

MEETING
STATE OF CALIFORNIA
ENVIRONMENTAL PROTECTION AGENCY
AIR RESOURCES BOARD
SCIENTIFIC REVIEW PANEL
ON TOXIC AIR CONTAMINANTS

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APPEARANCES

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1. Welcome and Introductions 1

2. Review of Isoprene Cancer Inhalation Unit Risk Factor (IUR) - Technical Support Document for Cancer Potency Factors.

Office of Environmental Health Hazard Assessment (OEHHA) staff will present a draft document summarizing the development of a cancer potency factor and an inhalation unit risk factor (IUR) for isoprene. Cancer IURs are used to estimate lifetime cancer risks associated with inhalation exposure to a carcinogen. OEHHA is required to develop guidelines for conducting health risk assessments under the Air Toxics Hot Spots Program (Health and Safety Code Section 44360 (b)(2)). In response to this statutory requirement, OEHHA developed a draft IUR for isoprene. Workshops and comment period for the document were offered from February through April 2024. No public comments were received. 4

3. Informational Item from OEHHA on Computational Toxicology and New Approach Methodologies for SRP. OEHHA is developing expertise in new approach methodologies (NAMS) to support CalEPA programs and regulatory activities. NAMS are new toxicological testing and analysis methods that allow for informed predictions of biological effects for data-poor environmental pollutants. There are several components to this effort, including the creation of the New Toxicology Evaluations Section within OEHHA and developing collaborations with academic organizations with NAMS expertise on data-poor compounds. The newly created section brings together experts in toxicology, bioinformatics, toxicokinetics and computational chemistry. This item will present an overview of the NAMS work at OEHHA and potential applications. 54

4. Consideration of administrative matters. The Panel may discuss various administrative matters and scheduling of future meetings. 70

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PROCEEDINGS

1
2 CHAIR ANASTASIO: Okay. Good morning, everyone
3 and welcome to the meeting of the Scientific Review Panel.
4 I'd like to welcome everyone who's in their various
5 locations and everybody who's on the web. Please note
6 that the meeting is being recorded. And Arash Mohegh is
7 going to be overseeing our Zoom technical operations and
8 he's got a -- just a brief announcement about our webpage
9 and additional information.

10 Arash, you want to say that now.

11 DR. ARASH MOHEGH: Thank you, Cort. So the
12 meeting is being recorded and you can find a recording in
13 a few days on webpage dedicated for this meeting. You can
14 find that page for the links that I'm going to put in the
15 chat or from QR code that is on the screen. On that
16 webpage, you can find materials related to this meeting,
17 including the slide deck that two of our presenters are
18 going to be sharing today.

19 Thank you, Cort.

20 CHAIR ANASTASIO: Thank you, Arash. So let's
21 introduce the Panel. Joe, can you start us off, a brief
22 introduction for yourself.

23 Joe, you're muted.

24 PANEL MEMBER LANDOLPH: Did that do it?

25 CHAIR ANASTASIO: Yep.

1 PANEL MEMBER LANDOLPH: Okay. Sorry. Thank you.

2 I'm Joseph R. Landolph, PhD. I work at the
3 University of Southern California. I'm Associate
4 Professor of Molecular Microbiology and Immunology and
5 Pathology. And I'm a member of the USC Norris
6 Comprehensive Cancer Center and I've been here for many
7 years. I've worked on the SRP for probably about 10 and I
8 also work on the CIC. And I do research in chemical
9 carcinogenesis morphological and neoplastic transformation
10 by carcinogens in cell culture.

11 CHAIR ANASTASIO: Thank you, Joe.

12 Paul.

13 PANEL MEMBER BLANC: Me?

14 CHAIR ANASTASIO: You.

15 PANEL MEMBER BLANC: I'm Paul Blanc. I'm
16 Professor Emeritus at UCSF and am continuing on the SRP
17 only until such a time as the appointment replacement is
18 in place. And I'm assuming that this would probably be my
19 last meeting.

20 CHAIR ANASTASIO: We're hopeful, Paul, but things
21 are moving slowly.

22 PANEL MEMBER BLANC: Yeah.

23 CHAIR ANASTASIO: Thank you, Paul.

24 Karen.

25 PANEL MEMBER MESSER: Good morning. I'm Karen

1 Messer. I'm a Professor of Biostatistics at UCSD and
2 Director of the Biostatistics Group at Moores UCSD Cancer
3 Center.

4 CHAIR ANASTASIO: Thank you, Karen.
5 Ahmad.

6 PANEL MEMBER BESARATINIA: Good morning,
7 everybody. I'm Ahmad Besaratinia. I'm Professor at the
8 Department of Population and Public Health Sciences at
9 University of Southern California here in Los Angeles and
10 I have been a member of SRP for the past five years.

11 CHAIR ANASTASIO: Thank you, Ahmad.
12 Mike.

13 PANEL MEMBER KLEINMAN: Good morning. I'm Mike
14 Kleinman. I am a Professor of -- in the Department of
15 Environmental and Occupational Health at UC Irvine in the
16 brand new School of Population and Public Health.

17 CHAIR ANASTASIO: Nice. Thank you, Mike.
18 Beate.

19 PANEL MEMBER RITZ: Hello, everyone. I'm Beate
20 Ritz. I'm a Professor of Epidemiology at UCLA School of
21 Public Health in the Department of Epidemiology
22 Environmental Health and Neurology. And my focus is on
23 pesticide and on air pollution research.

24 CHAIR ANASTASIO: Thank you, Beate.

25 And I'm Cort Anastasio. I'm a professor in the

1 Department of Land, Air, and Water Resources at UC Davis
2 and the Chair of the Panel.

3 Appreciate everybody coming, especially our four
4 members whose terms have officially ended, Paul, Mike,
5 Beate, and Kathy. So all of their terms are ended and we
6 really appreciate them participating today. And we're
7 trying to get replacements, but it's been a very slow
8 process.

9 Two items in today's meeting. The first is going
10 to be a review of the isoprene cancer inhalation unit risk
11 factor, the IUR. And the second will be an informational
12 item from OEHHA on computational toxicology and their new
13 approaches for developing health guidance values.

14 And then we're going to have some administrative
15 matters, including a formal send off for Paul Blanc, the
16 longest serving current member of the SRP.

17 All right. So move to the first item, the
18 isoprene cancer inhalation unit risk factor. So the staff
19 from the Office of Environmental Health Hazard Assessment,
20 OEHHA are going to present a draft document summarizing
21 the development of a cancer potency factor and inhalation
22 unit risk factor IUR for isoprene. Cancer IURs are used
23 to estimate lifetime cancer risks associated with
24 inhalation exposure to a carcinogen. OEHHA is required to
25 develop guidelines for conducting health risk assessments

1 under the Air Toxics Hot Spots Programs, which is part of
2 Health and Safety Code section 44360(b)(2).

3 In response to this statutory requirement, OEHHA
4 developed a draft IUR for isoprene. Workshops and comment
5 period for the document were offered from February through
6 April of 2024. No public comments were received. More
7 information regarding the document can be found at a long
8 website, HTTPS -- I'm not going to read the whole thing.
9 It's on the OEHHA website under isoprene.

10 So I'd like to now introduce Drs. Daryn Dodge and
11 Kenneth Kloc, who are staff toxicologists and the item
12 leads from OEHHA. Daryn and Ken, the floor is yours.

13 (Thereupon a slide presentation).

14 DR. DARYN DODGE: Okay. Thank you, Cort. As Dr.
15 Anastasio said that I'm a coauthor of this document and
16 I'll be presenting it today.

17 Okay. Next slide.

18 [SLIDE CHANGE]

19 DR. DARYN DODGE: Okay. This is the structure of
20 isoprene. It's a diene containing two carbon double bonds
21 with a methyl group on the second carbon. It is also
22 known as 2-methyl-1,3-butadiene. It is a 2-methyl analog
23 of 1,3-butadiene, which is a fairly ubiquitous compound,
24 also found in urban air and it is a known carcinogen.

25 [SLIDE CHANGE]

1 DR. DARYN DODGE: Isoprene is a colorless liquid
2 with a mild petroleum-like odor. It is soluble in many
3 organic solvents. The solubility in water though is 642
4 milligrams per liter, which in pharmacology references is
5 considered poor aqueous solubility. It has a boiling
6 point 34 degrees C, or Celsius, which is equivalent to
7 93.2 degrees Fahrenheit.

