is
15 the lower end of the range.

16 So they were using the lower end of the
17 concentration range and the shorter exposure times,
18 because some of the ones that showed actually showed
19 impact on hatching rate were actually -- were ones that
20 stopped and then added later. There's -- so that there --
21 it was -- there is a term there. And for survival rates,
22 the same thing. Four of them had loss of survival, in
23 other words, they didn't survive. They didn't move --
24 larva did not move on to become functional, but 12 of them
25 had no effect. Well, most of those no-effect ones are the

1 same ones that didn't have any effect on the hatching
2 rate, which you might expect if that's what -- if it's a
3 dose response. So I don't know about that.

4 In terms of what happens at the birth or the
5 birth size, most of the mice -- mouse studies that in
6 which the embryos survived, and became fetuses, and moved
7 to the point of parturition, there was no effect on body
8 weight, except for one study out of four. And
9 interesting, in all three rats study, not only were there
10 changes in body weight, but there was skeletal
11 malformations. And so, that there was an impact, and the
12 same thing happened with the chickens. Two of the -- two
13 of the egg studies had skeletal malformations and a
14 decrease in growth, but one of them had no effect at all.

15 In the zebrafish, it's the same sort of a thing.
16 You have the increase in body length, which was what was
17 used as a measurement of their -- of their growth. And
18 two of them had that, six had no -- had a decrease, and
19 five had no effect.

20 And again, I think it's probably -- when I
21 started going back and looking at who did those studies,
22 those are the studies that -- the short exposure times and
23 the lower end of the range. I mean, we're talking -- the
24 thing, I'll just say it once more, the thing that
25 overwhelmed me about trying to compare these studies is

1 that the dose range from one set of studies to another
2 could be over a thousand, a thousand -- 10 to the third or
3 10 to the fourth. So it's hard to compare these. You
4 have to -- that's why I thought I'd just bring it up this
5 way is that it -- we're not looking -- you just can't say
6 okay, so half of them there was no effect. Well, that's
7 the -- that looks like the lower end of the -- if they
8 were doing one study together, you'd put them all in there
9 together, and you would say, yeah, there's an effect at
10 the high dose and the longer timeframe, but not at the
11 lower dose and the shorter time frame. And I think that
12 was the case for the skeletal defects as well, which some
13 of them had them and some of them had no effect at all.

14 And finally, reproductive system. We've already
15 been over that before. I just want to emphasize that we
16 went through this in detail for males last year. And the
17 key thing here that I think is worth emphasizing is that
18 when this -- when the males were treated with -- and these
19 are surviving embryos now, that made it all the way out of
20 the mother, the -- they had -- there was a disruption in
21 the seminiferous tubules. And this was -- failed not only
22 their function, but also their spermatogenesis. And the
23 same was true for both the mice and the rats. And I've
24 thought it was interesting that some of them measured rat
25 studies, measured weight, and some didn't, but they all

1 found the same problem, the seminal vesicle was damages.
2 So that means that there was a seminiferous tubules were
3 damaged, and that there was a negative effect on the
4 ability of these exposed as embryos and fetuses, when
5 their testis mature, it doesn't mature. And this was also
6 reflected in the -- in sperm concentrations, which were
7 reduced in the three studies that were looked at.

8 For female reproduction, the same problem. In
9 the -- in the ovary, all of the studies, three female --
10 three mice and one rat study, all of them had severe
11 disruption and in ovarian function, including oocyte
12 formation. And remember these are the survivors. They've
13 already been exposed before, and they lived through it
14 all. And then, when it's time for them to be mature,
15 their ovaries don't function and. And this was -- they
16 weren't being exposed any more. These were -- they grew
17 up this way.

18 And then the same is true for the puberty onset
19 with being delayed in both mice and rats that were exposed
20 and affected. And I think, yeah, reproductive
21 performance, the same thing, what you'd expect if they --
22 if they didn't have -- if they didn't have ovaries that
23 worked or sperm that worked, then you would -- then you
24 would -- be sort of that there would be a drop in litter
25 size and a drop in the embryos in the impregnated animals

1 that had survived the initial perform -- permanent.

2 And then final just comments on two other things.
3 One that I thought was quite surprising was the
4 neurodevelopment and behavior, there were four studies in
5 mice and one study in rats. And all of them, except for
6 one, found that their -- they didn't look -- only one
7 studied hippocampal and found Hippocampal pathology. The
8 others, it was strictly behavioral, and really marked
9 behavioral, which means that the neurosystem was damaged
10 and nobody had just bothered to do the pathology on it.

11 The same thing was true for the -- for the
12 zebrafish studies. They've got a list of about eight
13 different functions that -- behavior functions or movement
14 functions. And almost all of the animal studies -- or
15 zebrafish studies, except six, had severe effects,
16 spontaneous movement speed, react -- social reaction to
17 other behavior locomotion. And they -- apparently,
18 there's somehow they could assess the hypothalamus and
19 found that there was some negative impact on the nervous
20 system in general.

21 And then finally, I'll just make one more
22 comment - sorry, I didn't mean to take this long - and
23 that's the circulatory system. And this seems to be a
24 severe problem. It's -- most of these studies were done
25 in -- virtually all of them were done in zebrafish and it

1 looked like -- with the exception we're talking about
2 almost 20 of them here. And only three of them had no
3 effect on heart rate. They all had an effect on heart
4 rate or on the organization of the blood -- or the
5 vasculature or on heart size. And our atrial or tract,
6 and the tract rate all essentially some sort of a
7 functional problem. And then five of them had very clear
8 detailed studies of vascular development and found that
9 even -- and these are the ones that survived now, that
10 their vessel organization was disrupted.

11 And one of the things that I thought was very
12 interesting is that they found that the red blood cells
13 get trapped in some of the vessels, so that they don't
14 actually move. Even though the heart is still beating,
15 the vessels -- the blood is not actually meeting.

16 So I probably took too much time, didn't I?
17 Yeah.

18 Let me just say that while I'd just like to
19 submit it by -- finish up by saying that it looks to me
20 like regardless of which part of the developmental system
21 from the formation of -- from the impregnation of an ova
22 through the formation of an embryo, and either into a
23 fetus or into a larval, what those developments, to make
24 them functional individuals that can then move on, they
25 are -- there is a negative effect of exposure to these

1 chemicals on the overall success of reproduction and the
2 developmental aspects of these animals. And I'll just
3 stop right there and I'll -- if you have any questions. I
4 don't -- didn't mean to take so long.

5 CHAIR LUDERER: Not at all. There were a lot of
6 studies to review. Next, we'll -- why don't we go on and
7 then go through the three discussants on the animal
8 studies and then we'll have questions and more discussion.

9 So, Diana.

10 COMMITTEE MEMBER AUYEUNG-KIM: All right. Thank
11 you. And thank you OEHHA staff for the -- for the summary
12 as well as to Dr. Plopper for going through the detailed
13 analysis. And so my analysis is actually very similar to
14 Dr. Plopper, in that I looked at the reproductive and
15 neuroeffect were the ones that were strongest for me. And
16 so I fully agree with his assessment as far those types of
17 studies. So I really don't have anything else to add,
18 other than -- and I don't want to take more time, so...

19 CHAIR LUDERER: Thank you. Larry.

20 COMMITTEE MEMBER BASKIN: Thanks for the
21 incredible analysis. It makes our job a lot easier. One
22 comment on the human studies, which I think make the
23 animal studies a lot more important is in the human
24 studies, we really don't know exactly what exposure is
25 causing the problem. So, we're looking for, you know,

1 BPS, of course, but it could be BPA or it could be some
2 other toxic issue in the epidemiologic studies, and I know
3 what I had to eat. One year ago on a Monday, cause I
4 always have the same thing every morning on a Monday, but
5 if you asked me about a Sunday, that could be pancakes or
6 something special. And so, these epidemiologic studies I
7 think are just fraught with issues.

8 Related to the animal studies, I kind of divided
9 it into two groups, the vertebral animals and then the
10 zebrafish/there was one chick study. And I'll quickly
11 just summarize that I -- there were a number of studies
12 which were negative, which was interesting. They weren't
13 all positive, but there were some very solid positive
14 studies.

15 I'm not going to pronounce his name right, but
16 the Chouchene study looking at thyroid function in rats I
17 thought was quite provocative. The Gao study looking at
18 apoptosis in ovaries, where you actually saw the
19 histology. I'm kind of a very visual structural person,
20 so that was powerful. The Molangiri study, looking at
21 reproductive function also testology -- or testicular
22 histology in rats.

23 Shi had three studies looking at both female and
24 male reproduction with adverse effects on spermatogenesis
25 in the testes, as well as transgenerational effects in

1 mice and also and abnormalities in the ovary. The Tiwari
2 study, Dr. Plopper referred to this, was the neuronal
3 study looking at the hippocampus in rats, which was
4 provocative. The Ullah study looking at reproductional --
5 reproductive access transgenerational. That was also in
6 rats. And then the Zhang study looking ovarian function
7 in mice.

8 So that's one, two, three, four, five, six,
9 seven, eight, nine studies that I thought were quite
10 provocative. Again, there were studies that were
11 negative. I'm not an expert on the dosing, but there are
12 controls. But if you give oxygen, you can kill people
13 with it. Okay. Oxygen sounds good, but dosing -- it's
14 all about the dosing. It's the same with water, you know,
15 you can obviously drink too much water and become
16 hyponatremic. So I trusted that in the materials and
17 methods, they tried to simulate quote/unquote reasonable
18 dosing, but I would leave that to the experts.

19 A quick comment on the invertebrate. The
20 majority of these were zebrafish, which we learned about
21 at this meeting many, many years ago had a spectacular
22 discussion on how this was relevant and avoided the use of
23 vertebral animals in research. And it affected, as Dr.
24 Plopper pointed out, all the systems, structural
25 abnormalities, immune system, pharyngeal cartilage

1 development, which was interesting, and angiogenesis, as
2 well as the ocular system, I thought pretty solid studies.
3 And then one provocative study in chicks on embryo
4 development.

5 So, overall, these are just BPS. So you give
6 BPS, you see the effect. That's the beauty of the animal
7 studies. If every single study was positive, that would
8 kind of make more sense, but they're done differently in
9 science. I wouldn't expect that, but I think there's
10 enough data here that I'd be concerned about the
11 structural effects of BPS, given at different times
12 directly on the specific animal and in a transgenerational
13 approach.

14 CHAIR LUDERER: Thank you very much, Larry.

15 Now, we have time for some discussion or
16 questions about the animal studies.

17 COMMITTEE MEMBER BRETON: I have a question. I
18 was just wondering whether any of the animal studies did a
19 multiple dosing at the -- in parallel at the same time or
20 was every study just their preferred dose of BPS and just
21 one only. Does anyone know?

22 CHAIR LUDERER: Most of the studies did more than
23 one dose, multiple doses.

24 COMMITTEE MEMBER BRETON: They did.

25 CHAIR LUDERER: Yeah.

1 COMMITTEE MEMBER BRETON: Okay. Because I was
2 just trying to get at like the question earlier about, you
3 know, just trying to -- trying to kind of think about
4 lining up what's low and what's extremely high relevant to
5 humans, and whether in the -- in the setting of one study
6 that might have looked at a continuum, did they see
7 different effects at the high and low or not?

8 COMMITTEE MEMBER BASKIN: I don't know the answer
9 to your question. I think some did. One of the issues
10 with the animal study is they're not just all BPS. They
11 may have given BPS. They may have given BPA. They were
12 looking at multiple different compounds. But unlike the
13 epidemiologic studies, you know, they were measured
14 separately.

15 CHAIR LUDERER: I mean, certainly there was
16 multiple orders of magnitude, you know, across studies in
17 terms of the doses that were used from -- I think Dr.
18 Plopper mentioned that too, the nanograms.

19 COMMITTEE MEMBER PESSAH: Sorry to be a stickler
20 here, but when Dr. Plopper mentioned that the low doses in
21 the spectrum of zebrafish studies and -- I can only go by
22 what's in the document that OEHHHA mentioned and some of my
23 own reading in the peer-reviewed literature of -- mainly
24 from analytical development of how do you measure BPS in
25 urine, cord blood, so forth?

1 The geometric means for women are somewhere
2 around 0.38 micrograms per liter. That translates to 1 to
3 2 nanomolar. Yes, there could be variations when you eat
4 a sandwich, or when you drink something, or come into
5 contact with something. But in some of these studies, at
6 least mechanistically, they're 60,000 times higher. And
7 when you mention water, and, you know, you have to provide
8 some basis for comparison. And so, I'm going to do that
9 for mechanistic studies, because it's absolutely essential
10 to try and interpret.

11 CHAIR LUDERER: Dr. Sandy. Martha.

12 DR. MARTHA SANDY: Yes. So, Dr. Harley had
13 mentioned that the document did talk about intraclass
14 correlation coefficients, and that's on page seven. And
15 that's from some of the -- looking at the studies that
16 measured BPS in women, taking urine at multiple time
17 points during pregnancy, the reported intraclass
18 correlation coefficients were generally low, and they
19 range from 0.01 to 0.45. So, there is a lot of
20 variability at all, you know, during the day. It depends
21 on what time you're taking your sample, just -- so I'm not
22 sure, yeah, given all that variability, if we can take
23 geometric means from biomonitoring studies. As -- you
24 know, we have to take it with a grain of salt is what I
25 would suggest.

1 CHAIR LUDERER: Thank you, Dr. Sandy.

2 Kim.

3 COMMITTEE MEMBER HARLEY: I feel like I'm
4 flogging the same dog with dead horses, as Isaac is
5 talking about, but I guess I need a little more
6 clarification from the people that looked at the animal
7 studies. Do we have any idea if any of the studies are
8 within sort of what we would expect to be the basic range
9 a human exposure. And, Dr. Pessah mentioned that the
10 geometric mean is about 0.3. But if you look at sort of
11 the upper -- the 75th percentile, it's about 0.9. I think
12 we could say like one nanogram per milliliter would be --
13 you know, could be a fairly high exposure for humans. Do
14 we have any idea if any of our animal studies are even in
15 that range? I mean, I'm talking orders of magnitude now.