8 The vapor pressure is 550 millimeters mercury or
9 torr. And this is high enough vapor pressure to be
10 considered a VOC or a volatile organic compound. The unit
11 conversion is one part per billion is equivalent to 2.79
12 micrograms per cubic meter.

13 [SLIDE CHANGE]

14 DR. DARYN DODGE: Isoprene is naturally emitted
15 for -- by plants and trees. It is produced endogenously
16 in humans and other mammals. It occurs as a byproduct of
17 the thermal cracking of naphtha. And it is used to
18 synthetic rubber for vehicle tires.

19 Other sources of isoprene include biomass
20 combustion, wood pulping, tobacco smoking, exhaust from
21 turbines and automobiles, and it is found in wildfire
22 smoke.

23 Emissions of isoprene in California. In 2017, it
24 was 186 tons per year, primarily from mobile sources.
25 There were three -- or, I'm sorry, there was 12 facilities

1 in the CEIDARS databse that emitted significant levels of
2 isoprene, although there's probably many more facilities
3 that do release isoprene. CEIDARS stands for the
4 California Emissions Inventory Data and Analysis and
5 Reporting Program.

6 [SLIDE CHANGE]

7 DR. DARYN DODGE: Urban air levels of isoprene
8 correlate with other chemicals such as benzene found in
9 vehicle emissions. Air concentrations reported in
10 California in the South Coast Air Basin or Los Angeles
11 area. The concentrations were 0.5 and 1.8 micrograms per
12 cubic meter respectively. That's the average in maximum
13 respectively.

14 In the San Joaquin Valley, it was 0.1 was the
15 average and 0.8 was the maximum. And that -- and that's
16 in micrograms per cubic meter.

17 In exhaled breath, the steady-state
18 concentrations are 195 to 371 micrograms per cubic meter.
19 In adults at rest, this represents the 25th to 75th
20 quantile range. I'll add that in infants and children,
21 the air -- the exhaled breath concentrations are less,
22 generally 70 micrograms per cubic meter or less.

23 [SLIDE CHANGE]

24 DR. DARYN DODGE: The cancer classifications for
25 isoprene in the California Proposition 65 program, it is

1 listed as a carcinogen since 1996. The International
2 Agency for Research on Cancer, or IARC, categorizes it as
3 a possible carcinogen or possibly carcinogenic to humans
4 Group 2B. And the United States National Toxicology
5 Program, or NTP, categorizes it as reasonably anticipated
6 to be a human carcinogen.

7 [SLIDE CHANGE]

8 DR. DARYN DODGE: The metabolism of inhaled
9 isoprene is similar in humans and rodents. This primarily
10 occurs through oxidative metabolism via P450 enzymes to
11 epoxide intermediates. This is followed by hydrolysis
12 conjugation with glutathione and further oxidation of
13 diols forms via hydrolysis.

14 The main urinary metabolites in rodents are
15 2-methyl-3-butene-1,2-diol and its glucuronide, and vinyl
16 lactic acid. The carcinogenicity of isoprene is thought
17 to be related to the formation of oxidized reactive
18 metabolites, including mono-epoxides, a diepoxide, and
19 diol-epoxides.

20 [SLIDE CHANGE]

21 DR. DARYN DODGE: There were no occupational
22 studies that looked at the carcinogenicity of isoprene.
23 However, we do have three sets of rodent -- or
24 carcinogenicity bioassays from which to examine. The
25 first was by NTP, National Toxicology Program, which came

1 out in 1995. This is a one-year stop exposure study in
2 only male rats and male mice. Exposures were for six
3 months, six hours per day, five days a week, plus a
4 six-month clean air period following which the animals
5 were necropsied and examined for tumors. There were five
6 exposure groups -- or five isoprene exposure groups per
7 species and one control group. And there were 30 rodents
8 per species, per group.

9 The next study was by Placke, et al., and came
10 out in 1996. This was a two-year study in male and female
11 mice. The isoprene exposures were for 80 weeks, eight
12 hours a per day, six days a -- five days a week, with
13 sacrifice at 105 weeks. There were five isoprene exposure
14 groups for male mice in one control group. However, for
15 the female mice, there were only two isoprene exposure
16 groups and one control group. There were 50 mice per
17 group per sex.

18 The final study was by NTP. It came out in 1999.
19 This was a two-year study in male and female rats. As you
20 might know, NTP often also examines the carcinogenicity in
21 male and female mice as well. However, the NTP felt there
22 was enough information on mice by this time, so they only
23 looked at the male and female rats. Exposures were for
24 104 weeks in the rats, six hours per day, five days a
25 week. There were three isoprene exposure groups per sex.

1 And there was one control group each. There were 50 rats
2 per group per sex.

3 [SLIDE CHANGE]

4 DR. DARYN DODGE: I'll go over the results -- the
5 tumor incidence results here first starting with the NTP
6 one-year stop-exposure study. In male rats, the only
7 treatment-related tumors were in the testes. This was the
8 adenomas. There was only a marginal increase in adenomas
9 with pairwise comparison with the control group. However,
10 there was a positive trend for this tumor type, so the NTP
11 felt this was likely treatment related.

12 [SLIDE CHANGE]

13 DR. DARYN DODGE: There was a higher tumor
14 incidence in the male mice however from this NTP
15 one-stop -- one-year stop-exposure study. There is an
16 increased incidence of tumors in one or more treatment
17 groups in the liver, lung, forestomach and Harderian
18 gland.

19 Now, this is -- table is simplified a bit. We
20 show the liver adenoma and carcinoma together combined
21 and -- as well as for the lung adenomas and carcinomas,
22 and the forestomach squamous cell papillomas or
23 carcinomas. We look at this infor -- we looked at the
24 combined benign and malignant tumors together for a tumor
25 site. This generally how we determine the cancer risk of

1 a chemical, the combined benign and malignant tumors.

2 There was a positive trend for all four of these
3 tumors -- at all for these tumor sites. For the last set
4 of tumors, there -- or tumor in this table, the Harderian
5 gland, there was only an increase in the adenomas. There
6 was no effect in -- due to Harder -- in the Harderian
7 gland concerning the carcinomas.

8 [SLIDE CHANGE]

9 DR. DARYN DODGE: In the next study by Placke et
10 al., this was 80-week exposure study in male mice and
11 male -- in male mice and female mice. They looked at the
12 same strain of male mice as the NTP stop-exposure study.
13 They found tumors at the same tumor types as that found in
14 the NTP stop-exposure study, that is in the liver, lung,
15 forestomach, and Harderian gland.

16 However, we show this information separate for
17 the adenomas and carcinomas for the liver and lung. And
18 this is because Placke et al. did not provide information
19 in their study in which we could show the combined benign
20 and malignant tumors at these tumor sites. So we show it
21 separately in this table.

22 In the forestomach, there was a increased trend
23 for squamous cell carcinoma. Although, the increase was
24 marginal in terms of incidence. In the Harderian gland,
25 there was an increase in adenomas, increased incidence at

1 the three highest exposure groups. Carcinomas, again,
2 this was a marginal increase here.

3 [SLIDE CHANGE]

4 DR. DARYN DODGE: In the female mice, from the
5 Placke et al. study, there was an increased incidence of
6 adenomas in the Harderian gland and pituitary gland in one
7 or both isoprene exposure groups. There was no increase
8 in carcinomas for -- at either of these tumor sites. In
9 the middle row there, the spleen hemangiosarcoma, there
10 was a marginal increase at the highest dose of 70 parts
11 per million. Even though this was not statistically
12 significant with pairwise comparison with the control, the
13 authors felt this was a treatment-related effect.

14 [SLIDE CHANGE]

15 DR. DARYN DODGE: And the final study, the
16 two-year NTP bioassays in male and female rats. The
17 information here includes both the male and female rats in
18 this table. In the male rats, there was a increased
19 incidence in one or more exposure groups in the male
20 kidney, renal tubule adenoma or carcinoma; in the mammary
21 gland fibroadenoma or carcinoma; and in the testes, there
22 was an increase in adenoma.

23 As you might notice, there are two sets of
24 incidence data in each cell of this -- of this table. The
25 first or top set of incidence data, that's the overall

1 incidence, so it's the number of tumors in the -- over the
2 number of animals exposed. The bottom set of incidence
3 results in each cell, that is the effective tumor
4 incidence, that -- it's in the -- it's bolded and
5 italicized in each cell.

6 The effective tumor incidence is the number of
7 animals alive at the appearance of first tumor. This is
8 specific for each -- at each tumor site. This is the
9 information, if it is provided in the study, that we use
10 to determine cancer risk. So if this information is
11 available, in other words, this is what we use to estimate
12 the inhalation unit risk.

13 Now, in the female rats, there was an increased
14 incidence in mammary gland fibroadenoma in all three
15 exposure groups. However, the incidence was essentially
16 the same for all three exposure groups. So it hit
17 somewhat of a plateau starting at the lowest
18 concentration. The incidences were essentially the same
19 as -- it's 35 out of 50, 32 out of 50, and 32 out of 50
20 going from 220 to 7,000 parts per million. So this was
21 a -- what's likely a pre-treatment related effect.
22 However, because of the plateau effect, the positive -- a
23 positive trend was not attained.

24 [SLIDE CHANGE]

25 DR. DARYN DODGE: Okay. On this side, we have a

1 summary of the genotoxicity results. Studies on the
2 genotoxicity of isoprene have been conducted in various in
3 vitro and in vivo systems in humans cell lines, including
4 peripheral blood mononuclear cells, leukemia cells, and
5 hepatocellular carcinoma cells. Isoprene and its
6 monoepoxides were shown to cause DNA damage using the
7 comet assay.

8 In vitro assays for bacterial mutagenicity were
9 largely negative when isoprene in its primary metabolites
10 were tested, but was positive for the metabolite
11 2-methyl-1,2,3,4-diepoxybutane. In mice, in vivo
12 inhalation exposure to isoprene-induced micronuclei
13 formation and sister chromatid exchange in bone marrow
14 cells.

15 [SLIDE CHANGE]

16 DR. DARYN DODGE: We also evaluated three
17 publicly available models, PBPK models, which stands for
18 physiologically based pharmacokinetic models. We were
19 interested in seeing if we could use this information to
20 improve our dose metrics, such as the rate of metabolism
21 of isoprene to an epoxide.

22 While these models were excellent in terms of the
23 specific goals they were attempting to achieve, the models
24 did not provide enough information for pharmacokinetic
25 extrapolation from rodents to humans. Therefore, we

1 relied on our usual applied dose or inhaled concentration
2 of isoprene as the dose metric for estimating cancer
3 potency.

4 Next slide.

5 [SLIDE CHANGE]

6 DR. DARYN DODGE: So this is our overall cancer
7 hazard evaluation. We have no epidemiology studies from
8 which to determine the carcinogenicity of isoprene.
9 Therefore, we relied on the three available rodent
10 long-term inhalation bioassays. These Rodent bioassays
11 found that isoprene was carcinogenic in multiple species
12 and induced tumors at one or more sites in rats and mice.

13 There were positive genotoxicity studies
14 primarily in in vitro DNA damage assays and in vivo
15 chromosomal damage assays. Isoprene is also structurally
16 related to the compound 1,3-butadiene, a known human
17 carcinogen.

18 [SLIDE CHANGE]

19 DR. DARYN DODGE: So that's the incidence data.
20 The other part that we need to use in terms of determining
21 the cancer potency of isoprene is the average daily dose.
22 So we convert the air exposure concentration to isoprene
23 to an average daily dose in milligrams per kilogram body
24 weight per day. And this is done within the equation in
25 this slide. ADD is equivalent to -- or equal to the IR,

1 or inhalation rate, times concentration, divided by the
2 body weight. So C, or the concentration, is time adjusted
3 to an annual average. And that is six or eight hours per
4 day, depending on the study, divided by 24 hours. And
5 this is multiplied by five days per week divided by seven
6 days.

7 The body weight is the body weight of the -- or
8 average body weight of the animal over the period of
9 exposure. An inhalation rate is a species-specific
10 calculation. The equations are shown here at the bottom
11 of the slide for rats and one for mice.

12 [SLIDE CHANGE]

13 DR. DARYN DODGE: So these are the average daily
14 doses in mice from the Placke et al. bioassays. In the
15 male mice, we have five exposure groups. But if you
16 recall for the female mice, we only had two exposure
17 groups.

18 [SLIDE CHANGE]

19 DR. DARYN DODGE: And these are the average daily
20 doses for rats from the NTP bioassay for males and
21 females. As you might have noticed already, we do not
22 have the average daily doses from the first study, the
23 stop-exposure study, from NTP. And this is because that
24 study was only for one year. If we have -- if we can use
25 or have access to lifetime studies in rodents, that is

1 what we use to determine and inhalation unit risk. Since
2 we had that information in two studies, Placke et al. and
3 NTP 1999, we didn't go any further with the one-year
4 stop-exposure study.

5 [SLIDE CHANGE]

6 DR. DARYN DODGE: So to determine the cancer
7 slope factor, we used the U.S. EPA multi-stage cancer
8 model in the Benchmark Dose Software. We use a benchmark
9 response rate of five percent tumor response to calculate
10 the benchmark dose, which is the BMD. The 95 percent
11 lower confidence bound on the dose producing a five
12 percent tumor response is the BMDL05. And this is used to
13 calculate the cancer potency. So the cancer slope factor
14 is equal to 0.05 divided by the BMDL05.

15 Now, in male mice and male rats, there is
16 multiple tumor sites. So the combined tumor potency was
17 determined for these animals using the U.S. EP -- U.S. EPA
18 multi-site model.

19 [SLIDE CHANGE]

20 DR. DARYN DODGE: So we determined cancer slope
21 factors. Let's start with the Placke et al. data. We
22 determined cancer slope factors in the liver, lung, and
23 Harderian gland, these tumor sites, both individually and
24 combined using the multi-site model. We also did this for
25 the -- in the female mice, the pituitary and Harderian

1 that's the dotted vertical black line that falls in around
2 500 milligrams per kilogram day. The yellow dotted
3 vertical line, that is the lower confidence bound. And
4 that falls at about 295 milligram per kilogram day.

5 So the intersection of the yellow dotted line,
6 the lower confidence bound, and the horizontal gray line,
7 which is the five percent incidence above control, that
8 intersection is where you find the begin -- where you get
9 the cancer slope factor. That's the dashed green line
10 that you see -- straight green line that starts at that
11 intersection and goes to the control level. So that is
12 our cancer slope factor from which we derive the -- well,
13 that's where we derive the cancer slope factor.

14 [SLIDE CHANGE]

15 DR. DARYN DODGE: And this is the graphical
16 output from the Benchmark Dose Software for mammary gland
17 fibroadenoma and carcinoma combined in male rats.

18 [SLIDE CHANGE]

19 DR. DARYN DODGE: And this is the graphical
20 output from the Benchmark Dose Software for the testicular
21 adenomas in male rats. And what's interesting in this
22 particular graph is the control group had a quite high
23 incidence rate. This is close to 70 percent incidence in
24 the controls. However, with exposure to isoprene at the
25 highest concentration here, you get an increased incidence

1 of almost 100 percent.

2 [SLIDE CHANGE]

3 DR. DARYN DODGE: So now we extrapolate the
4 animal cancer slope factors to a human cancer slope
5 factor. This is done by multiplying the cancer slope
6 factor of the animals by the ratio of human to animal body
7 weights raised to one-fourth power. And this is expressed
8 in units of milligram per kilogram day to the minus one.

9 This interspecies scaling factor accounts for
10 pharmacokinetic differences, such as breathing rate and
11 metabolism, but also takes into account pharmacodynamic
12 considerations, such as tissue responses to chemical
13 exposure.

14 [SLIDE CHANGE]

15 DR. DARYN DODGE: So in the table, this is the
16 benchmark dose results, including the calculated human
17 cancer slope factor in the last column on the right. So
18 in this table, we show the multi-site data for -- in male
19 mice from the Placke et al. study, degeneration of the BMD
20 and BMDL of -- in the Benchmark Dose Software. So, the
21 BMD is 28.8. The BMDL is 23.69. This results in an
22 animal Cancer slope factor of 2.11 times 10 to the minus
23 three. In using the equation, we just showed in the
24 previous slide, we calculated human cancer slope factor of
25 1.47 times 10 to the minus two.