16 Like do we have anything that's within one order
17 of magnitude. And that's urine measures. I don't know if
18 we -- does anybody take urine on their house after they
19 dose it, because that would be really handy?

20 CHAIR LUDERER: No.

21 (Laughter).

22 CHAIR LUDERER: It's the doses that we get in the
23 animal studies for the most part.

24 COMMITTEE MEMBER PLOPPER: The experts are
25 sitting down there.

1 CHAIR LUDERER: I mean, we're going to hear from
2 the mechanistic studies, so -- but those -- yes. Do we --
3 we don't have -- do we have any information about urine
4 levels or serum levels? Very -- I don't think any of the
5 studies did that in the animal studies, yes.

6 COMMITTEE MEMBER HARLEY: I wish they would.

7 COMMITTEE MEMBER PESSAH: There is one study
8 reported in Table 1.1, 90th percentile for a sample of
9 women, when it was taken, and what the distribution is,
10 but it's the 90th percentile. That translate to 2.42
11 nanograms per milliliter, which translates to a
12 concentration of just under 10 nanomolar. That's the 90th
13 percentile. That's the only data that I could draw from
14 that's in the document. Now, if --

15 CHAIR LUDERER: Is that urine or blood?

16 COMMITTEE MEMBER CULTY: You speak about Table
17 1.1. Oh, in Table 1.1, I saw for these women open, --
18 yeah 318 nanogram per liter in the geometric mean of the
19 CARE-LA women. So it's -- yeah in the high nanomolar --

20

21 COMMITTEE MEMBER PESSAH: Yeah, that's one --

22 COMMITTEE MEMBER CULTY: The nanomolar - sorry -
23 per liter -- nanogram per liter. Sorry, so which was
24 in --

25 COMMITTEE MEMBER BASKIN: I recall that one of

1 the sheep studies they very carefully measured BPS in the
2 plasma multiple times and in the urine. And being quite
3 naive about the dosing, some -- one person at least I
4 would imagine, if not many, when these papers were peer
5 reviewed would probably have asked that question, but I
6 can't -- I don't have the expertise to, you know, confirm
7 that. It would make no sense in my mind to design a study
8 and not make it relevant to dosing, but it looks like we
9 have some questions with that.

10 CHAIR LUDERER: Okay. Not seeing --

11 COMMITTEE MEMBER CULTY: The thing or -- so I
12 think in the animal study, we always apply the factor like
13 four for the mouse and six for the rat. I don't know for
14 zebrafish. So, it will be higher than what the humans
15 were exposed to, because we do that correction, but yeah,
16 still it was in the -- like, for example, the rat study
17 was like, you know, 10 nanomolar. Like I tried to
18 calculate some other one in liquid, at least in molarity.
19 And it goes from -- you know, from an open 0.01 micromolar
20 for the -- for the mouse studies, to 0.2 micromolar, to
21 something like 10 micromolar. So it's telling the range
22 of a micromolar or high nanomolar, maybe it's a bit
23 higher, but we consider that we have to apply the
24 factor -- you know, the species correction factor, it
25 might not be too far for some of these studies, I think.

1 But of course, it's only BPS, so that assumes
2 that it's -- like we know for the animal studies that this
3 is what we are putting on, but it's not reality, because
4 as you said for epidemiological studies, we have a
5 mixed -- you know, mixture of compounds, potentially
6 acting on either similar mechanism or mechanism that are
7 cross-talking to each other. So we are, I think, really
8 underestimating in the animal studies the potential
9 effect, because we are using only one compound and that
10 doesn't really fir with human exposure, where we are
11 exposed to multiple compounds.

12 That can even change the pharmacokinetics of the
13 other guy, you know, so, we are really oversimplifying, I
14 think. So that's why, for me, if we manage to see some
15 significant differences in a system where it's very
16 oversimplified and we expose to only one chemical, whereas
17 we know we are exposed to multiple chemicals, it's already
18 a bit of a concern, because we are really minimizing the
19 risk by the way the studies are designed.

20 So using this, you know, unique compound and even
21 multiple dose, it's still just one compound. It's not
22 very realistic for human exposure I believe. I'm the
23 proponent of a mixture, I have to say.

24 CHAIR LUDERER: Okay. Do we have any other
25 comments or questions before we move on to the mechanistic

1 studies?

2 Okay. Not seeing them, then Isaac, if you'd like
3 to start.

4 COMMITTEE MEMBER PESSAH: Thank you. I want join
5 in and thank OEHHA for making this comment -- this
6 document very understandable and made my job easier with
7 the tables. And unlike previous documents, you actually
8 took the time to convert microgram per liter to molar
9 concentration. This is extremely important for trying to
10 assess the mechanism or mode of action studies and their
11 relevance to what we just heard in animals and humans.

12 Having said that, you really did make my life a
13 lot easier, because I started with Fan et al., 2021, which
14 was the first one that you presented. I wanted to use
15 that as a test case. And I used some criteria to evaluate
16 this paper. One, what was the static concentration used
17 in the model and how did it compare to human levels that
18 are reported in the same document? Two, what was the
19 model that they used? Was it relevant to embryonic
20 development, early embryonic development, placental
21 implant, so forth? And third, what were the mechanisms
22 that they considered? Were they relevant to what was
23 previously reported, chronologically previous, to human
24 studies reported in the literature?

25 So what they did was they exposed human

1 endometrial adenocarcinomas, cancer cells, which are also
2 called Ishikawa cells using in an vitro model of human
3 blastocyst implantation. And this is based on their
4 ability to attach. They measured a significant reduction
5 in attachment as seen only at the highest BPS
6 concentration of a hundred micromolar. Now, if you --
7 trying to give biological plausibility for really great
8 epidemiological studies, you're using adenocarcinoma at
9 40,000 times the concentration of BPS that you find as the
10 geometric mean in urine of pregnant women, 10,000 times
11 higher than the 90th percentile of exposure measured in
12 urine.

13 They saw a modest suppression of ERs, estrogen
14 receptors. And these included both the nuclear receptors
15 as well as GP30, which was a cell surface receptor, but it
16 had a very weak concentration effect. They had at least
17 three doses relative to control. You also have to realize
18 that with our discussion I just realized that all the
19 studies that I'm going to present are static
20 concentrations over time. They're not going up and down
21 like the human condition, so that's -- but that's with all
22 the studies.

23 Exogenous estrogen, which they had as one
24 positive control was dosed at 10 nanomolar. So think
25 about that difference between endogenous signaling, and

1 now you're putting in BPS at 10,000 times minimally human
2 reported concentrations.

3 So, I just did something that you might not agree
4 with. I looked over the tables and any study that used
5 one micromolar or more, I felt was not going to give me
6 much credible information about mode of action or
7 mechanism of action.

8 Now, fortunately, there are many studies that
9 actually were in the range of the human exposure, not
10 using adenocarcinomas to try to make a point, because
11 they're easy to use. These are transformed cancer cells,
12 so you don't know where they're starting, but use
13 primarily explants from placenta or other legally
14 available fetal tissues. And so I'd like to focus on
15 those and try to relate it to some of the results in
16 animals and especially humans.

17 So one study, Di Credico in 2023, isolated fetal
18 membrane mesenchymal stromal cells, I'm just going to call
19 them S -- MSCs. Although, I'm going to get tongue tied.
20 These are from human placenta. And amniotic fluid stem
21 cells, I'm going to call them AFCs, from amniochorionic
22 membranes. Okay. So these are from women and they
23 include both sides of the causeway, the embryo and the
24 maternal environment. Such models, in my opinion, possess
25 intrinsic components of embryonic development

1 investigating the effects of bisphenol A. And it may have
2 relevance to what you're seeing in high ordered studies.

3 All right. So, 100 nanomolar of BPS enhanced
4 proliferation in a time-dependent manner, which read --
5 reach statistical significance within 48 hours. And this
6 was based on a measure of electrical impedance as the
7 cells come together and it's very accurate. Okay. They
8 validated those electrical measurement using nuclear
9 proliferation biomarker of GM2 phase. This includes KI67
10 in the nuclei eye. And this reaffirmed that indeed there
11 was a change in the ability of these cells to organize and
12 mature, again at 10 and 100 nanomolar, very close to what
13 we've been talking about.

14 There was no effect -- so if you think about
15 people using 100 micromolar, where you're blowing out the
16 mitochondria most likely, they found no effect on the
17 mitochondrial health in either model at these dosages or
18 these concentrations.

19 They then proceed to do QPCR for pluripotency
20 markers and epigenetic regulators, which -- and these
21 studies suggest a unique fingerprint for BPS, which isn't
22 really identical to BPA, because they also looked at BPA,
23 that at 100 nanomolar in each of the cell models, they
24 found that -- they activated both genetic and epigenetic
25 regulators, especially a regulator called TET3, which had

1 much less of an effect with BPA. And the effects really
2 are startling. They're like a fivefold change from their
3 control. And that's at 100 nanomolar.

4 So, there are clearly changes in pluripotency
5 markers and epigenetic markers. So, in summary, the
6 findings from Di Credico et al. suggests that low BPS in
7 an in vitro and -- an in vitro model of developmental --
8 very early develop disrupts biological characteristics of
9 stem cells in support of developmental toxicity.

10 Okay. Next is Liang et al. -- Liang, I guess
11 it's pronounced, et al., in 2021. This was even a more
12 biologically relevant model. It's a three-dimensional
13 embryoid body cultured from H1 ESC line, derived from
14 human blastocyst. A hundred nanomolar of BPS for 21
15 days -- again, it's a static exposure, but that's what we
16 have to deal with. Decreased expression of ectodermal
17 factors, KRT14. There was a 40 percent of control. And
18 OTX2, which is a very widely used marker, which decreased
19 by over 25 percent. This was without effect on endodermal
20 markers or mesodermal gene markers, which select --
21 suggest a selective potency toward ectodermal effects.

22 Compared to other BPs that they did in this
23 study, that they tested in this study, BPS, at a hundred
24 nanomolar, elicited the largest number of upregulated
25 genes. And this was using RNA-seq analysis. A large

1 number of the strongest upregulated genes, such as --
2 well, again, so we're talking about a significance of
3 0.01, 0.05. So these differences were quite pronounced,
4 again at a hundred nanomolar.

5 Most of these genes, and this is going to sound
6 familiar, were related to lipid metabolism, including
7 cholesterol metabolism, PPAR signaling pathways, and
8 hedgehog pathways. And these were confirmed using KEGG
9 analysis. So, these are very robust differences. Okay.
10 Again, this is BPS at a hundred nanomolar.

11 So, what they proceeded to do, which was really
12 logical, is they took these cells, sprinkled a
13 transforming factor on them, a small molecule to drive
14 them to hepatic lineage, because they wanted to know
15 whether or not these guys would be normal as hepatic cells
16 and have normal function. Well, they hit the ephemeral
17 brick wall and they didn't find anything with BPS.

18 So, they concluded that really what -- and they
19 provided more evidence, that the real effects of BPS in
20 this model is to influence early embryonic development
21 with regards to cell fate commitment and cell fate
22 speciation. These are very important processes. If you
23 interfere with those that early on, you have a problem.
24 So they didn't see any hepatic markers when went on to
25 differentiate these cells, but clearly they saw markers

1 prior to differentiation.

2 Now, this is really important, because there's
3 another paper coming up that decided they were going to go
4 to hepatocytes. They were going to go to neurons,
5 cerebel -- cerebellar neurons. Cerebral neurons. Sorry.
6 Yeah. And they found huge changes in these biomarkers to
7 commitment to the neural lineage. That's really
8 important. I'll get to that in a second. I'll do it very
9 briefly. Okay.

10 I also pulled in Abdulla et al., last year. I
11 love really, really good development of assays. Okay.
12 Here's what they did. Very clever. They developed a
13 multi-channel, microfluidic, chip-based assay. And they
14 used H9 cerebral organoids in culture to test very low
15 doses of BPS exposure. Continuous culture for 34 days
16 that expressed essential properties of real cerebral
17 organoids. So they did a full genetic and expression
18 profile on these guys and they did go to where they were
19 supposed to go or where they intended them to go.

20 What they found was exposure to BPS at 0, 10, or
21 100 nanomolar initiated on day 20, which is as these guys
22 are now committing to neural lineage, and then they kept
23 exposing it for an additional two weeks. Inhibits neuron
24 differentiation based on decreased MAP2 levels and
25 decreased Fluorescence, decreased organoid

1 thickness, and these effects are concentration dependent.
2 So zero compared to 10 was lower, even lower with a
3 hundred relative to control.

4 So, BPS also produced about 500 differentially
5 expressed genes under this protocol at 10 nanomolar, and
6 800 differentially expressed -- I'm sorry. These are
7 proteins not genes. These are differentially expressed
8 proteins. Five hundred differentially expressed proteins
9 at 10 nanomolar, 800 differentially expressed genes --
10 proteins at 100 nanomolar. About half of those were
11 upregulated, half were down regulated relative to the DMSO
12 control.

13 What types of proteins were affected using, what
14 we call, you know, where you organize them into pathways
15 ontogenic pathways. The PPAR signaling system, which is
16 related to lipid metabolism, was significantly altered.
17 Proteins related to neural differentiation, lipid
18 metabolic process, and brain development were also altered
19 at both 10 and 100 nanomolar.

20 When signaling, which is critical to neuronal
21 differentiation, and RTN1, which is an inhibitory factor,
22 which is seen upregulated in a response to neural injury.
23 These were significantly downregulated.