1 In the NTP study, this was multi -- this is the
2 multi-site results in male rats. The resulting human
3 cancer slope factor is slightly higher. It's 1.88 times
4 10 to the minus two. It's bolded in this table. So this
5 is -- this is actually the number from which we determined
6 the inhalation unit risk, or IUR, for isoprene. Now, the
7 NTP results here, the cancer slope factor, is slightly
8 higher in the rats compared to the mice, but we had some
9 reservations anyway for using the Placke et al. study.

10 [SLIDE CHANGE]

11 DR. DARYN DODGE: So the Placke et al. mouse
12 study had limitations in terms of it -- the combined
13 adenoma and carcinoma incidence was not reported for
14 liver, lung, and Harderian gland tumor sites. Therefore,
15 modeling was only performed with the adenoma incidence
16 data. In addition, no data on individual survival or
17 appearance of first tumor was supplied in the study, so we
18 could not determine the effective tumor incidence. Thus,
19 we used the overall incidence rate to determine the cancer
20 slope factors.

21 Now, this information doesn't mean we can't use
22 it to determine the IUR. It's just that we had all this
23 information from the NTP study in the rats, so that's what
24 we used to determine the IUR.

25 [SLIDE CHANGE]

1 DR. DARYN DODGE: So that's this final step. So
2 again, the isoprene IR -- IUR is based on the male rat
3 data in NTP. And this equation is the IUR is
4 equivalent -- or is equal to the cancer slope factor in
5 humans times the breathing rate in humans, which is 20
6 cubic meters per day. This is divided by the body weight
7 in humans, 70 kilograms, and multiplied by a conversion
8 factor going from milligrams to micrograms. The resulting
9 IUR is 5.54 times 10 to the minus six. And this is in
10 units of micrograms per cubic meter to the minus 1.

11 Now, in -- to explain or show what this number
12 means. Lifetime adult exposure to is one microgram per
13 cubic meter isoprene results in an extra cancer risk of
14 5.4 cases in a million.

15 [SLIDE CHANGE]

16 DR. DARYN DODGE: So at this point, we would
17 present the public comments in our responses, but as Cort
18 has already pointed out, there were no comments that came
19 in during the public comment period. We did hold
20 workshops though in Southern California and Northern
21 California during the public comment period.

22 And that concludes my presentation.

23 CHAIR ANASTASIO: Great. Thank you very much,
24 Daryn. So the two SRP leads on this IUR are Ahmad and
25 myself. So Ahmad, would you like to go first.

1 PANEL MEMBER BESARATINIA: Sure. Well, first of
2 all, I want to recognize the work of the authors and
3 contributors to this report, including the presenter,
4 Daryl[SIC] today. This is a well prepared and nicely
5 written report. It seems to have covered most of the
6 relevant literature. It's used established methods to
7 derive a cancer slope factor and IUR to estimate cancer
8 risk for isoprene in humans. The results are presented
9 clearly and discussed very well and conclusions are made
10 accordingly.

11 I have a few general comments and some specific
12 comments that I can share here. Firstly, as it was
13 mentioned during the presentation and described in the
14 report, humans are exposed to isoprene through multiple
15 sources. We have occupational exposure in certain
16 industrial workers. We have environmental and dietary
17 sources of exposure. We have lifestyle exposure, for
18 example, through tobacco smoking. We, of course, have
19 endogenous exposure to this chemical.

20 So human exposure to isoprene is substantial and
21 variable. With this in mind, it's quite surprising to see
22 that there was no human study or epidemiologic data in
23 this report. The CSF and the IUR, there derived
24 exclusively from two animal study, one in inhalation
25 experiment in mice and the other in rats. I'm assuming

1 that there is either no epidemiologic data on isoprene or
2 the available epidemiologic data are not adequate quality.
3 Either way, it would be helpful and certainly important to
4 underscore this fact and explain why no human study or
5 epidemiologic data were used for risk assessment in this
6 report.

7 There was a one-line sentence somewhere in the
8 report, I think it was in page five, there was a mention
9 that there is no carcinogenicity data for isoprene in
10 humans. I saw that Daryl's[SIC] slide also contained a
11 bullet point on this. My recommendation would be just to
12 create a subheading in the introduction section of the
13 report and provide this information up front and explain
14 why only animal data were used to derive CSF and IUR.

15 Along the same line, I think it will be helpful
16 to discuss the challenges of exposure assessment for this
17 chemical in humans, especially given the multi-source
18 nature of exposure and the lack of consensus on how and
19 where to measure isoprene or its metabolite in human
20 samples. For example, in occupationally exposed
21 individual who also have endogenous exposure to this
22 chemical, as well as exposure to other sources, definitely
23 exposure assessment must be very complicated.

24 My second point has to do with the way that the
25 CSF was calculated for rodents and then extrapolated to

1 humans to derive the IUR. It's proven that there are
2 major differences in pharmacokinetics of isoprene within
3 humans and rodents. These differences can reach orders of
4 magnitude depending on the endpoints measured. My
5 understanding from reading this report was that
6 interspecies differences were not accounted for in this
7 report and there was no adjustment made when converting
8 the CSF from animals to humans to derive an IUR.

9 Daryl[SIC] in one of his last slides, I think
10 slide 25, mentions something different in the formula that
11 he presented. He said that this formula accounts for
12 interspecies difference. So it will be helpful to provide
13 some clarification on this. If it was not adjusted for,
14 definitely some justification as to why you believe that
15 there is no need to adjust for interspecies differences,
16 considering the significant pharmacokinetic differences
17 between humans and other mammals, including rodents. I
18 think there was one mention of this somewhere at the last,
19 last part of the report. I think it was the last page,
20 page 36, of this report, but probably it needs more -- it
21 needs to be more clear.

22 My next point is on the statistical analysis in
23 Table 2A and 2B, and Table 3, it is indicated in the text
24 and footnote of this table that pairwise comparison
25 between the exposed and control groups were made by

1 one-tailed Fisher's exact test. Looking at this data in
2 this table, the directionality of effect is not one-sided.
3 By way of example, in Table 3 in page 13, if you look at
4 last row from the bottom, you see that the incidence rate
5 for all exposed groups are lower than that in the control
6 group.

7 The same is in Table 2A, page nine, you can see
8 it in the second and third row. So I'm not a
9 biostatistician, but as far as I know, to apply a
10 one-sided test, you need to make an assumption that the
11 relationship can only go in one direction. Looking at
12 this data, it doesn't seem that this assumption can be
13 made. And I'm not sure what the rationale is for using a
14 one-sided test instead of a two-sided test. So it will be
15 helpful to clarify what the justification is for the
16 analysis performed for the data in this table.

17 I think a short clarification in the text will
18 do. I would imagine any guidelines or recommendation that
19 you might have, you must have a provision for cases where
20 there is a bi-directionality of effects, like data in your
21 table. Probably Dr. Messer, Karen is -- has more
22 expertise on this. Definitely she knows more than me and
23 she can later comment on this and help us better
24 understand the appropriateness of this test.

25 And just a couple of minor comments. I think it

1 is important for all these technical support documents,
2 including this present report to have a designated section
3 within the main text with a soft heading, where the
4 research strategy and time frame of coverage is stated.
5 It will help the readers to understand how comprehensive
6 and how up to date these reports are. I saw a line in
7 preface where it reads publicly available documents are
8 reported through July 2023 per review. I think it will be
9 more helpful for reader to have this information and
10 specific information about search strategy, search engine
11 that was used. Was it PubMed, MEDLINE, EMBASE, Google
12 Scholar; what search term was used; what type of
13 publication were considered; and definitely the start and
14 end of coverage.

15 And my last point is the footer in all pages
16 contains a statement that reads, "Please do not cite or
17 quote". I'm assuming that this will be removed once the
18 report is finalized.

19 And that's all I have. Thank you.

20 CHAIR ANASTASIO: Thank you, Ahmad.

21 So I'm going to put Karen on the spot for a
22 second about this one-tailed versus two-tailed Fisher
23 test. Karen, can you weigh in on that?

24 PANEL MEMBER MESSER: Yeah. I -- first, I want
25 to echo that I thought the report was nicely presented and

1 clearly done. I think a one-tailed test is fine here.
2 The rationale for the one-tailed test is really more the
3 intent of the analysis than whether the data show trends
4 in one direction or another. And here, the intent of the
5 analysis is to detect an increasing signal. If, for some
6 reason, the subject -- the compound being investigated is
7 protective against cancer where you would see a decreasing
8 signal, well, that's not -- that's not of interest in this
9 setting. It wouldn't lead to air quality standards. But
10 if there's an increasing signal, that's where you would
11 find a public health need for air quality standards.

12 Since a one-sided test gives you more power, and
13 the data are necessarily limited in these animal studies
14 and indeed in epidemiologic studies, I think it's a good
15 idea to use a one-sided test. I agree there might be a
16 comment in the report about why a one-sided test is used.

17 Does that help?

18 CHAIR ANASTASIO: Yeah, that's great.

19 PANEL MEMBER BESARATINIA: Great. Thanks.

20 PANEL MEMBER BLANC: Cort, I wondered if I could
21 comment specifically on this one question.

22 CHAIR ANASTASIO: Sure.

23 PANEL MEMBER BLANC: It would seem to me,
24 however, as a nuance to this that in those analyses for
25 which there was no positive -- statistically significant

1 test for trend, one should not carry out pairwise
2 comparisons, because really the test for trend is you're
3 asking is there overall a monotonic dose response? And if
4 there isn't a monotonic dose response, why would you be
5 checking doing multiple testing to compare various levels
6 in a pairwise way with the control. I'm being a bit of a
7 purist, but it could even make your lives simpler.

8 CHAIR ANASTASIO: Beate, you have a response to
9 that.

10 PANEL MEMBER RITZ: Yes. I would have a problem
11 with the ceiling effect then, because you are throwing out
12 all of those results, right? There was one that showed an
13 increase that was kind of similar at every level of
14 exposure and I think that's something we should consider.
15 And as I understood the trend test did not show anything.

16 CHAIR ANASTASIO: Thank you. Okay. I'm going to
17 give my comments and then we'll open it up to the rest of
18 the Panel. So I just had very few comments as well. I
19 thought the document was well written. I thought it was
20 well justified. I thought everything worked out very
21 smoothly.

22 Just some minor comments. Well, one was on line
23 45. You've got a melting point that's above the boiling
24 point, which is not physically possible. So I wonder if
25 you're missing a negative sign on the melting point or one

1 of the numbers is wrong, so that's one item.

2 The second item was a question I had. So I'm on
3 524. You talked about the process for doing the risk
4 assessment. And in step four, you talk about intercurrent
5 mortality. And I'm just not sure what that is. Can --
6 could you explain it to me now?

7 DR. DARYN DODGE: Ken. Dr. Ken Kloc, would you
8 like to explain that, take that one on?

9 DR. KEN KLOC: I can give it a shot. So
10 basically what we're -- intercurrent mortality, it's an
11 expression, which is supposed to stand for mortality that
12 is not due to the chemical being investigated. I mean,
13 I'm sorry. It's not due to tumor formation in the
14 chemical being tested, but to just regular toxicity. And
15 so what that -- what that does is it creates a situation
16 where you have animals that are being removed from the
17 denominator of the -- of the estimate, estimated potent --
18 cancer potency. And so you need -- when possible, you try
19 to adjust for that.

20 CHAIR ANASTASIO: I see. Thank you. The third
21 comment or question I had was about combining incidence of
22 different cancer types or tumor types. So I know in one
23 case, you looked at a tumor type that included both benign
24 and malignant tumors and you -- and you did a risk
25 assessment on that, and -- but then there was another case

1 where there were only benign tumors and so you said, okay,
2 we're not going to consider that, and that makes sense to
3 me.

4 You also do a combining of tumor types that if
5 they have I think it was either the same tissue or the
6 same cell type. But I'm wondering why don't you combine
7 all the tumor types that were malignant? You would think
8 that, you know, any incidence of cancer would count
9 towards the overall possibility of getting cancer in the
10 human population. So why not combine all incidences
11 across cell types, across tissue types.

12 DR. DARYN DODGE: Well, we do have with the
13 multi-site model, U.S. EPA's model. If the -- if there is
14 a -- if it's believed that the adenomas and carcinomas at
15 a cell site are treatment related, the increases in
16 incidence, then we combine it. So it's adenomas or
17 carcinomas combined, so that's what we plug into the
18 multi-site model.

19 CHAIR ANASTASIO: So the -- okay. I guess I
20 missed that distinction then. So the multi-site model is
21 multiple tissue types or multiple cell types.

22 DR. DARYN DODGE: Yes. Yes.

23 CHAIR ANASTASIO: Ah, okay. Somehow I missed
24 that in the description.

25 Okay. Thank you. Well, that's great.

1 The last thing I wanted to say was -- give some
2 compliments to the authors, because there were a lot of
3 kind of -- mostly style points that were made that I
4 thought were great, and we've been talking about it over
5 the last few years. So I just wanted to thank you for
6 putting line numbers in there. That was very helpful.
7 I'd like to thank you for putting p-values and not just
8 having say bold, if it's P less than 0.05. I thought the
9 comparison with derived IUR for the TCEQ numbers was very
10 helpful to me. And to know that EPA doesn't have an IUR,
11 that was helpful information. So thank you for making
12 that comparison.

13 I also thought the IUR comparison with butadiene
14 was helpful, to see the relative toxicity of isoprene to
15 butadiene. And, you know, they're at least ballpark. And
16 then finally, the BMD plots in the appendices, I always
17 find it helpful to see the plots of the data and the fits,
18 so we get some sense of, you know, is that a reasonable
19 fit or not. So thank you for including those as well.

20 Those were all my comments. So I'm just going to
21 go in order of the video boxes on my screen to see if
22 other Panel members have comments.

23 Joe, any comments from you?

24 PANEL MEMBER LANDOLPH: I echo everybody's
25 statements that it's an excellent document. A lot of work

1 went into it.

2 I had two questions. One is for the two primary
3 reviewers and the author, what do you think about isoprene
4 in a relative cancer potency toxicity comparison? Is this
5 something we should really worry about? Is it higher on
6 the priority list of OEHHA and the Air Board? What are
7 your thoughts there? And then I'll have another one after
8 they answer that.

9 DR. DARYN DODGE: Thank you, Dr. Landolph. Yeah,
10 because of its structural similarity to butadiene, there
11 was in its kind -- its ubiquitous nature exposure, there
12 was interest in developing an IUR for isoprene. That's
13 pretty much the main reason we -- CalEPA wanted to develop
14 an IUR for isoprene.

15 As you noticed, the cancer potency of isoprene is
16 in comparison to 1-but -- 1,3-butadiene is not as high.
17 However, we feel that any incremental increase in
18 isoprene, other carcinogens that people are exposed to
19 will increase the cancer risk. So it's good to have
20 this -- an IUR for this compound, because when we do an
21 assessment -- an overall assessment to what people are
22 exposed to, we should include all the carcinogen --
23 carcinogens that we know about in determining cancer risk.

24 PANEL MEMBER LANDOLPH: And that's -- would
25 you -- on a scale of what you've already done, which

1 compound -- the compounds that you've already measured
2 IURs on, where does it fit quantitatively.

3 DR. DARYN DODGE: Well, isoprene doesn't appear
4 to be as potent a carcinogen as 1,3-butadiene and some
5 other -- diesel exhaust, for example, that people are
6 exposed to in urban air. So overall, it's probably not as
7 big a concern as the main contributors.

8 PANEL MEMBER LANDOLPH: Um-hmm. That answers it.
9 Thank you.

10 CHAIR ANASTASIO: So on that topic, you know, the
11 IUR was, what, roughly five times ten to the minus six or
12 micrograms per cubic meter. And the Ambien data was
13 coming in at around one microgram per cubic meter. So
14 you've got a -- kind of a general urban population risk of
15 five in a million. Is that above the threshold where the
16 hotspots kicks in and they start to look at point sources
17 and try to understand risks around those sources?

18 DR. DARYN DODGE: Yeah. Those are sort of
19 general urban air levels of isoprene. I'm in -- we
20 probably don't have a lot of data on facility emissions
21 that might release isoprene. We do know that there are
22 measurable levels of isoprene coming from
23 petroleum-related industries. And the level of isoprene
24 could be -- could be considerably higher than what you
25 find in just your general urban air. So we have to take

1 that into consideration.

2 CHAIR ANASTASIO: Yeah. It's a tricky compound,
3 because the lifetime is short, right? It's a few hours in
4 the atmosphere, but there are also enormous biogenic
5 sources. So it's really a tricky risk assessment, which
6 is, you know, beyond the, well, risk management really.
7 So it's beyond the scope of the IUR document, but it's
8 something that risk management needs to consider. Yeah.