24 So, they concluded that BPS at relevant
25 concentrations alt the Wnt signaling pathway critical to

1 neurodevelopment and altered signaling molecules involved
2 in brain regionalization. And these are all driven by
3 some of the things you heard in the animal studies, and --
4 which is fatty acid metabolism and neural-specific genes.

5 Ning in 2023 used mouse in vitro fertilization
6 model to study the effects of BPS in early development.
7 This was reported in Science Reports. Their
8 concentrations was relatively high, 1 micromolar delayed
9 blastocyst stage, 100 micromolar induced two-cell block in
10 mouse implantation embryos. There were no significant
11 changes at one nanomolar, again suggesting maybe they were
12 really pushing their model's system to produce an effect.

13 They also saw oxidative stress. And as soon as
14 some -- who works in cells say, oh, you have oxidative
15 stress. You need to immediately go back and say, well,
16 how much did they use, because oxidative stress, unless
17 it's very low dose, is just a general reaction to not
18 being nice to the cells.

19 Okay. So, I'm going to stop here. There are at
20 least four more papers that were in this dose range that
21 also measured outcomes in terms of neurogenesis and later
22 development of neural development, and they all saw
23 effects to varying degrees at relatively low doses.

24 All the others that I looked at, I actually
25 didn't look at any further, because they were all in the

1 micromolar, some were as high as 500 micromolar, which I
2 would argue probably is close to the solubility limit of
3 BPS in cell culture media. And they also used fetal
4 bovine serum in many of these studies. And you know what
5 happens to a lipophilic molecule when you add it to an
6 aqueous solution. Most of it's going to either to the
7 plastic or to the -- and none of that can be judged
8 because cell culture levels were not measured, so -- okay.

9 So I'm going to stop there, but it seems like
10 fatty acid metabolism is a very early effect that you can
11 see at relevant concentrations in vitro. And I think that
12 these studies suggest mode of action pathways that may
13 lead to some of the findings in epidemiological studies.
14 I'll just leave it there. Thank you.

15 CHAIR LUDERER: Thank you very much, Isaac for
16 that detailed discussion of the mechanistic studies.

17 And now, Martine.

18 COMMITTEE MEMBER CULTY: So I took a totally
19 different strategy. Instead of selecting a few studies, I
20 tried to bring out some type of conclusion from putting
21 all the stories together and trying to see what type of
22 mechanisms were in general observed in -- throughout the
23 studies. So I didn't -- I considered all the studies, but
24 some of them, like the -- some of the drosophila were
25 really too high like millimolar range. But most of them

1 were -- like, for example, if you take the mouse ovary
2 study, so in -- you know, in utero exposure. They were
3 using -- so that is the one that were given in drinking
4 water 3.33 microgram per, liter, which I calculated to
5 0.01 micromolar, like 10 nanomolar. So it's not -- it's
6 still in the range.

7 If you take the adult -- the study in utero
8 exposure to rate and they were looking at the adult, they
9 used 50 microgram per liter again in the drinking water,
10 which was 200 micromolar. So it's high, but it's --
11 sorry, 200 nanomolar. So it's still, you know, in the
12 high nanomolar to low micromolar. So this one this mammal
13 like the mouse and the -- and rats were in the, you know,
14 what maybe you would say acceptable high nanomolar range,
15 where even the mouse was actually 10 nanomolar. So, it
16 was still acceptable in range.

17 The zebrafish was around on 0.4 to 4 micromolar.
18 So that went a bit higher. But the two mammalian studies
19 actually, you know, were in the range that I think you
20 would, you know, judge as acceptable compared to human
21 exposure. So I was trying to see, you know, what comes up
22 and what makes sense within all these animal studies or
23 human studies.

24 And you mentioned oxidative stress seems to be
25 really the first type of a mechanistic effect that BPS was

1 exerting. So, of course, they looked different endpoint.
2 Like, they were -- the mouse study looked at different
3 tissues, but the main one was the ovary, neonatal ovary
4 after fatal exposure. The rat study looked at the adult
5 testes after -- all of these are fatal exposure. The
6 exposure periods were sort of similar range, not exactly
7 the same, but they were like after organogenesis or just
8 at the end of organogenesis all the way to birth or close
9 to birth. So, you know, they were not too different in
10 exposure range.

11 They use, unfortunately, you know, drinking
12 water. So how do they verify how much really the animal
13 were exposed to? There were previous studies in the past
14 where we really add in parallel the measuring the animals,
15 which helps to know but, you know, what's what we have.

16 But so between these mouse, rat study, a number
17 of zebrafish study, we have also rat embryonic cardiac
18 cell lines, which are -- again, this is a bit higher, 10
19 to 100 micromolar exposure. We have JEG-3 cells that you
20 mentioned. All of these studies came up with an increase
21 reactive oxygen species, so increase ROS. We sort of all
22 agree at least they're going the same direction. We have
23 an increased oxidative stress reflected by reactive oxygen
24 species that we measure in these different tissues.
25 Zebrafish is like homogenate of the whole, you know,

1 tissue of all the animal organism.

2 When the second type of oxidative stress
3 mechanism was Lipid peroxidation, where they -- it went
4 all in the same direction or so, but different model. So
5 from a mammalian, to zebrafish, and to some of the human
6 cells. It's an increase of lipid peroxidation, which
7 basically leads to damage of membranes and potentially
8 cell depo, cell dysfunction.

9 In the antioxidant enzyme, there is sort of a
10 differential and viable endpoint, but that could
11 potentially maybe discussed, depending how you take the
12 antioxidant mechanism, because it can be either depleted
13 like it's over -- so and embryo of antioxidant enzyme, for
14 which the expression were decreased, so -- glutathione
15 peroxidase decrease is very critical, because when you
16 don't -- you lose your -- you know, your reservoir of
17 reserve of glutathione, you know, protection.

18 So they saw that in mice, in rat, in zebrafish,
19 even drosophila, but these one were higher level of
20 exposure. So that was sort of going the same way.
21 Decrease glutathione peroxidase of SODs were also
22 decreased. Catalase I found was the main antioxidant
23 enzyme that was making like, you know, consistent sense
24 where it was decreased in most of the model catalase.

25 And -- yeah, and they were looking at --

1 sometime -- as you mentioned, sometime they were looking
2 at the gene -- depending on the study, the genes of a
3 protein or some studies looked at both transcriptome and
4 proteomics or specific, you know, antioxidant markers.
5 And that's where we start to get some type of viable
6 effect, but it's a bit hard to interpret, except if you
7 say that sometime you can see a decrease in an antioxidant
8 gene or protein, because it has been depleted or you can
9 see an increase as response to the previous damage, where
10 you need, you know, like a recuperation mechanism, where
11 your tissue is going to try to produce more of antioxidant
12 factor to try to recover and protect from that oxidative
13 stress injury, insult.

14 So I guess it depends also of the timing of
15 tissue. So, it but -- so it was a bit harder to, you
16 know, interpret like you are the GPX1 that was decreased,
17 but you -- so -- and GPX4, so it was decreased in rat and
18 ovary, and testes, but then it was increased in the
19 zebrafish eyes. And the peroxiredoxin were also something
20 that was more homogeneous where they were increased. And
21 these are again an oxidative respond protection type of
22 enzyme. So, it can make sense that you peroxiredoxin will
23 be increased in response the oxidative stress to try to
24 rebalance and get rid of all these, you know, extra
25 reactive oxygen species that tissue has been exposed, so

1 that makes sense.

2 So we have a SOD increase. I already -- for
3 SOD1, but then you have an SOD2 decrease. So it's sort of
4 difficult to make a picture of these, you know,
5 antioxidant enzyme, because you have basically sometime
6 the same enzyme or you a similar enzyme going to either
7 the gene of a protein or even reactivity. Sometime you
8 looked at looking in a different direction. So that was,
9 but they might -- at least, we have a catalase that -- and
10 a few of us that shows, you know, going into the majorly
11 same direction.

12 So overall, I think the oxidative stress effect
13 due to BPS makes sense. And you have reactive oxygen
14 species increasing in most of the model from mammalian to
15 non-mammalian, and you have a few antioxidant enzymes,
16 such as catalase -- catalase. And few of those that are
17 also basically going in a direction that you'd expected in
18 oxidative stress. Although, as I said, it can different
19 way depending on where -- in the timeline of the stress,
20 you know, if it's trying to repair or if it's right in the
21 middle of the insult.

22 So I think this is one of the main mechanism that
23 came out for me from all these studies. Then an
24 over-mechanism that was -- that came repeatedly, that was
25 important is the epigenetic effect. We have a change in

1 the methylation profiles of DNA and histones, which are
2 classical epigenetic mechanism, not much on the microRNA.
3 It was mainly, you know, the DNA and histone. And these
4 also sort of make sense. Throughout these studies, I
5 found that they were -- so we didn't go in all the -- you
6 know, the detail -- the certain detail in all the studies,
7 but you had definitely disruption of the DNA methylation
8 profile and histone methylation profile. Sometime again,
9 in a specific tissue for the mouse and over the rats, like
10 we were looking more at reproductive tissues, which would
11 also make sense, because these are the ones that are going
12 to make your gamete and those are the ones that are going
13 to do intergenerational and transgenerational, you know,
14 in irritants of some type of epigenetic alteration.

15 So, you know -- but for the zebrafish, we tend to
16 look more at -- in general, at the homogenic tissue.
17 Epi -- so the epigenetic effect were also looked, I think
18 you mentioned, in the placenta. They can -- they could
19 actually see specific DNA methylation change in some CPG
20 island related to genes, which is very rare most of the
21 time, you know, in these studies you get CPG islands that
22 are in non-generic areas and then you have to try to see
23 if it's potentially and enhancer of a gene that is, you
24 know, free kilobase forever or something.

25 So in a way, that was actually very convincing

1 that they were able to see this CPG island changing in
2 human placenta. It was epidemiological studies. So, I
3 think that's transferred my belief that there is really
4 epigenetic changes by being exposed to BPS that makes
5 sense, and between the animal studies and human. So
6 it's -- the placenta would reflect what the fetus
7 experience and we are over when we started to look at the
8 genes involved in epigenetic changes. That's where we
9 start to -- we see more viability again.

10 As you mentioned, it could be due to doses
11 differences to model differences, but -- so you have, for
12 example, DNMT1, which is important for DNA methylation,
13 which in some of the model was increased and others were
14 decreased, and the same for DNMT3. So depending of
15 zebrafish, human, or over models they were basically not
16 going the same way. And you have a TET1 and TET3, I
17 think, were mentioned before that were -- these one
18 demethylated with DNA, and they mainly increased. So
19 these one were more sort of consistent between the model.

20 But so, I think it's clear for me that there is
21 definitely epigenetic alteration due to BPS in utero
22 exposure. And even in the placenta, that would be very
23 critical, not only in the conceptus, in the embryo fetus.

24 The third mechanism that BPS seems to act upon
25 it's apoptosis. And so this one also they are many. SO

1 we had mammalian. Again, more reproductive tissues. They
2 also have the human vascular cells, the HUVEC, zebrafish
3 the placenta on a chip, which is a very nice model where
4 you can control, you know, what you are doing. This one
5 was 100 nanogram ml. So, I mean, I didn't do a more
6 analytical calculation, but -- so -- and they were looking
7 also at DNA fragmentation. So I think apoptosis is also a
8 mechanism that there is enough -- should essentially be
9 done between all these studies to support BPS increasing
10 apoptosis in different tissues in the developing organism.

11 And proliferation was already discussed, so --
12 proliferation was not. There was less studies and was
13 sometime decreased and one model was increased, so -- but
14 there is the story of the organ -- of organo -- in human
15 organ. That was nice. And then it's a whole bunch of
16 hormonal changes. So you have, you know, the pituitary
17 effect with luteinizing hormone being decreased in rate.

18 FSH again was some model up, some model down.
19 AMH was increased. Testosterone was decreased in most of
20 the model they looked or they studies. Whereas, estrogen
21 and estrodial tended to be increased. And there were also
22 some studies that suggested that BPS, at least from
23 modeling, can bind actually estrogen receptor and would
24 bind estrogen receptor beta better than the alpha, which
25 is a bit like, you know, some of this xenoestrogen

1 compounds.

2 So overall -- and thyroid was an important target
3 I think. And it was mentioned already the levels of T3,
4 T3 and thyroid receptors were also altered by BPS. And
5 this is critical not only for general metabolism of
6 developing, you know, organism of fetus, but it's also --
7 all these endocrine systems are speaking to each other.
8 So if you have less thyroid hormone, you will have
9 potentially less testosterone produced. So, androsterone
10 is the same, adrenal and testosterone -- and testis have
11 an effect. For the ovary, I'm not sure.

12 But -- so, you -- yeah, so you have -- when you
13 touch one of these endocrine system, you think it's far --
14 thyroid is far away from reproductive system, but no it's
15 not.

16 On the there side, glucocorticoid is going to
17 inhibit testosterone production. And there were some
18 studies also where they saw cortisone increase. So all of
19 these sort of suggest first overall metabolism disruption,
20 protein lipid disruption, and potentially reproductive
21 effect, which we have already discussed before.

22 So I think these are the main mechanisms that I
23 got out of trying to make sense of all these studies. And
24 most of them are supported by a good number of studies.
25 Some of them I agree are in maybe higher range, but most

1 of them you had two, or three, or four type of doses. And
2 at least one of them, you know, would be potentially in a
3 reasonable range compared to human.

4 But, yeah, that -- so that's what sort of a
5 mechanistic analysis I pulled out of these amount of data.
6 I mean, it was, you know, so many different model, and we
7 are lucky that we can get some patterns of something out
8 of this viable type of a approaches, I think. At least,
9 we get an idea of what BPS can act on in developing
10 organism, I think.