9 Joe, any other comments?

10 PANEL MEMBER LANDOLPH: Yeah. Just one quick
11 one. What is the philosophy of the SRP in terms of what
12 we should put our most strength into looking at?
13 Obviously, we've got, you know, millions of compounds we
14 could look at, but we don't have the time or the money to
15 do that. Today, what are the top five you're focused on?
16 What are really serious about in terms of regulation,
17 generating data that can lead to useful regulation
18 mitigation?

19 CHAIR ANASTASIO: Sorry, this is a question for
20 OEHHA?

21 Sorry, Joe. I'm trying to get clarification.
22 Are you asking Daryn and company what their top toxicant
23 targets are for health guidance values?

24 PANEL MEMBER LANDOLPH: Yeah, that would be fine,
25 just fine.

1 CHAIR ANASTASIO: Yeah.

2 THE WITNESS: High the Dr.

3 DR. RIMA WOODS: Hi. This is Dr. Rima Woods.

4 I'm the Chief of the Air Toxicology and Risk Assessment
5 Section. And we work closely with CARB on the Hot Spots
6 Program. And typically our top priorities are set in
7 conjunction with CARB. So it's a combination of high
8 emission compounds that CARB is seeing and then we combine
9 that with information from what we know about toxicity.
10 So there are a few chemicals that we are working on
11 currently.

12 Am I allowed to say them? No.

13 So -- yeah, so we have a few risk assessments in
14 the works. We are working on ethylene oxide, which we
15 have brought to the SRP previously. Also, a few other
16 that we may be working on assessments in the future. So I
17 would check in with CARB if we're okay to mention any of
18 those.

19 Okay. Great. Just wanted confirmation.

20 So acrolein is one that we're currently looking
21 at. N-methylpyrrolidine is another compound that has sort
22 of floated to the top of the list. And also
23 1,4-dichlorobenzene is a compound that we've been working
24 on for a non-cancer value, which should come to the SRP
25 fairly soon.

1 PANEL MEMBER LANDOLPH: Thank you very much.

2 CHAIR ANASTASIO: Thank you, Joe.

3 Paul, comments.

4 PANEL MEMBER BLANC: Let me start off with the
5 epidemiologic question. Although, Beate Ritz may also
6 have comments. Clearly, there's epidemiologic data about
7 the synthetic rubber industry, pro and con. And, in fact,
8 the European document, which you refer to and which I
9 think your document is highly influenced by, the European
10 Union document, has a far more extensive discussion of why
11 there is not epidemiologic data that looks solely at
12 isoprene, but there is epidemiologic data that has looked
13 at the synthetic rubber trade. So I think it would be
14 actually more useful for you to look at their language on
15 that and perhaps expand your statements by a couple of
16 sentences.

17 But the one thing they didn't do either was to
18 say whether that epidemiologic literature, which can't be
19 interpreted easily for any one of the components in the
20 industry suggests that there's cancer in the industry or
21 not. That would be highly interesting, even if you
22 couldn't say what the culprit was. So I suggest you look
23 at that wording. And also specifically, is there
24 literature for mixed Exposures that's positive.

25 In that vein, the Europeans, as you noted, upped

1 their categorization from their equivalent of 2B to 1B
2 carcinogenic in animals. And the IARC evaluation was done
3 30 years ago I think before these NTP studies. Do you
4 know or can you easily find out is a relook, a second
5 look, at isoprene on the IARC agenda? Is this a chemical
6 they're actually working on now?

7 DR. DARYN DODGE: Thank you, Dr. Blanc. This is
8 Daryn Dodge. I did look to see if IARC was doing any
9 investigations further into isoprene and I didn't see
10 anything in their future plans regarding isoprene.

11 PANEL MEMBER BLANC: And on the other? On the
12 epidemiologic front?

13 DR. DARYN DODGE: No, I don't believe so. This
14 is just from --

15 PANEL MEMBER BLANC: No, I mean, what do you
16 think about language which expands a bit on the statement
17 there are no epidemiologic data?

18 DR. DARYN DODGE: I agree with that. We will add
19 that to the document.

20 PANEL MEMBER BLANC: Now, maybe, Beate, do you
21 have a specific comment on the epi of isoprene -- of the
22 synthetic rubber industry, because it's not -- I'm not a
23 deep --

24 PANEL MEMBER RITZ: Yeah, I'm not an expert
25 either, but IARC has written on the rubber industry.

1 There is a monograph, but it -- I think it's pretty old.

2 PANEL MEMBER BLANC: Yeah.

3 PANEL MEMBER RITZ: It's 1987. I just looked it
4 up.

5 PANEL MEMBER BLANC: Yeah.

6 PANEL MEMBER RITZ: But they looked at the whole
7 industry and that's probably useful.

8 PANEL MEMBER BLANC: The -- another technical
9 question I have for you is that in your multi-cancer
10 model, you do include the Harderian gland tumor endpoint,
11 is that -- that's correct?

12 DR. DARYN DODGE: In the male mice?

13 PANEL MEMBER BLANC: In the male rats, I would
14 guess, because that's what drives you. Both. I think it
15 was commented on in both of the -- both species, no?

16 DR. DARYN DODGE: Yeah, that was a tumor
17 incidence that increased in male mice. The adenomas.
18 There was a statistically significant increase in the
19 three highest doses, but for carcinomas, there was not.

20 PANEL MEMBER BLANC: So does that mean it didn't
21 make it into your multi-cancer model?

22 DR. DARYN DODGE: This was the Placke et al.
23 information, which we ultimately didn't use to determine
24 an IUR, but I -- we did -- yeah, we did include it in the
25 multi-site analysis.

1 PANEL MEMBER BLANC: I don't know if you want in
2 the text or not to comment on the -- some of the issues
3 that the -- the Harderian gland as an endpoint. It may be
4 a moot point, since from what you're saying, it was not in
5 the rat data. So, I didn't remember offhand which ones it
6 was in, because that -- obviously, its's not a -- it's not
7 a gland that exists in primates, as far as we know. So --
8 and it's -- some commenters, you know, say it's a kind of
9 more sensitive endpoint, which is interesting in light of
10 the adenomas, but, I mean, it's a very small point, so I
11 just wanted to bring it up and clarify.

12 To me, a more salient issue is the metabolism of
13 the isoprene since you argued convincingly that it's the
14 metabolites that are carcinogenic. And you're
15 particularly suspicious of one metabolite. I understood
16 that correctly?

17 DR. DARYN DODGE: Well, there is genotoxicity
18 data for, I believe, the diepoxide --

19 PANEL MEMBER BLANC: Right.

20 DR. DARYN DODGE: -- metabolite. And I guess
21 there is some agreement that that could be the most
22 carcinogenic metabolite of isoprene, but we're talking
23 about at least four different --

24 PANEL MEMBER BLANC: Right.

25 DR. DARYN DODGE: -- epoxides that could be

1 generated during metabolism of isoprene. And any one of
2 those could be the prime culprit, where, you know, it's
3 just not known.

4 PANEL MEMBER BLANC: Okay. But your comments on
5 CYP2E1 are -- is the P450 that is most important for
6 metabolism to all of the epoxides?

7 DR. KEN KLOC: I could jump in here, if you want.

8 DR. DARYN DODGE: Okay. Sure. Go, Ken.

9 DR. KEN KLOC: It's seemed -- so there -- we had
10 reviewed a number of studies early on in the -- in the
11 preparation of the document, where the researchers
12 specifically attempted to ferret out which isoenzymes were
13 responsible primarily for epoxidation of isoprene. And
14 that's what they found that it was primarily 2E1 isoform,
15 which was creating most of the epoxides. It wasn't
16 exclusive though, but it was primarily --

17 PANEL MEMBER BLANC: Okay. But it was the
18 important.

19 DR. KEN KLOC: Yes.

20 PANEL MEMBER BLANC: So one of the problems with
21 the figure, which only refers to P450 generically as
22 opposed to the paragraph of text that follows the figure,
23 which highlights 2E1 is there's no footer in the table --
24 the figure, I'm sorry, which says when we say P450, it
25 most likely is the isoenzyme -- the isoenzyme that we're

1 concerned about is CYP2E1. So I think it would be even
2 clearer to whoever reads this that that's the isoenzyme
3 that re -- that is relevant to the figure which only
4 generically talks about P450 in all of the arrows.