11 That's my idea. I don't know if you agree.

12 CHAIR LUDERER: Thank you very much, Martine.

13 We have time now for some additional Committee
14 discussion. It can be about any of the studies. So
15 either the epi, or the mechanistic, or the animal studies,
16 or is everyone ready for lunch?

17 (Laughter).

18 CHAIR LUDERER: All right. We can then turn to
19 public comment at this point or do we want -- that's the
20 next item on the agenda.

21 So, Tina, can you share the slides on the
22 instructions, there they are, for public comment.

23 So as a reminder, if you are here in person and
24 you want to make an oral comment at today's meeting,
25 you're asked to fill out a blue comment card. And these

1 cards are at the back of the room. We'll be calling on
2 those present in person to provide public comments first.
3 So -- and then please approach the microphone to provide
4 your comment. If you're willing to share your name and
5 affiliation, please provide that before beginning your
6 comment, though, as I mentioned -- or as it was mentioned
7 at the start of this meeting, you can also comment
8 anonymously, if you wish.

9 Those joining virtually who wish to make a
10 comment -- an oral comment at today's meeting are asked to
11 join the Zoom webinar and make sure that you join under
12 the name you would like to be identified, including if you
13 would like to remain anonymous. If you would like to make
14 a public comment, you can click on the Zoom webinar "Raise
15 Hand" icon to indicate you would like to speak. When
16 you're called, you will be prompted to unmute yourself.
17 And then you would unmute yourself, state your name and
18 affiliation, if you want to do so, and provide the
19 comment. And we're limiting the public comments to five
20 minutes per speaker, so that everyone has time to comment.

21 So do we have any in-person?

22 I don't think so.

23 MS. TINA COX: No in person.

24 CHAIR LUDERER: Okay. And then do we have any
25 raised hands on Zoom?

1 MS. TINA COX: No. I'm not seeing any raised
2 hands.

3 CHAIR LUDERER: All right. Thank you.

4 So, then do the -- any of the Committee members
5 have clarifying questions for the commentators?

6 Yeah. And is there anyone else wishing to
7 provide public comment?

8 MS. TINA COX: No.

9 CHAIR LUDERER: Thank you.

10 All right. So, then now we have an opportunity
11 for more Committee discussion to talk about the -- what
12 we've -- what we've heard today and what we all gleaned
13 from reading this -- the wealth of information that was
14 provided and very well summarized in the document that we
15 received.

16 So, Kim.

17 COMMITTEE MEMBER HARLEY: I'm just interested in
18 people's opinion that have looked at the mechanistic and
19 animal studies. I found in the epi study I thought it was
20 interesting that there was some indications of behavioral
21 problems in children associated were in utero exposure to
22 BPS. And I was just -- I know we've talked about so many
23 things here. I just was hoping that maybe somebody from
24 the animal literature and somebody from the mechanistic
25 literature could just summarize if there's any evidence

1 that supports that from their two kind of fields that --
2 how well that supports what we found in the -- in the epi
3 studies.

4 CHAIR LUDERER: I mean, there were certainly some
5 behavioral studies that looked at maternal behavior and
6 poor care for the pups, you know, not picking them up when
7 they were out of the nest, you know, various types of
8 behavioral -- maternal behavioral alterations that were
9 found. But, I'm not remembering any that were a behavior
10 of the offspring, but maybe I'm just forgetting.

11 Anyone else?

12 COMMITTEE MEMBER BASKIN: I mean, I think it's
13 hard to correlate the zigzag studies in zebrafish with
14 autism.

15 (Laughter).

16 COMMITTEE MEMBER BASKIN: So I don't know if we
17 can put much, you know, credence in that.

18 COMMITTEE MEMBER PESSAH: I just wonder if there
19 would be any value -- and again, this is beyond the scope
20 of the Committee obviously, but there are very, very large
21 study, 50,000, probably close to a hundred thousand
22 genomes that are available. And it would be interesting
23 to see how much overlap of differentially expressed
24 proteins or differentially expressed genes, which there is
25 a lot of data in at least the in vitro, but also in vivo

1 exposure, whether they overlap and to the extent they
2 overlap, because that's something you can just do on a
3 computer, again for autism risk genes. Yeah.

4 COMMITTEE MEMBER BRETON: I thought one of the
5 summary slides that you presented suggested that all --
6 what was it, because I wrote it down, all my studies
7 showed socioemotional changes. But I guess the question
8 is was that in the dams or was that in the offspring?

9 DR. GABRIEL TUKEMAN: Those were in the offspring
10 that were gestationally exposed.

11 COMMITTEE MEMBER BRETON: They were. Okay.
12 Thanks.

13 DR. MARTHA SANDY: Could I ask staff to clarify.
14 There was some maternal behavioral effects. Were those in
15 the F1 females?

16 DR. GABRIEL TUKEMAN: Yes. That particular study
17 looked at both F0 and F1 and they did find effects in F1
18 as well.

19 CHAIR LUDERER: Isaac.

20 COMMITTEE MEMBER PESSAH: Just -- I probably
21 wasn't paying enough attention to the concentration range
22 in water for some of these studies. What were they in
23 just a range that you had mentioned?

24 COMMITTEE MEMBER CULTY: For the mouse study it
25 was 3 microgram per liter. So, I calculated to basically

1 10 nanomolar. And for the rat study -- I mean, some of
2 the studies that were looking at oxidative stress. Some
3 of the studies look -- come back with same study in
4 different mechanism. The rat was on 0.2 -- so 200
5 nanomolar or 0.2 micromolar. So it was a bit higher. It
6 was 15.

7 COMMITTEE MEMBER PESSAH: So in terms of how
8 would you compare those exposures in drinking water? What
9 would be the most relevant in human condition would be
10 drinking water, just in general or --

11 COMMITTEE MEMBER CULTY: I think it -- that would
12 be sort of a model for dietary -- like normally I would
13 prefer gavage, because put in the animal and we know how
14 much goes in the stomach. But there are a lot of studies
15 which choose to do drinking water as a way for oral
16 exposure.

17 COMMITTEE MEMBER PESSAH: But clearly, that's
18 only one way --

19 COMMITTEE MEMBER CULTY: Yes.

20 COMMITTEE MEMBER PESSAH: -- because food is a
21 major source.

22 COMMITTEE MEMBER CULTY: Yeah. But we -- so
23 we're -- at least normally, you're supposed to measure how
24 much the animal has drank or if it's in mixed with a
25 pellet, they measure how much the animal has eaten and

1 when we can -- normally, they would -- be able to say how
2 much they can make the calculation of how much has been
3 ingested, especially for -- from the food, like mixed in
4 with food. And I would think for the water, they would be
5 able to do the same, because every day they should measure
6 how much has been consumed.

7 And so from that, we know the molarity, because
8 Even microgram per liter, we can calculate, you know, the
9 microgram, at least that have been ingested or drank. So
10 the --

11 COMMITTEE MEMBER PESSAH: Because of the
12 discussion, I looked up is there any studies that actually
13 measured it in river water, drinking water, bottled water?
14 And the highest value I could find was 15 nanograms per
15 liter.

16 COMMITTEE MEMBER CULTY: Yeah.

17 COMMITTEE MEMBER PESSAH: And in -- the median is
18 more like 1.5, 1.6 nanograms per liter. That's in water,
19 so --

20 COMMITTEE MEMBER CULTY: So I think what we are
21 trying to reproduce with the drinking water is more than
22 the drinking is ingestion. So, for example, that mouse
23 study would be 3,000 nanomgram, you know, per liter, but
24 that -- assume that BPS is absolutely not coming just from
25 the water. We actually have some of the studies. It

1 comes from the -- and they -- I like the study where
2 they -- they had this woman, you know, not using any type
3 food wrapped and containers, and so on. It was -- I think
4 it was a California study.

5 And the women were eating only from glass, and
6 like trying -- but, of course, they're also common in many
7 other places, but at least from the diet and drink they
8 are in, and they show 50 percent reduction of BPS in urine
9 of these woman. So I liked it because it shows we can
10 actually be proactive and decrease our exposure, if we are
11 careful enough, but I guess also buying glass container
12 cost more money and it's more -- it's a very technical
13 issue and financial issue, but it's feasible.

14 CHAIR LUDERER: Any other additional questions,
15 comments, discussion?

16 All right. Yes.

17 COMMITTEE MEMBER HARLEY: I mean, this is going
18 to be our last chance to talk about it. I just -- I'm
19 comparing this conversation to the conversation we had a
20 year ago when we were talking about the male reproductive
21 effects. And I'm just really missing the consistency and
22 the throughline that I felt like we had last year. I
23 just -- there's -- maybe it's because there's so many
24 different endpoints, but I just -- last year, I felt like
25 things fit together better and I could feel and see

1 throughline from the mechanistic, to the animal, to the
2 human that I -- I don't know how other people feel, but I
3 just am not feeling that same sort of consistency this
4 year.

5 COMMITTEE MEMBER CULTY: I think it's just maybe
6 that the reproductive system is so sensitive to chemicals
7 that can either disrupt androgen or, mimic estrogen, or --
8 you know, that it's easier to see in the reproductive
9 system. But when you are looking at overall, you know,
10 amniotic and fetal development, and even the placenta,
11 maybe it's just the reproductive system is most
12 susceptible to this type of insult. And I think we are
13 not totally clear yet how BPS, with which exact target BPS
14 act like. They were also suggesting that it can bind to
15 the estrogen receptors. But I know from BPA genistein
16 they have so much more effect. By themselves, they
17 actually change the DNA methylation of animals, you know,
18 it has been shown and in opposite direction.

19 So, is BPS -- we see some epigenetic effect. So
20 is it also acting -- and also -- not only that, but -- so
21 we are not only binding -- assuming it's similar to BPA,
22 it's not only estrogenic compound. We can also alter the
23 expression of activator, you know, of estrogen receptors,
24 for example, or modulator like activity or So we
25 have much more complex effect. And so maybe that's why

1 when we look at overall development, it becomes so
2 complicated.

3 But I think that -- like some of these studies,
4 which chose to focus on the gonads, maybe because it was
5 the more obvious target of anything related to steroid
6 hormones, perturbation, and we see, you know, steroid
7 hormone perturbation.

8 So, I think it's just looking at the overall
9 development is complex maybe. And not only that, but when
10 we expose in vivo, we also potentially alter the dam, the
11 mother. And the response of the mother can affect the
12 development of the baby. So, you know, it's -- I think
13 it's just more complicated. I don't know. I don't know
14 if anybody else has another idea to explain. For me also,
15 it was much more difficult to make sense of it.

16 CHAIR LUDERER: Do we have any other comments,
17 Panel members, discussion?

18 Okay. So then, if there are no further questions
19 or comments, then is everyone read to vote?

20 All right. So, then we will move on to the vote.
21 The question before the Committee is this, has bisphenol S
22 been clearly to shown through scientifically valid
23 testing, according to generally accepted principles to
24 cause reproductive toxicity based on developmental
25 toxicity?

1 Okay. And I will now call each of your names and
2 ask you to vote yes, no, or abstain on this question. So
3 we'll start on this side.

4 Larry?

5 COMMITTEE MEMBER BASKIN: Yes.

6 CHAIR LUDERER: Carrie?

7 COMMITTEE MEMBER BRETON: Yes.

8 CHAIR LUDERER: Martine?

9 COMMITTEE MEMBER CULTY: Yes.

10 CHAIR LUDERER: Kim?

11 COMMITTEE MEMBER HARLEY: No.

12 CHAIR LUDERER: I'll move on to Charles?

13 COMMITTEE MEMBER PLOPPER: Yes.

14 CHAIR LUDERER: And Isaac?

15 COMMITTEE MEMBER PESSAH: No.

16 CHAIR LUDERER: And Diana?

17 COMMITTEE MEMBER AUYEUNG-KIM: Yes.

18 CHAIR LUDERER: All right. And I also vote yes.

19 So, we -- is someone keeping the tally? We have
20 two noes. All right. So we had two noes and six yeses.
21 All right, and there were no abstentions.

22 So, six yes votes are required to add a chemical
23 to the list, which is the majority -- a majority of the
24 appointed members.

25 So, then let's. It's actually afternoon, so we

1 have provided the tally, six out of eight. And since it's
2 close to noon, then it would be -- or afternoon, it would
3 be time to take a lunch break now.

4 So, I would like to remind all the members of the
5 Committee that during breaks, we shouldn't talk about
6 our -- amongst ourselves about the subject matter,
7 about -- of the meeting, including phone calls, texts, and
8 chats. And it would be best -- it is best to not talk to
9 third parties about the items that were just being
10 discussed at this meeting. If you do, you need to
11 disclose the fact that you had a discussion with someone
12 and give general content of that discussion, so that it's
13 part of the public records. So, it's better to just chat
14 about other things over lunch.

15 (Laughter).

16 CHAIR LUDERER: All right. Okay. So -- and the
17 lunch break will be 45 minutes. And so will resume in 45
18 minutes, so about 1:30 or so.

19 (Off record: 12:41 p.m.)

20 (Thereupon a lunch break was taken.)
21
22
23
24
25

1 AFTERNOON SESSION

2 (On record: 1:31 p.m.)

3 CHAIR LUDERER: All right. It looks we're all
4 back from lunch and well fed. So, this afternoon, we're
5 going to start out -- we're going to be talking -- getting
6 input from the Committee about a proposal for development
7 of hazard identification materials for p,p'-bisphenol
8 chemicals. And these would be to support consideration
9 for listing those by the Committee, that DARTIC in 2026.

10 So, I'm going to now turn it over again to Dr.
11 Martha Sandy, Chief of the Reproductive and Cancer Hazard
12 Assessment Branch to begin.

13 (Slide presentation).