5 And the reason I say that is, A, in this era to
6 simply talk about P450 is quite antiquated. And secondly,
7 we know a lot about inducers of CYP2E1. And since if that
8 is responsible for the carcinogenic -- carcinogenesis of
9 this chemical, then -- and if we want to make any comments
10 about vulnerable populations, then that is -- could be
11 highly relevant. And the strongest known inducer of that
12 isoenzyme is ethanol ingestion. And yet, that wasn't
13 mentioned in the report. I just think since we -- in
14 other work that OEHHA has done, we give consideration to
15 vulnerable populations. I think it's worth alluding to in
16 my -- in my view. It wouldn't change any of your analyses
17 to. It just has to do with some text additions. I don't
18 know if you would feel comfortable editing the text in
19 that light.

20 DR. DARYN DODGE: No. I think you're correct,
21 Dr. Blanc. We can add some language like that.

22 PANEL MEMBER BLANC: And then just to clarify
23 where you talk about anthropogenic sources of isoprene,
24 but in that -- in that -- those sentences, you don't talk
25 about the industrial synthetic rubber production. Did you

1 mean anthropogenic other than industrial?

2 DR. DARYN DODGE: Are you referring to a slide,
3 I'm sorry?

4 PANEL MEMBER BLANC: No. It's in your text, in
5 your body. Very early in your text, your introductory
6 information about this chemical, and what it's used for,
7 and where it comes from. We don't have to belabor it
8 here, but would you go back and look over it.

9 DR. DARYN DODGE: Um-hmm.

10 PANEL MEMBER BLANC: I'm not sure that the text
11 is as lucid as it might be in that regard.

12 DR. DARYN DODGE: Okay. Yeah, sure. We could
13 clear that up.

14 PANEL MEMBER BLANC: Also just, not to be a
15 stickler, but, you know, isoprene is used -- yes, it is
16 important for tires, but just -- that's not the only thing
17 that synthetic rubber is used for. And so it's a little
18 bit telegraphic in that. I mean, just with a few more
19 words you can say "and other end products", because it
20 really oversimplifies, I think where this is used
21 industrially.

22 DR. DARYN DODGE: Okay. We can --

23 PANEL MEMBER BLANC: I think the European
24 document would help you. I would go back to that --

25 DR. DARYN DODGE: Okay.

1 PANEL MEMBER BLANC: -- if I were you.

2 DR. DARYN DODGE: Okay. We'll --

3 PANEL MEMBER BLANC: And similarly, you know when
4 you talk about it's released naturally - well, it was even
5 in one of your slides -- by vegetation and trees, I mean,
6 trees are vegetation, you know, so careful about the
7 wording. But, you know, it's --

8 DR. DARYN DODGE: Um-hmm.

9 PANEL MEMBER BLANC: I was sort of shocked when
10 you -- surprised, you know, when you said -- in the main
11 text, you say something like moss, and ferns, and trees.
12 And I said to myself, well, so you mean no other plants.
13 You know, bushes don't matter. Shrubs don't matter, which
14 I don't -- I think is probably not true. So just, you
15 know, the wording. Just if you said including especially
16 trees, but, you know, obviously, it can't be just trees,
17 right?

18 DR. DARYN DODGE: Yes. We'll clear that up as
19 well.

20 PANEL MEMBER BLANC: Okay. Those were my takes
21 as I read through the thing.

22 CHAIR ANASTASIO: Great. Thank you, Paul.
23 Karen, comments.

24 PANEL MEMBER MESSER: Yeah. Thank you.
25 My comments are similar to those of my

1 colleagues. So from a technical point of view, I thought
2 this document was well written, well explained, well
3 presented, well justified, no major technical flaws. But
4 it was -- it felt like we are reading a technical
5 assessment in isolation without understanding its context,
6 without a good understanding of the need for assessment of
7 this compound, especially given the introduction, where it
8 seems to be ubiquitous with these large, both natural- and
9 human-caused, sources that are very dispersed. So it was
10 a little bit -- it just raised the question in my mind, as
11 in some of my fellow reviewers why this was prioritized
12 for the hot spots assessment. You know, what's the
13 motivation? What's the opportunity for risk reduction if
14 an IUR is established, given that there were no
15 descriptions of point sources or human exposure?

16 So I guess my comment is quite general following
17 on the more specific comments of my colleagues. This is
18 the report that I've read so far that seems to be most
19 lacking in that kind of context. All the prior reports,
20 we could read some epidemiologic data that raised concerns
21 and some descriptions of industry point sources, where --
22 or situations where workers might have extremely high
23 exposures.

24 But none of that came to mind when reading this
25 report. So all the way through, I had two questions,

1 which is, you know, who's at high risk for exposure, are
2 there people, and are there point sources other than
3 wildfires which could be usefully monitored and mitigated?
4 So it was that context generally that was -- that was
5 missing from this document in a way that it hasn't been
6 missing in prior reviews. That seemed a little bit
7 different for this document. So that's my general
8 comment.

9 You know, it just raised a lot of questions. If
10 wildfires spew this stuff out and humans produce it
11 endogenously, what's the risk and what's the opportunity
12 for risk mitigation.

13 DR. RIMA WOODS: Thank you, Dr. Messer, for that
14 comment. We'll definitely add some information in the
15 introduction for some context and relevance. And as Dr.
16 Dodge had mentioned previously, it was detected near
17 petroleum sources. So isoprene actually came on our radar
18 for an assessment, because it was detected in the SNAPS
19 program. And SNAPS stands for Study of Neighborhood Air
20 near Petroleum Sources. So that kind put it towards top
21 of our list so that we could get an IUR value for it, so
22 we could am are you for it, so we could accurately assess
23 the risk to the communities near those petroleum sources.
24 So we can add that information into the report.

25 PANEL MEMBER MESSER: Yeah, that would be super,

1 super helpful.

2 CHAIR ANASTASIO: Great. Thank you, Karen.

3 Beate.

4 PANEL MEMBER RITZ: Yeah. I just put two
5 reference sources in the chat box on rubber and tire
6 workers. And, you know, IARC has given them a number one
7 rating for carcinogenesis, but that's mostly -- there are
8 hundreds of chemicals. There are PAHs, nitrosamines, all
9 sorts of things, benzene, butadiene that are exposures in
10 these workers. And it's a big mixture, lots of cancer
11 sites. So it's clearly human carcinogenic in the mixture
12 as well. And that's what IARC evaluated. Maybe that's
13 worth mentioning and maybe those two citations could be
14 used.

15 Clearly, in the environment, it's also a mixture,
16 right? And how much it is just isoprene versus the
17 combination with other carcinogens, we really don't know.
18 But from the worker studies, at least we know that the
19 whole mixture overall is a carcinogen. And I don't know
20 again whether they are -- whether there are hot spots
21 where these mixtures also are an issue, and where maybe
22 the source that contributes to that mixture should be
23 controlled. And, you know, whether you control butadiene,
24 benzene, or isoprene may not be the question, but that the
25 whole mixture will be controlled, and isoprene is one part

1 of it. That's basically it.

2 CHAIR ANASTASIO: Thank you. Yeah, that's an
3 interesting point, right, when you've got these very
4 complex mixtures, but we consider risk on an individual
5 compound basis. But hopefully, if you mitigate emissions
6 of one, you're mitigating multiple emissions.

7 Okay. Thank you, Beate.

8 Last, but not least, Dr. Mike Kleinman.

9 PANEL MEMBER KLEINMAN: Well, thank you. I first
10 want to echo, you know, that I really appreciated the
11 presentation. And the document is, you know, an extremely
12 well written document. I wanted to agree with Ahmad's
13 comment on improving the way that the literature search
14 was documented. Critical literature reviews are now
15 becoming fairly standard and the methodology is fairly
16 straightforward. And I think it would make the -- lend a
17 lot of credence to the objectivity of this review to
18 actually go through the process and show what were the
19 search terms, how many articles were accumulated, how many
20 were rejected that -- what didn't meet the cut, that sort
21 of thing, until you get down to the articles that are
22 critical for what you're doing. So, yeah, I think -- you
23 know, I don't see a need to do for this document, but I
24 think going forward that sort of methodology should be
25 more firmly incorporated.