14 DR. MARTHA SANDY: Thank you and good afternoon.
15 So at last year's meeting, the Committee members had some
16 discussion and noted that many other bisphenols have
17 greater biological activity than BPS for some endpoints.
18 And they raised the possibility of looking at a wider
19 spectrum of bisphenols in a single meeting. And in
20 response to these comments and suggestions, we've
21 developed a proposal to look at multiple bisphenols
22 specifically, para para prime bisphenol chemicals in the
23 coming year.

24 And we're speaking the committee's advice and
25 consultation on this proposal. And now, I'll turn it over

1 to Dr. Moran, who will present the proposal in a little
2 more detail.

3 DR. FRANCISCO MORAN: Thank you, Dr. Sandy. Good
4 afternoon. Well, as you heard, we have one more agenda
5 item for consideration. And this is the proposal for the
6 development of hazard identification materials for
7 multiple bisphenol chemicals. I will like to now -- I
8 would now like to give you -- (clears throat). Sorry --
9 an overview of the key points.

10 NEXT SLIDE

11 DR. FRANCISCO MORAN: Now, this is true, over the
12 next five to ten minutes, I will introduce you to our
13 proposal and the group of bisphenols that we are
14 considering, our methodology, and new hazard
15 identification material design.

16 NEXT SLIDE

17 DR. FRANCISCO MORAN: Currently, there are two
18 para para prime bisphenols on the Prop 65 list for
19 reproductive toxicity. BPA was listed for female and
20 developmental toxicity. And after today, BPS will be
21 listed for all reproductive endpoints.

22 NEXT SLIDE

23 DR. FRANCISCO MORAN: Para,para-bisphenol
24 chemicals include para,para-bisphenols, and ethers, and
25 esters of these. In this generic chemical structure, the

1 two phenol rings are connected by a bridging atom,
2 indicated by the letter R. The X represents hydrogen or
3 various substituents attached to a phenol group, and the Y
4 represent hydrogen or various substituents attached to the
5 bridge between two phenol groups

6 In ether and esters of para,para-bisphenols, the
7 hydroxyl groups are replaced by ether and ester groups
8 respectively. Besides BPA and BPS, there are many other
9 chemicals classified as para,para'-bisphenols due to their
10 shared structure. The scientific literature related to
11 the developmental and reproductive toxicity of this group
12 of chemicals is large and growing.

13 NEXT SLIDE

14 DR. FRANCISCO MORAN: In the past few years, our
15 approach has been to develop a comprehensive hazard
16 identification document for a single chemical and sometime
17 for a single endpoint, as it was for BPS, where -- (clears
18 throat) Sorry -- where we create a document for each DART
19 endpoint.

20 We would like to cast a larger net to examine
21 many additional para,para-bisphenols in 2026. This allows
22 for the examination of this group of chemicals that may be
23 introduced to replace BPA and BPS, though could have had
24 similar reproductive toxicity.

25 With consideration for public health and the

1 potential for regrettable substitutions, in addition to
2 workload and time limitations that surround the
3 development of HIDs, we propose a modified approach for
4 conducting hazard identification on this group of
5 chemicals.

6 NEXT SLIDE

7 DR. FRANCISCO MORAN: Specifically, for our
8 potential 2026 hazard identification document, we propose
9 to modify our process using a targeted outcome approach.
10 This include, first, focusing on a limited number of
11 outcomes per endpoint and then modifying the scope and
12 type of information provided in summary tables. We are
13 seeking the DARTIC advice and consultation on this
14 proposal.

15 NEXT SLIDE

16 DR. FRANCISCO MORAN: To inform this proposal, we
17 conducted an exploratory literature search using search
18 terms for both select para,para-bisphenol chemicals and
19 DART outcomes. We conducted a title and abstract-level
20 screen of the studies and tagged the studies by DART
21 outcome. Then, we counted the number of studies that
22 report a finding related to a para,para'-bisphenol and
23 each outcome in the abstract text. We visualized the
24 study counts via heatmap. In addition, we also summarized
25 information on the detection of para,para'-bisphenol

1 chemicals in humans.

2 NEXT SLIDE

3 DR. FRANCISCO MORAN: Based on studies identified
4 in the exploratory literature review, we found that 16
5 para,para'-bisphenol chemicals were detected in study
6 samples from 14 countries spanning three continents. The
7 median detection frequencies for most of these
8 para,para-bisphenols chemicals were between 45 and 60
9 percent, with high variability observed across the
10 studies.

11 NEXT SLIDE

12 DR. FRANCISCO MORAN: As mentioned earlier, from
13 the abstract level screen, we counted studies that
14 reported effects for each para,para-bisphenol chemicals by
15 outcome. We visualized these counts in heatmaps to
16 identify outcomes that were most frequently associated
17 with bisphenol exposure, and to give a sense of the
18 breadth of the literature.

19 NEXT SLIDE

20 DR. FRANCISCO MORAN: Here is -- here is the
21 heatmap display for studies in humans. The
22 para,para-bisphenol chemicals identified in our search are
23 represented on the X axis. The DART outcomes examined per
24 endpoint are on the Y axis. The shading of each square
25 represent the number of studies that report associations

1 or effects between the bisphenols and the specific
2 outcome.

3 Note, that the literature search did not include
4 search terms for BPA and BPS, thus those chemicals are
5 excluded from the heatmap portion of this visualization.
6 Instead, we use black dots to represent that there are
7 some data linking those bisphenols to each of the
8 outcomes.

9 In human studies, nine bisphenols were identified
10 to have significant associations with DART endpoints.

11 NEXT SLIDE

12 DR. FRANCISCO MORAN: In mammalian studies,
13 similarly 17 bisphenols were found to have DART effects,
14 especially for female and male reproductive endpoints.

15 NEXT SLIDE

16 DR. FRANCISCO MORAN: And in non-mammalian
17 studies, 19 bisphenols were found to have DART effects,
18 especially for the developmental endpoint.

19 NEXT SLIDE

20 DR. FRANCISCO MORAN: Based on the heatmaps, we
21 select target outcome for each DART endpoint. These
22 include: Oocyte and ovarian, uterine, and endocrine
23 effects for female reproductive toxicity; sperm and
24 testicular, and endocrine effects for male reproductive
25 toxicity; and somatic, neurodevelopmental, reproductive

1 development, and endocrine effect for the developmental
2 toxicity endpoint.

3 NEXT SLIDE

4 DR. FRANCISCO MORAN: This is an example of a
5 tabulation from the current BPS developmental HID that I
6 don't expect you to read on this slide. It is a
7 comprehensive study tabulation based on data from a single
8 chemical and all the outcomes assessed in this study. In
9 order to streamline the development of the HID for
10 multiple bisphenols, we propose a modification of our data
11 extraction to create tabulations that focus on selected
12 outcomes.

13 NEXT SLIDE

14 DR. FRANCISCO MORAN: Let me walk through the
15 proposed tabulation design. We will summarize the study
16 design information and briefly describe the test system
17 and dose regimen.

18 NEXT SLIDE

19 DR. FRANCISCO MORAN: In the previous HID, we
20 provided a comprehensive overview of all outcomes assessed
21 in the study. Now, the proposed tabulation will be on
22 targeted outcomes represented in the study and provide
23 relevant details necessary for analysis.

24 NEXT SLIDE

25 DR. FRANCISCO MORAN: Similarly, the tabulation

1 of major findings will contain target outcomes assessed in
2 the study, providing a summary of relevant effect with
3 each outcome.

4 NEXT SLIDE

5 DR. FRANCISCO MORAN: As a result, the proposed
6 tabulation will be more concise and allow for the summary
7 of data from multiple bisphenols from a single study with
8 a focus on targeted outcomes.

9 NEXT SLIDE

10 DR. FRANCISCO MORAN: We are seeking the
11 DARTIC's -- DARTIC feedback on this proposal.
12 Specifically, we'd like to know whether you have feedback
13 on the approach we used to select a subset of outcomes to
14 examine the DART endpoints. And also, we'd like to hear
15 from you whether you think the proposed modified tables
16 have enough information to inform your discussion on these
17 bisphenols in the future, or would you like to see
18 different data displayed.

19 NEXT SLIDE

20 DR. FRANCISCO MORAN: Thank you for your
21 attention.

22 CHAIR LUDERER: Thank you very much for that
23 proposal. I think it might be -- let's see. So we have
24 the discussion questions. And I'm sure that we'll -- the
25 Committee members might want to go back to that -- to

1 those table comparisons as well as we're talking.

2 So, as we can see here, so the first discussion
3 is whether we have feedback on the approach used to select
4 these subset of outcomes for the DART endpoint and whether
5 we think the proposed modified tables have enough
6 information to inform discussion. So thoughts on that
7 from Committee members.

8 Kim

9 COMMITTEE MEMBER AUYEUNG-KIM: Actually, I have a
10 question before we answer these questions. So, since
11 we're going to be looking at multiple chemicals, and some
12 of them actually we've reviewed already, BPA and BPS, is
13 it like -- and some of them have already been listed. The
14 BPS and BPA have been listed. Dr. Sandy.

15 (Laughter).

16 DR. MARTHA SANDY: Sorry. So, the concept is,
17 yes, you've already looked at BPA and BPS. And hopefully,
18 those results are fresh in your minds.

19 CHAIR LUDERER: Yes.

20 DR. MARTHA SANDY: We are considering looking at
21 more broadly the bis -- para,para-bisphenol chemicals,
22 where you have -- and we can concisely summarize for the
23 selected outcomes, the effects -- you know, refer you back
24 to what's been known and decided upon for BPA and BPS.
25 That was the idea. So you've got these two

1 COMMITTEE MEMBER AUYEUNG-KIM: Okay. And so --
2 but having -- already have those com -- BPA and BPS
3 listed, would that affect that -- you know, this as a
4 class -- the PB, as a class, would be considered already
5 to be listed or should be listed. Sorry.

6 DR. MARTHA SANDY: So, currently, we just have
7 two --

8 COMMITTEE MEMBER AUYEUNG-KIM: Yeah. Yeah.

9 DR. MARTHA SANDY: -- chemicals on the list. The
10 concept is we -- we're proposing to look more broadly,
11 give you --

12 COMMITTEE MEMBER AUYEUNG-KIM: Yeah.

13 DR. MARTHA SANDY: -- a document that summarizes
14 the evidence and then the Committee will ultimately make a
15 decision as to --

16 COMMITTEE MEMBER AUYEUNG-KIM: As a class.

17 DR. MARTHA SANDY: It could be --

18 COMMITTEE MEMBER AUYEUNG-KIM: Okay.

19 DR. MARTHA SANDY: -- as broad as a class. It
20 could be individuals within the class or subsets. You
21 will -- that will bill be your --

22 COMMITTEE MEMBER AUYEUNG-KIM: Okay.

23 DR. MARTHA SANDY: -- decision in the meeting
24 next year, but we're just proposing how can we do all in
25 one year and get you something? What do you need?

1 COMMITTEE MEMBER AUYEUNG-KIM: Okay.

2 DR. MARTHA SANDY: We're looking for feedback on
3 that.

4 COMMITTEE MEMBER AUYEUNG-KIM: Okay. Thank you.

5 CHAIR LUDERER: I think Kim you had --

6 COMMITTEE MEMBER CULTY: No, I was just looking
7 at the table for the human. I just hope we have enough
8 data to work on, because it seemed much -- the human
9 studies, they -- you know, your A, B, and C. A is human.
10 It looks much less studies and endpoint with -- like I'm
11 afraid like will we have enough data to discuss on the
12 human or are we going to rely mainly on mammalian and
13 non-mammalian animals, I guess?

14 DR. FRANCISCO MORAN: Well, we normally use all
15 set of evidence, you know, human, animals, and mechanistic
16 to present to you. When we have human data, of course, we
17 prefer that, and we analyze, and then we'll summarize
18 that. Most of the cases I think in the -- my experience,
19 the driving force has been animal data, you know, for
20 listing decisions. But that is, again, your decision, not
21 our. We'll summarize the data for you and you will use it
22 as necessary. No -- and -- with analysis.

23 COMMITTEE MEMBER CULTY: I'm just -- I'm just
24 wondering if it's too premature for human studies, but we
25 might -- you know, how are we going to get more human

1 studies on these? I don't know, because it's -- from
2 here, I see like one, two, three, four that seem to have
3 some shades of something --

4 DR. FRANCISCO MORAN: Right.

5 COMMITTEE MEMBER CULTY: -- having some effect in
6 some humans to these.

7 DR. FRANCISCO MORAN: Yeah. Let me add some -- a
8 good piece of information. This is a preliminary -- the
9 result of a preliminary search --

10 COMMITTEE MEMBER CULTY: Okay.

11 DR. FRANCISCO MORAN: -- reading title and
12 abstract only. So we are just counting from a very, very
13 preliminary exploratory search to have the idea where we
14 are in term of how many bisphenols are -- have assessed
15 many outcomes for each endpoint. You know, and the table
16 should be close horizontally to see, you know, how many
17 bisphenols, how many little boxes you have for the
18 outcomes.

19 That helps?

20 But we expect that we should get way more studies
21 to analyze. You know, with this primary search,
22 exploratory, we got about 1,500. So if we do a full
23 literature search from all the databases, I expect to --
24 this number to increase a lot.

25 COMMITTEE MEMBER CULTY: And what do we know

1 about the abundance in human now of these bisphenols --
2 like bisphenols, what are the type of levels in humans?
3 Like, have they already been studied in human urine and
4 blood?

5 DR. FRANCISCO MORAN: In the -- in the previous
6 table, we have 16, 17 bisphenols identified in human
7 studies --

8 COMMITTEE MEMBER CULTY: Oh, it was before?

9 DR. FRANCISCO MORAN: -- with the average of 40
10 to 60. Will you put the slide before --

11 COMMITTEE MEMBER CULTY: Yeah. Yeah. I see it.

12 DR. FRANCISCO MORAN: Yeah, that one. Yeah.
13 Yeah, I think there's 16. And the number in parentheses
14 indicate the number of studies for each bisphenol --
15 para,para-bisphenol

16 COMMITTEE MEMBER CULTY: This is the --

17 COURT REPORTER: Your mic. Your mic.

18 COMMITTEE MEMBER CULTY: Oh, sorry. So for this
19 one, there were only one measurement done with this one.

20 DR. FRANCISCO MORAN: Because it's one study.

21 COMMITTEE MEMBER CULTY: Okay.

22 DR. FRANCISCO MORAN: Yeah. For -- on the -- if
23 you -- on the right side of the figure, it is only one
24 study.

25 COMMITTEE MEMBER CULTY: Whereas here it's

1 multiple.

2 DR. FRANCISCO MORAN: Here is many, you know,
3 from six to 76. So, that's the reason you have a bar, you
4 know.

5 DR. MARTHA SANDY: And let me, again, remind the
6 Committee, you are engaged in hazard identification. Does
7 something cause reproductive toxicity? And because of
8 sub -- possible substitution of different bisphenols,
9 levels that are measured in people right now might not
10 reflect what exposure might be down the line.

11 CHAIR LUDERER: Kim, did you want to ask your
12 question or have a comment?

13 COMMITTEE MEMBER HARLEY: Yeah. I have two, I
14 guess. The first one is easy. I couldn't see when you
15 were showing the tables, but I'm pretty sure -- I want to
16 make sure that you still put in where you don't find an
17 effect, that we -- it's still very clearly labeled that
18 they looked at these things and found no association,
19 because --

20 DR. FRANCISCO MORAN: Absolutely.

21 COMMITTEE MEMBER HARLEY: -- the null effects are
22 really important.

23 DR. FRANCISCO MORAN: Absolutely. That's part of
24 the data, yeah.

25 COMMITTEE MEMBER HARLEY: And then the other

1 question, I'm not exactly sure what my question is, but
2 I'm thinking as a Committee member about making a decision
3 as -- about a class of chemicals as opposed to making
4 decisions about these individual chemicals. And when we
5 look at this document, I think it's going to show us
6 individual chemicals. It's going to show us BPF, for
7 example. I know there will be quite a bit on that. And I
8 noticed there's nothing on BADGE, it looked like, for
9 human studies.

10 And I guess what I was wondering is, is there a
11 way that we can kind of think about what the commonalities
12 across this class are, so that even if there's no direct
13 evidence about some of these other p,p-bisphenols, is
14 there some way that we can, I don't know, make
15 interpolations or something about the other chemicals
16 based on their structure or based on the similarity of
17 this group as a class rather than just thinking about them
18 one by one. And I don't know the answer to how we do
19 that, but I can --

20 COMMITTEE MEMBER BRETON: Well, I would suggest
21 that for -- at least for the human studies, to the extent
22 that there are studies out there now that are looking at
23 mixtures of these chemicals, that in your summary stable,
24 you specifically summarize or call out the evidence of the
25 mixtures analyses and whether -- whether -- regardless,

1 because I'm sure it's going to be -- some looked at
2 certain mix -- the mixtures are going to differ, right,
3 based on what they can detect in their populations. But
4 on the whole, did you -- did they see an effect of the
5 mixture class they evaluated and what was that effect.
6 And if that could be summarized separately from
7 individual -- or certainly to make it clear that -- yeah,
8 I guess -- I guess what I'm asking for is it's sort of a
9 separate category for whatever evidence there is for
10 mixtures analyses, because I think that that would be
11 helpful when thinking about the class.

12 CHAIR LUDERER: Isaac.

13 COMMITTEE MEMBER PESSAH: I think it would really
14 helpful, especially when you don't have really critical
15 mass of epidemiological studies. I mean, epidemiological
16 studies, that is the exposure, whether it was measured or
17 not, where it was measured, if you see an effect -- do you
18 see an effect?

19 But if you don't have enough human
20 epidemiological studies and you're going to rely on animal
21 and mode of action studies, you need to bring in an
22 exposure person that will -- or a section of the document
23 that simply says these are the levels found in humans or
24 exposure levels in the environment, and really flesh that
25 out, so it provides some basis for you discussing a study

1 in zebrafish, or a study in mice ex vivo or in vitro.

2 Otherwise, you can come up with studies that
3 throw enough of the chemical on there are going to -- and
4 then they all partition differently. BPA has a hugely
5 different partition than BPS. It's more lipophilic. It
6 will go to fat more. So, that would be really helpful
7 that -- you know, at least on my end of the spectrum for
8 mechanistic or mode of action studies and relating them --
9 how does it relate to real life exposure?

10 If that's not possible, then I'd gladly
11 substitute me for somebody that has expertise in exposure
12 for the Committee, as opposed to putting it on OEHHA. I
13 think that just makes so much more sense, especially when
14 you're talking about a class of however many bisphenols
15 that they're there -- and then metabolites, which I think
16 aren't there, right, which do -- you do have exposure to.

17 That really, I think, would be very helpful, at
18 least from my perspective. Yeah.

19 CHAIR LUDERER: Yep. Go ahead

20 COMMITTEE MEMBER BASKIN: I may have missed it,
21 but, you know, these tables for BPS are outstanding. Are
22 we shortening these tables and what was the reason for
23 that?

24 DR. MARTHA SANDY: So, you were given this
25 document in full --

1 COMMITTEE MEMBER BASKIN: Yeah.

2 DR. MARTHA SANDY: -- and our slides are just
3 giving some examples. The comment and discussion last
4 year was, you know, you've brought us Bisphenol one
5 endpoint at a time for three years. Can you do more
6 chemicals at once? And we're trying to do that. We
7 physically can't do that at the level of detail of the
8 document you reviewed today.

9 So, what we're proposing, if we go back to the
10 questions, we're proposing to only talk about a select
11 number of outcomes for each of the three endpoints, male
12 reproductive, female reproductive, and developmental
13 toxicity. And we're also proposing to present less
14 information in the tables. We will give you the PDFs for
15 the papers. And so we're looking for your feedback. Is
16 that going to be okay?

17 COMMITTEE MEMBER BASKIN: I think it's probably
18 okay. I just remember when we didn't have the tables.

19 (Laughter).

20 COMMITTEE MEMBER BASKIN: We said we should have
21 some tables. And now, we have tables. Now, you're taking
22 them away.

23 (Laughter).

24 COMMITTEE MEMBER BASKIN: So I personally like
25 the detail. I get exactly what you're saying. And just

1 to be short, I agree with Isaac. I maybe took this for
2 granted that people writing a paper and a paper being peer
3 reviewed, they would use a reasonable dose that would
4 simulate reality. And I could be wrong on that.

5 So, maybe a little bit -- can that -- that
6 comment I think I was -- somewhat was a little blindsided
7 when that came up today. So, that might be something to
8 emphasize in terms of is this an appropriate paper that
9 even should be looked at. And that's out of my expertise,
10 so you need -- you guys have some expertise in that.

11 DR. MARTHA SANDY: I don't want to do all the
12 talking here, but the concept of doing testing and either
13 in vitro or in vivo in animals, the concept is to test
14 before the chemical gets out and gets into exposure in the
15 human population theoretically, and find out if it -- if
16 there's some toxicity, some hazard.

17 And so you usually test at a high dose, a
18 minimally toxic dose, and then step down for lower doses.
19 And it has nothing to do with, you know, especially for a
20 chemical that hasn't been approved for use yet, the
21 testing is done without knowing what levels people will be
22 exposed to. And we also know that exposures change over
23 time as use of chemicals, new uses and increased uses,
24 change. We can do our best to find out the exposure
25 information, but sometimes it's not there.

1 COMMITTEE MEMBER CULTY: I wanted to mention --
2 so speaking of that -- the example of DINCH, which, you
3 know, BASF did a number of studies, and they found some
4 adverse effect, but the argument of the chemical company
5 was that this is at a much higher level that the human
6 will ever be exposed. And 15 years down the road, it's in
7 the blood of everybody, because, you know, some of the
8 phthalates were replaced by DINCH, supposedly the green,
9 you know, non-phthalate analog, which has endocrine
10 disrupting activities. You know, multiple lab have been
11 able to go -- also, DINCH is a mixture. You know, it has
12 the -- it's not just one single depending of a -- of fatty
13 acid -- I mean, a long chain, aliphatic chains, and branch
14 or a long one. But, you know, for -- I don't know if it
15 will be a problem.

16 Like, we want people to study this chemical, but
17 it can be difficult actually to obtain these chemicals
18 from the manufacturer, because, you know, they want to be
19 the ones running the toxicology studies that you
20 mentioned. And even if I give to you universities, at
21 least in the case of DINCH, most of the time you could see
22 in the -- you know, in the orders, that we were -- receive
23 some type of subvention from BASF. And those who didn't
24 and did totally blinded study thinking, oh, DINCH will be
25 a good positive control that as no effect. And then you

1 tried to go publish your effect, and then before you know
2 it there is lawyers from the company that comes to your
3 university and try to discredit your work.

4 So I don't know if these might be different and
5 maybe BASF now is -- we've seen some data. I mean, they
6 might, you know, have turned down the fright against the
7 chemicals. I don't know. Maybe they have enough of them
8 they can look forward you to -- but that's one thing that
9 we might be facing when we want more human studies or
10 animal studies. And some of -- maybe some of these
11 chemicals there are not too many studies, either because
12 we don't have an easy access to them or, you know,
13 depending where you are in your career, it might not be a
14 good idea to study it, depending what you find, you know.

15 So I don't know it's just a comment on -- ideally
16 we want as many studies as we can, but we might have some
17 issues to get more within a year. I don't know, this
18 year, one year.

19 CHAIR LUDERER: Isaac.

20 COMMITTEE MEMBER PESSAH: Could we go back to the
21 exposure graph? Percent detected I guess it would be.

22 Yeah. You've got a whole family here. And this
23 graph is based on exposure. They must have exposure
24 levels associated with this. So, you already have
25 extensive exposure, even if it was one steady, unless the

1 study was flawed or contradicted. Again, when you're
2 dealing with this many individual compounds, even though
3 they're from a class, they don't all do the same thing.
4 And it would be really informative to the Committee if you
5 took this -- if you were going to shorten the tables --
6 which I really like the tables. I think we all do.

7 (Laughter).

8 COMMITTEE MEMBER PESSAH: -- that you have
9 somebody that just basically discuss the parameters.

10 Now, for us, it would be really helpful if
11 somebody at OEHHA could go through that data with some
12 expertise, and whittle out those that are just absurd
13 exposures. I mean, again 60,000-fold above anything you'd
14 ever see in a human, of course, you're going to change Wnt
15 signaling, or transcriptomics, or genomics expression. So
16 it can -- either can be done by the Committee or a least
17 reduce the data set based on what you see in terms of
18 exposure levels. I mean, that just seems --

19 CHAIR LUDERER: I mean, I guess one issue though
20 is like -- that half of these -- you know, of the ones
21 that are depicted here, there's only one study, so there
22 aren't going to be a lot of -- so that's -- you know --

23 COMMITTEE MEMBER PESSAH: But it provides --

24 CHAIR LUDERER: Yeah.

25 COMMITTEE MEMBER PESSAH: -- a huge sort of --

1 CHAIR LUDERER: Yeah.

2 COMMITTEE MEMBER PESSAH: -- reference point.

3 CHAIR LUDERER: Right. Yeah.

4 COMMITTEE MEMBER PESSAH: It may be off, and
5 somebody could say, oh, no, they miscalculated or, you
6 know -- and then you could throw it out, but...

7 CHAIR LUDERER: Yeah.

8 COMMITTEE MEMBER CULTY: Maybe don't discount
9 them, but put them on a separate category. But, you know,
10 we can look at it for toxico -- and at least high dose the
11 effect might be totally different from the realistic dose
12 effect anyway. But it could still be informative for --
13 you know, and not totally wean them out, but put them on
14 the side like a high exposure or something. I don't know
15 if it's -- ideally, we would want two tables, the big
16 tables and the summary tables.

17 (Laughter).

18 CHAIR LUDERER: Kim.

19 COMMITTEE MEMBER HARLEY: One of the questions
20 you asked us is how do we feel about the way you're
21 choosing the outcomes? I'm not sure I totally understand
22 how the outcomes are being chosen, so if you could just
23 explain that again.

24 DR. FRANCISCO MORAN: Yes. Can we put the -- one
25 of the heatmap, please.

1 MS. TINA COX: Which one.

2 DR. FRANCISCO MORAN: Anyone. It doesn't matter.

3 Mammals probably. Yeah, the studies in mammals.

4 What we did here, you know, is count the studies
5 on title and abstract again, you know, very preliminary,
6 that have an effect on any of the outcomes. And then we
7 plotted against the bisphenols that had that. So we
8 select the outcomes that have more boxes. So, you have to
9 look at this horizontal, imaginary lines. Now, for
10 instance, the very obvious here is sperm or testicular
11 effect. That is a heavy hit. You know, many, many
12 bisphenol has this outcome described as an effect. And
13 for -- and that was the -- a little bit arbitrary. If you
14 want, we didn't have a minimum or a maximum number of
15 studies for each outcome, but we're just using this
16 criteria. Yes.

17 COMMITTEE MEMBER HARLEY: So then a follow-on to
18 that question is, so looking at the mammalian studies, we
19 would do sperm and testicular effects and endocrine
20 effects maybe from the mammal studies. Will you also look
21 at those similar outcomes in the human studies and the
22 mechanistic studies.

23 DR. FRANCISCO MORAN: Yes.

24 COMMITTEE MEMBER HARLEY: So as long as
25 they're -- yeah. Okay. Thank you.

1 DR. FRANCISCO MORAN: Yes. Yes. Yeah, the --
2 yeah, you're right. Yeah, that's it.

3 DR. MARTHA SANDY: Yeah, and so --

4 COMMITTEE MEMBER CULTY: And here we select on --
5 oh, sorry.

6 DR. MARTHA SANDY: In selecting the endpoints for
7 male reproductive, for example, we looked at all three of
8 the heatmaps. I just -- I thought this one had the most
9 evidence to look at.

10 COMMITTEE MEMBER HARLEY: Right, but if --

11 DR. MARTHA SANDY: But if you disagree -- you
12 know, so --

13 COMMITTEE MEMBER HARLEY: No. No. I just --
14 just to be clear, if it's -- if it's showing up here in
15 the mammalian as a good endpoint, but it's not very --
16 there's not very many studies in the epi and in the
17 mechanistic, do we still get to see the studies that are
18 in the --

19 DR. FRANCISCO MORAN: (Nods head).

20 COMMITTEE MEMBER HARLEY: Okay. That was --
21 that's --

22 DR. FRANCISCO MORAN: Absolutely. Yes.

23 COMMITTEE MEMBER CULTY: My question. So it's
24 about a number of them. So we will -- you said 9 or 10 of
25 them -- not --

1 DR. FRANCISCO MORAN: No. Nine on the human, 17
2 or 19 on the -- I think 17 here. If we count the green
3 boxes, on horizontal axis, you will find -- I believe
4 there are 19.

5 COMMITTEE MEMBER CULTY: These ones here they
6 don't seem to have effect much in non-mammalian and like
7 nothing is really known in human. You know, the middle
8 one. If you go up or down. Yeah. So do we -- do we have
9 enough information to even bother with them? There's
10 nothing much on mammalian, non-mammalian, and human.

11 DR. MARTHA SANDY: There is some. And if we go
12 to the next one, the non-mammalian, there are -- that's
13 where the data lie. Do we have another slide? There, for
14 the middle group. You're right. It's -- the data are
15 sparse, yes. That's true.

16 DR. FRANCISCO MORAN: So the development -- yeah,
17 the developmental effect in non-mammalians drive the force
18 for the inclusion of these four or five bisphenols that
19 appear like you're empty on the other two plots.

20 COMMITTEE MEMBER CULTY: There's like two or
21 three studies on --

22 DR. FRANCISCO MORAN: Right. Those are very
23 tiny. It mean probably one study each, you know, like the
24 color code.

25 DR. MARTHA SANDY: But we're using these heatmaps

1 to choose the outcome -- or the endpoints within --
2 yeah --

3 DR. FRANCISCO MORAN: No, the outcomes --

4 DR. MARTHA SANDY: The outcomes within the
5 endpoints.

6 DR. FRANCISCO MORAN: The outcomes in each
7 endpoint -- for each endpoint, yeah.

8 CHAIR LUDERER: I see. Other questions,
9 comments.

10 DIRECTOR THAYER: I may have one. Sorry. This
11 is Kris. I hate to go back to the table issue, but, you
12 know, Martha brings up a good point. So it's not all or
13 none. There are tables. They will be streamlined. So --
14 and you are speaking to a group of very detailed-oriented
15 people. So you can imagine what they're hearing when they
16 hear we like the tables. I think if you're -- you know,
17 again, you would be provided access to the PDFs. I think
18 if you want to sort of opine on the tables, it might be
19 helpful to say what specifically about the streamline
20 table would you find problematic or perhaps you can live
21 with it, given that you have access to the PDF, because
22 it's a very -- I mean, I was just sort of comparing the
23 points. Tables take a lot, a lot of work. And Martha is
24 right, this is a lot of -- a lot of work that we're trying
25 to do on a lot of chemicals under a pretty compressed time

1 frame.

2 COMMITTEE MEMBER CULTY: Can you show that?

3 CHAIR LUDERER: Do we want to see those table
4 again, the sample tables?

5 COMMITTEE MEMBER CULTY: Yeah.

6 DR. FRANCISCO MORAN: It should be here. Don't
7 you have a monitor?

8 COMMITTEE MEMBER CULTY: That's a good table.

9 DR. FRANCISCO MORAN: For -- just to explain what
10 you have today is the left panel. What you will have next
11 year is the right one.

12 COMMITTEE MEMBER CULTY: Both good.

13 DR. FRANCISCO MORAN: Both are good. I know.
14 The difference is if we want to do the --

15 COMMITTEE MEMBER CULTY: I know.

16 DR. FRANCISCO MORAN: -- the left panel with 16 a
17 list, you know, recognizing that for the 16, we do have
18 exposure data, we need a couple of years probably to do
19 that.

20 COMMITTEE MEMBER CULTY: I think I can -- I could
21 live with the sensitive tables and go back to the paper
22 see if I want to see more of the case.

23 DR. FRANCISCO MORAN: Yes.

24 COMMITTEE MEMBER CULTY: That's what you want us
25 to do.

1 DR. FRANCISCO MORAN: No. What I didn't mention,
2 you will have it. You know, you will have it. You know,
3 you will have access to all the PDFs. You will have all
4 the similarity. You will have mechanistic. So, this is
5 just the human and animal data presentation. Yeah.

6 COMMITTEE MEMBER CULTY: And you have will have
7 in bracket the reference and we can go and see the
8 details.

9 DR. FRANCISCO MORAN: Exactly, yes. And the
10 reference list, everything.

11 COMMITTEE MEMBER BRETON: I guess one question I
12 would have just looking at the new tabulation, so when it
13 somatic effects only for BPA, BPF, and BPS and then you
14 list these neurodevelopmental ones, are each of those
15 outcomes being associated with all or each of BPA, BPF,
16 and or is it a mixture, like one might be associated with
17 one, another with another. And I'm just like wondering if
18 it would be -- yeah, I don't know, helpful to know like
19 how many with each one or if that is necessary? I don't
20 know, because it's already sort of in the heatmap maybe.

21 COMMITTEE MEMBER CULTY: You can see an area of
22 papers --

23 COURT REPORTER: Microphone. Microphone.

24 COMMITTEE MEMBER CULTY: Oh, sorry. I see on the
25 heatmap you can see how many papers dealt with no

1 developmental issue, for example. It's just the number of
2 studies. It doesn't --

3 COMMITTEE MEMBER BRETON: Well, I guess, here on
4 the major findings, you actually -- if you've listed all
5 three of them, presumably, it means each -- that you saw
6 that intraocular distance for each of those then, right?
7 So, it is -- it is there then.

8 But then the -- this comes back to my original
9 question, which would be -- or suggestion which would be
10 those were presumably individually looked at. But if
11 there was any evidence for a mixture effect, it would be
12 good to have the mixture effect also listed there, so that
13 you know that like it adds a little bit more info.

14 DR. MARTHA SANDY: Sure. We can do that. What's
15 being shown here is a separate, you know --

16 COMMITTEE MEMBER BRETON: Right.

17 DR. MARTHA SANDY: -- only exposed to BPA they
18 saw --

19 COMMITTEE MEMBER BRETON: Right. Oh, cause
20 the -- yeah. Okay, cause this is like animal too, right
21 here. Sorry. Yeah.

22 DR. FRANCISCO MORAN: Yeah. Having the data on a
23 matrix, definitely we probably will do it. Which is
24 important here, that separation that you just -- you note
25 is BPA, BPF, and BPS was analyze. Only those chemicals

1 were analyzed for somatic effect. That way it saves only
2 those three, you know, but the rest -- the other seven
3 were analyzed for everything.

4 CHAIR LUDERER: Yeah. I mean, I think in some
5 ways that looking at this kind of holistic approach where
6 you're looking at all these chemicals as a class is more
7 like the human -- what you see in the human data, right?

8 DR. FRANCISCO MORAN: Right.

9 CHAIR LUDERER: Isaac.

10 COMMITTEE MEMBER PESSAH: Except the human data.

11 COURT REPORTER: Microphone.

12 COMMITTEE MEMBER PESSAH: Oh, sorry. The human
13 data is concurrent exposures at infinitely variable
14 ratios. And so these individual results can't be used to
15 interpret combinations and -- anyways, you have to be
16 cautious.

17 COMMITTEE MEMBER CULTY: All of these studies
18 were done on single compound basically. Yeah.

19 DR. FRANCISCO MORAN: (Nods head.)

20 COMMITTEE MEMBER CULTY: That's -- there is no
21 study you can find that were using mixture of two or
22 three? No?

23 DR. MARTHA SANDY: We don't know. This was a
24 preliminary --

25 COMMITTEE MEMBER CULTY: Okay. So there might be

1 some.

2 DR. FRANCISCO MORAN: There might be.

3 COMMITTEE MEMBER PESSAH: So one of the better
4 studies in organoid cultures from human looked at a
5 combination of two bisphenols. And the results were
6 unexplained by each individually. I meant to say that,
7 but one of the studies was very clear on that. It was a
8 huge combination effect.

9 COMMITTEE MEMBER CULTY: That's like what the
10 gray group does with the phthalates and they get effect
11 that at very low dose that should not have been like
12 we're, you know, below the NOEL. And what we do in our
13 team was like two different families and the same. We
14 have totally different detecting the mixture at very low
15 level compared to what people, you know, see with a single
16 compound. We do a single or higher level. So we -- yeah.
17 Cross talks are important. If you find mixture, you will
18 include that, like you suggested.

19 DR. FRANCISCO MORAN: Yes. Should I add that...

20 CHAIR LUDERER: And even with the in vitro
21 studies, I mean, there are very few where they looked at
22 multiple different combinations, right, of the doses? It
23 gets more and more complicated the more you have.

24 Other thoughts from members of the Panel?

25 DR. FRANCISCO MORAN: So the selected outcomes

1 for each endpoint, you know, that are in the presentation
2 and your document were selected based on this preliminary
3 approach. That's clear. So the question to you, do you
4 feel comfortable with those -- with that selection, or
5 will you use a different approach, or you prefer to see
6 everything? And that everything imply a little bit more
7 difficulty for us time-wise, not other. You know, it's
8 the same neurons, but more time, yeah.

9 (Laughter).

10 DR. FRANCISCO MORAN: So that was the preliminary
11 question, the question on this -- for the selected
12 outcomes. It's important to know if you agree with us,
13 our proposal.

14 COMMITTEE MEMBER HARLEY: I would be happy to
15 look at the outcomes that have the strongest evidence. I
16 think that that -- if there are a few that have the most
17 evidence and we can just focus on those --

18 DR. FRANCISCO MORAN: Yes.

19 COMMITTEE MEMBER HARLEY: -- and not have to
20 spend a lot of time on the ones that have very little
21 evidence, I'm okay with that, which I think is what you're
22 proposing.

23 DR. FRANCISCO MORAN: Good to know.

24 CHAIR LUDERER: And you're still planning on
25 including all the different types of studies, right, so in

1 vivo animal studies, the in vitro studies, and also the
2 human data, yeah.

3 DR. FRANCISCO MORAN: Yes.

4 CHAIR LUDERER: So we would still have all that.

5 And I think this was sort of alluded to, but if
6 there are studies that include multiple -- exposures to
7 multiple of these compounds at once, then you would
8 also -- you would present the results of those. The
9 mix -- it would be nice if there would be more studies
10 where they would look at different combinations, but
11 anyway. As we know that's challenging, yeah.

12 DR. FRANCISCO MORAN: Yeah. Until now in our
13 HIDs, we try -- I don't remember to have done mixtures,
14 because we need to find one chemical that --

15 CHAIR LUDERER: Right.

16 DR. FRANCISCO MORAN: -- to put it on the list.
17 But for this special situation probably mixtures may have
18 some information. Not clear how, you know, considering
19 Dr. Pessah comment, how they interact with each other.
20 And we know that from whole -- and everything, yeah.

21 CHAIR LUDERER: Yes.

22 DR. FAYE ANDREWS: Just one clarifying. For the
23 epi studies, like the BPS HID we just did, we included all
24 of the mixture results that if BPS influenced, and then
25 that would be similarly for this new aspect, just so that

1 we were clear.

2 CHAIR LUDERER: Carrie.

3 COMMITTEE MEMBER BRETON: I guess this is a
4 question, and I don't know how much this type of data
5 exists, but I'm wondering whether particularly for the
6 chemicals that look like there's really no data on so far
7 in these -- in actual studies, whether at the very least
8 there might be some data on sort of the confirmational
9 similarities or the likelihood that one chemical might act
10 like one of the better known chemicals or not, and whether
11 if that type of basic chemistry, I guess, data exists,
12 whether that might be summarized sort of in that intro
13 section where you talk about the chemical, in this case,
14 you know, a single chemical, in case that's at all helpful
15 for thinking about just the likelihood that something that
16 we don't have a lot of data on might act in similar ways
17 to some of the ones we do have more data on

18 COMMITTEE MEMBER CULTY: I think now we can also
19 go further when we look at functional pathways --

20 COMMITTEE MEMBER BRETON: Okay.

21 COMMITTEE MEMBER CULTY: -- not only chemical
22 structure analogy, but also if they target the same type
23 of signaling pathways now, that's what is also done. At
24 least --

25 DR. MARTHA SANDY: So we can do our --

1 COMMITTEE MEMBER CULTY: -- for development,
2 that's what we do.

3 DR. MARTHA SANDY: So we'll do our best to do
4 that, yes, to help say whether the -- you know, this group
5 acts similarly or...

6 CHAIR LUDERER: Other questions or comments from
7 the Panel members?

8 Okay. Let's see not seeing any, then I guess we
9 can move to the public comment period. So do we have any
10 public comments, either in person or online?

11 MS. TINA COX: No in-person and I'm not seeing
12 anybody raising their hands on Zoom either.

13 CHAIR LUDERER: All right. And I see we have the
14 instructions up for public comment.

15 So, if we don't have any public comments, then --
16 and not seeing anyone in the room, anyone else who would
17 like to provide a public comment, then I think we can move
18 on to the consent item, which is an update of the
19 California Code of Regulations Title 27, 2700[SIC] list of
20 chemicals, which have not been adequately tested as
21 required.

22 So we're being asked to affirm -- the Committee
23 is being asked to affirm changes in response to
24 submissions from the California Department of Pesticide
25 Regulation, the Office -- the U.S. EPA's Office of

1 Pesticide Programs have indicated that there are no
2 changes. No response was received from the UCA -- U.S.
3 EPA Office of Pollution Prevention and Toxics. And just
4 to let -- just to remind everyone, this is a ministerial
5 duty of the Committee, in that and rely on information
6 provided by -- to OEHHA by the Department of Pesticide
7 Regulation and U.S. EPA in order to identify chemicals
8 that need to be added or removed to the Section 27000
9 list.

10 So, I would like to invite Senior Environmental
11 Scientist in the Proposition 65 Implementation Program,
12 Tina Cox to give the staff presentation on this item.

13 MS. TINA COX: Thank you, Dr. Luderer and thank
14 you for the Committee for being here today.

15 (Slide presentation).

16 MS. TINA COX: So Proposition 65 requires the
17 State to publish and update annually a list of chemicals
18 that are required to be tested under State or federal law
19 for carcinogenicity or reproductive toxicity and that not
20 have -- and that have not yet been adequately tested as
21 required. This list can be found in Title 27, Section
22 27000 of the California Code of Regulations and is
23 commonly referred to as the Section 27000 list.

24 It is separate and distinct from the Proposition
25 65 list of chemicals known to cause cancer or reproductive

1 toxicity. The Section 27000 list has no regulatory
2 impact. It does not require that any testing be done.
3 Rather, it is a source of information concerning chemicals
4 that need further testing, pursuant to State or federal
5 law.

6 To update the list, OEHHA requested information
7 from the California Department of Pesticide Regulation and
8 the U.S. Environmental Protection Agency's Office of
9 Pollution Prevention and toxics, and Office of Pesticide
10 Programs each year. This year, OEHHA staff reviewed the
11 responses received and identified four recommended changes
12 to the Section 27000 list.

13 Those changes are the removal of: butoxy
14 polypropoxy polyethoxy ethanol, or iodine complex;
15 chlorophacinone; sodium chlorate; and tetraglycine
16 hydroperiodide. Based on information received from DPR,
17 the data requirements for these chemicals have been
18 fulfilled.

19 NEXT SLIDE

20 MS. TINA COX: The letter from DPR, along with
21 additional background, a response letter from OPP, and a
22 mock-up of the proposed changes are available in the staff
23 report provided to the Committee and posted online on
24 October 7th. The proposed change is also shown on the
25 slide.

1 As Dr. Luderer mentioned, this is a consent item
2 and a ministerial duty of the Committee, in that the
3 DARTIC and CIC committees use the information provided by
4 DPR add U.S. EPA to identify the chemicals that need to be
5 added or to remove -- be removed from the Section 27000
6 list. We ask the Committee members to vote in favor of
7 the proposed change, so OEHHA can update the list. I'll
8 now turn it back to Dr. Luderer and I'm happy to take any
9 questions.

10 CHAIR LUDERER: Okay. Thank you very much.

11 Do we have any questions from any Committee
12 members?

13 Oh, sorry. Do we have a -- is there something
14 that you wanted -- that you need to add or no?

15 MS. TINA COX: No, I was just preparing her for
16 the next slide.

17 CHAIR LUDERER: All right. Okay. So, the
18 next -- so the next slide from DPR is that what we're
19 going to now or is that what we already have?

20 MS. TINA COX: This is the -- this is the slide
21 that DPR provided as part of their letter.

22 CHAIR LUDERER: All right. Okay. So, then we
23 need to now vote. Are there any questions from the
24 Committee members regarding that?

25 So the question we're voting on is, as was said,

1 should Section 27000 of the Title 27 of the California
2 Code of Regulations be amended, as indicated in the staff
3 report? And I will now just -- I will call on each of
4 your names and ask you to vote yes, no, or abstain on this
5 question.

6 So, I'm just going to go through the Committee.
7 Dr. Auyeung-Kim?

8 COMMITTEE MEMBER AUYEUNG-KIM: Yes.

9 CHAIR LUDERER: Dr. Baskin?

10 COMMITTEE MEMBER BASKIN: Yes.

11 CHAIR LUDERER: Dr. Breton?

12 COMMITTEE MEMBER BRETON: Yes.

13 CHAIR LUDERER: Dr. Culty?

14 COMMITTEE MEMBER CULTY: Yes.

15 CHAIR LUDERER: Dr. Harley?

16 COMMITTEE MEMBER HARLEY: Yes.

17 CHAIR LUDERER: Dr. Pessah?

18 COMMITTEE MEMBER PESSAH: Yes.

19 CHAIR LUDERER: Dr. Plopper?

20 COMMITTEE MEMBER PLOPPER: Yes.

21 CHAIR LUDERER: And I also vote yes. So
22 unanimously the Committee votes yes. So that -- six
23 vote -- the six yes votes are required to confirm change
24 and we have eight.

25 So, now we have some time for staff updates. And

1 the -- on the Proposition 65 listings, regulations, and
2 litigation that have taken place since our last meeting.

3 (Slide presentation).

4 CHAIR LUDERER: So Tina, are you going to present
5 this as well?

6 MS. TINA COX: Yes. All right. Thank you. I'll
7 be providing you with an update on important Prop 65
8 development since the last DARTIC meeting. I'll start by
9 going over the chemicals or endpoints added to the
10 Proposition 65 list or under consideration for potential
11 listing. Then, I'll review the safe harbor levels that
12 have been adopted or proposed. And after that, I'll turn
13 it over to our Counsel Kristi Morioka who to provide a
14 brief update on other regulatory actions.

15 NEXT SLIDE

16 MS. TINA COX: Following the Committee's last
17 meeting, the male reproductive endpoint was added to the
18 listing of bisphenol S for reproductive toxicity.
19 Additionally, vinyl acetate was added to the Proposition
20 65 list as a carcinogen.

21 NEXT SLIDE

22 MS. TINA COX: The Carcinogen Identification
23 Committee was -- will be considering
24 N-methyl-N-formylhydrazine for listing as a carcinogen at
25 the upcoming meeting on November 18th, 2025.

1 NEXT SLIDE

2 MS. TINA COX: And since the Committee's last
3 meeting, we adopted a no significant risk level for
4 Titanium Dioxide, airborne, unbound particles of
5 respirable size, where both of the following intake levels
6 must be met: 440 micrograms per day for airborne, unbound
7 titanium dioxide particles with diameters of 10
8 micrometers or less, and 44 micrograms per day for
9 airborne, unbound titanium dioxide particles with
10 diameters of 0.8 micrometers or less. The effective date
11 for the adoption of the NSRL was October 1st of 2025.

12 NEXT SLIDE

13 MS. TINA COX: Since the Committee's last
14 meeting, we proposed to adopt a no significant risk levels
15 for 1-bromopropane and diethanolamine. For
16 1-bromopropane, the proposed NSRL is 54 micrograms per
17 day. For diethanolamine, the proposed NSRL is 6.4
18 micrograms per day for dermal exposure. We are still in
19 the regulatory process for these proposed NSRLs.

20 Now, I'll turn it over to Kristi.

21 KRISTI MORIOKA: Thank you, Tina.

22 Okay. Next slide, please.

23 NEXT SLIDE

24 KRISTI MORIOKA: There we go.

25 So this is a potential amendment to Title 27,

1 Article 6, Section 25302(f) to facilitate the work of the
2 CIC and the DARTIC. This amendment where we would remove
3 the word "appointed" and insert the word "present", would
4 all the Committees to take action based on affirmative
5 vote of the majority of the members present as opposed to
6 the number of members appointed

7 In the past, because of committee vacancies and
8 absences, the committees have had several situations where
9 the number of votes required to pass an action needed to
10 be unanimous instead of a majority of the members, which
11 is not really the intent of the law. So OEHHA will
12 propose this regulatory amendment through the required
13 Administrative Procedures Act process, which includes
14 notice to the public, a 45-day public comment period, and
15 review by the Office of Administrative Law sometime we
16 hope in 2026.

17 And we wanted to present this to you all in case
18 you had anything that you'd like to talk about or had
19 questions.

20 Any questions, any comments?

21 CHAIR LUDERER: Questions or comments from
22 Committee members?

23 No.

24 KRISTI MORIOKA: All right. And now I'd like to
25 turn it over to my colleague Corey Friedman to talk about

1 the litigation update.

2 NEXT SLIDE

3 COREY FRIEDMAN: Thank you very much.

4 So, these are grouped by trial court and
5 appellate court opinions. The first is Chamber of
6 Commerce versus Bonta. This was a First Amendment
7 challenge to the Proposition 65 warning requirement for
8 acrylamide in food. Under U.S. Supreme Court precedent,
9 the Government can compel commercial speech that is
10 factual and noncontroversial. You might remember this
11 case. It has been going on for a number of years. It has
12 been before the Ninth Circuit before after the trial judge
13 issued a temporary injunction, which point to the Ninth
14 Circuit upheld the preliminary injunction. And then the
15 matter was returned back to the trial court.

16 So this year, the Chamber of Commerce moved for
17 summary judgment, which is basically a motion arguing that
18 a party has shown that it should win as a matter of law
19 with no real factual dispute to go before a jury or to the
20 judge, if it's judge type of case. It's a little bit like
21 a trial on paper only. It's based on -- based on
22 declarations and deposition testimony.

23 The Judge did grant summary judgment and issued a
24 permanent injunction against enforcing the warning
25 requirement for quote/unquote dietary acrylamide. And at

1 this time, the Attorney General has filed a notice of
2 appeal.

3 The second case, Personal Care Products Council
4 versus Bonta is also a First Amendment challenge to
5 warnings for titanium dioxide airborne, unbound particles
6 of respirable size, but only in cosmetics and personal
7 care products. So you saw that an NSRL was developed for
8 titanium dioxide. That will still be applicable to that
9 chemical in other products. Like in the previous case I
10 just mentioned, a preliminary injunction became a
11 permanent injunction as a result of a summary judgment
12 motion.

13 The next case there is Physicians Committee for
14 Responsible Medicine versus OEHHA. This is the only case
15 on this list for which OEHHA is actually a party. PCRM
16 sought a writ requiring OEHHA to list processed meat as a
17 carcinogen under the Labor Code listing mechanism, which
18 adds certain listings when designated by IARC. So OEHHA
19 had argued that the IARC monograph was very unclear about
20 what actually constituted quote "processed meat". So
21 therefore, it was unclear what had actually been
22 identified as a carcinogen.

23 And the judge in that case at the trial level
24 agreed that OEHHA had reasonably exercise its discretion
25 in making the determination not to list. So, the judge

1 then denied the writ. The time to appeal has not yet
2 expired, so we do not know if PCRM is going to appeal that
3 again.

4 Finally, in -- there was an appellate decision.
5 This was between private parties. I'm going to just
6 mention this very briefly. The published portion of this
7 decision, which is therefore binding on the State trial
8 courts, held that an arbitration agreement that was part
9 of an online purchasing process did not apply to
10 Proposition 65 claims, and that is because, Proposition 65
11 encourages private enforcement by giving plaintiffs a
12 share of penalties and allowing them to recover attorney's
13 fees. But it is actually validating a public right, not a
14 private right. So, although a consumer can agree to
15 arbitration and give up some of their own private rights
16 of action, they cannot do so for a public right, such as
17 Proposition 65.

18 And that is the update. And if anyone has any
19 further questions about it.

20 CHAIR LUDERER: Not seeing any further questions
21 from the Panel. Thank you.

22 All right. So then I would like to ask Kris
23 Thayer, the OEHHA Director, to summarize our actions
24 today.

25 DIRECTOR THAYER: You're moving right along.

1 (Laughter.)

2 DIRECTOR THAYER: All right. So on agenda item
3 1, the DARTIC voted with a vote of six to two to list
4 bisphenol S as known to the State to cause developmental
5 toxicity.

6 Agenda item 2, in terms of getting feedback on
7 our proposal for looking a para,para'-bisphenol chemicals,
8 what I heard was support for the approach used to selected
9 outcomes moving forward in the assessment. Support for
10 streamlined tables, recognizing members have access to the
11 PDFs. I also -- we affirmed that we will be including
12 mixture studies. Aspirationally, we will try to do
13 something on sort of consideration of exposure to sort of
14 better contextualize the concentrations and dose levels
15 used in experiments. Consider if we can summarize
16 something along chemical similarity or sort of, you know,
17 signaling pathways to help bridge between very data-poor
18 members and those with more data.

19 On agenda item 3, a tough vote, eight to zero,
20 to -- in support of updating the California Code of
21 Regulations Title 27, Section 27000, list of chemicals
22 which have not been adequately tested as required.

23 CHAIR LUDERER: All right. Thank you very much.

24 COURT REPORTER: You microphone.

25 CHAIR LUDERER: I turned it off.

1 Thank you very much, Kris, for that.

2 And now it is time to adjourn our meeting. So
3 thank you, everyone.

4 (Applause).

5 (Thereupon the Developmental and
6 Reproductive Toxicant Identification
7 Committee adjourned at 2:33 p.m.)

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CERTIFICATE OF REPORTER

I, JAMES F. PETERS, a Certified Shorthand Reporter of the State of California, do hereby certify:

That I am a disinterested person herein; that the foregoing California Office of Environmental Health Hazard Assessment, 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 19th day of October, 2025.



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