1 The other comment that I had -- oh, I also wanted
2 to thank you for a very lucid explanation of the use of
3 the Benchmark Dose Methodology and how it's applied. I
4 think that was great. I'm going to incorporate it in the
5 lecture. So thank you for that.

6 (Laughter).

7 PANEL MEMBER KLEINMAN: The other thing I think
8 that's been alluded to is putting this -- you know, these
9 values into context especially in the context of the
10 endogenous isoprene reduction. When you look at the
11 information, I think it's on page 11, endogenous isoprene
12 production, the steady state end-tidal breath
13 concentrations are on the order of about 100 parts per
14 billion, which, you know, you need to put into context how
15 does that relate to ambient exposures and why, you know,
16 if you put a couple of humans in a box, are they not at
17 risk? It's just -- it's sort of, you know, is something
18 you look at it without context I think needs a little more
19 explanation.

20 And I think I'll stop there. Thank you.

21 CHAIR ANASTASIO: Okay. Thank you, Mike.

22 Did any other Panel members have any follow-up
23 comments?

24 PANEL MEMBER KLEINMAN: Oh, excuse me, Cort.

25 CHAIR ANASTASIO: Yes.

1 PANEL MEMBER KLEINMAN: I did have one other
2 minor thing, and that was you had mentioned the missing
3 minus sign in the properties of isoprene. And that was
4 actually corrected in the more recent draft that's on the
5 website.

6 CHAIR ANASTASIO: Ah, okay.

7 PANEL MEMBER KLEINMAN: They are ahead of you on
8 that.

9 CHAIR ANASTASIO: Perfect.

10 Karen, you have a comment.

11 PANEL MEMBER MESSER: Yeah, just a follow-up on
12 the context comment. I guess that's my hobby horse this
13 meeting. I agree. With the ambient exposures and the
14 endogenous exposure, you know, I had to make a little
15 spreadsheet and compute them all and put them all out to
16 make -- to see how they compared to each other and see how
17 they compared to the levels in the experiments. So it
18 would be helpful to do some of that work for us. And
19 also, I forget which colleague made the comment, it would
20 be helpful to put the final cancer slope factor or
21 inhalation unit risk into context also, especially given
22 Beate's comment that this chemical occurs in mixtures
23 usually. I mean, we know the usual components in the
24 mixture from an oil well or from a fire.

25 And if those are the major exposure sources, then

1 I think it would be very important to say whether this is
2 the most -- is likely the most carcinogenic species in the
3 exposure, or among them, or whether it's maybe a more
4 benign one. I think it would be helpful to have some
5 context there.

6 CHAIR ANASTASIO: Thank you, Karen.

7 Sorry, Joe, did you have your hand up for a
8 second?

9 PANEL MEMBER LANDOLPH: Yes. What do you want
10 from the members of the Panel? Do you want written
11 comments or is what's in the transcript sufficient?

12 CHAIR ANASTASIO: I'll leave that up to OEHHA.

13 DR. DARYN DODGE: Yeah, this is Daryn. We --
14 well, we'll get transcripts and so we'll operate off that
15 in terms of answering your -- the questions from the SRP.
16 But if you do have additional comments that you'd like to
17 send to me in written form, I can look at those too.

18 PANEL MEMBER LANDOLPH: Okay. And let me ask you
19 for something as well. Do you have the -- you must have
20 the listing now, a huge long listing of all the cancer
21 slope factors for inhalation. Do you have that in a
22 document? Could I get a copy of that and whoever else
23 wants one?

24 DR. RIMA WOODS: Yes. We do have that list.

25 It's on our website, but we can also send you a copy of

1 that PDF directly. It's a table that contains all our
2 current cancer values.

3 PANEL MEMBER LANDOLPH: Thank you. And I could
4 print the whole document out myself too, if I wanted?

5 DR. RIMA WOODS: Yes. Yeah.

6 PANEL MEMBER LANDOLPH: Do you know the website?

7 DR. RIMA WOODS: It's on our website, but I can
8 send it to you directly to save the time for searching for
9 it.

10 PANEL MEMBER LANDOLPH: That's very nice of you.
11 Thank you very much.

12 DR. RIMA WOODS: Sure.

13 CHAIR ANASTASIO: Okay. Any other Panel
14 comments?

15 All right. Seeing none, we're going to take a
16 break. Let's reassemble at 11:15. And then we'll have
17 the informational item about computational toxicology from
18 OEHHA.

19 So I'll see you all at 11:15.

20 (Off record: 11:04 a.m.)

21 (Thereupon a recess was taken).

22 (On record: 11:15 a.m.)

23 CHAIR ANASTASIO: Okay. Welcome back, everyone.
24 Before we move on to our next item, I forgot to conclude
25 the isoprene discussion with next steps. So given that

1 the comments from the Panel were significant, but
2 relatively minor in the sense of what the IUR value is,
3 I'm going to suggest that OEHHA sends the revised isoprene
4 document to the leads, me and Ahmad, and then we sign off
5 on it, and that will be the SRP approval.

6 Can I get a vote on this? So all in favor of my
7 proposal, you can just raise --

8 (Ayes).

9 (Hands raised).

10 CHAIR ANASTASIO: Sorry, Mike, did you want to
11 make a comment?

12 PANEL MEMBER KLEINMAN: No, I was just saying
13 aye.

14 CHAIR ANASTASIO: Oh, you were saying aye. Okay.
15 Let's do the hands and I can count more easily.

16 (Hands raised).

17 CHAIR ANASTASIO: Okay. We've got --

18 PANEL MEMBER BESARATINIA: Cort, can I -- can I
19 ask would it be possible for the OEHHA to either mark or
20 highlight the revised version, the changes that are made,
21 so it's -- it would be easier for us to kind of go through
22 the modification and figure out whether the amendments
23 were made in response to the comments that were made.

24 CHAIR ANASTASIO: Yeah. That's been their
25 standard practice. They'll give us a tracked change

1 version of the document, so we can see exactly what has
2 been changed.

3 PANEL MEMBER BESARATINIA: Okay. Great.

4 CHAIR ANASTASIO: Which is very helpful.

5 PANEL MEMBER BESARATINIA: Thank you.

6 CHAIR ANASTASIO: Okay. So let's see, is
7 everybody on now?

8 So let me do the vote one more time of the Panel.
9 So all in favor of the leads approving the revised
10 documents?

11 (Hands raised).

12 CHAIR ANASTASIO: Mike I already saw your hand
13 before. Okay. So it looks like it's unanimous. Okay, so
14 we'll do that. So Rima, if you could send it to me and
15 Ahmad and then we'll sign off on it.

16 DR. RIMA WOODS: Great. We will send it to you
17 as soon as we complete all of the revisions that were
18 requested. Thank you very much.

19 CHAIR ANASTASIO: Thank you.

20 Okay. So our second major item today is an
21 informational item from OEHHA on computational toxicology
22 and their new approach methodologies. So OEHHA, as we've
23 talked about in prior meetings is developing expertise in
24 what they're calling New Approach Methodologies, or NAMs,
25 to support CalEPA programs and regulatory activities. So

1 NAMS are new toxicological testing and analysis methods
2 that allow for informed predictions of biological effects
3 for data-poor environmental pollutants. The idea being
4 you can develop a health guidance value without having
5 animal or epidemiological data.

6 There are several components to this effort,
7 including creation of new Toxicology Evaluation Section
8 within OEHHA, and developing collaborations with academic
9 organizations with NAMS expertise on data-poor compounds.
10 The newly created section within OEHHA brings together
11 expertise in toxicology, bioinformatics, toxicokinetics,
12 and computational chemistry. So the item that we're going
13 to have presented to us now is an overview of the NAMS
14 work at OEHHA and the potential applications. So it's my
15 pleasure now to introduce Anatoly Soshilov, who is the
16 supervisor of the new Toxicology Evaluation Section from
17 OEHHA.

18 Welcome, Anatoly.

19 DR. ANATOLY SOSHILOV: Welcome, everyone. Let me
20 start my presentation

21 (Thereupon a slide presentation).

22 DR. ANATOLY SOSHILOV: And please let me know, if
23 you can see the screen. And you should see the first
24 slide now.

25 CHAIR ANASTASIO: Yes, looks like.

1 PANEL MEMBER LANDOLPH: Yeah.

2 DR. ANATOLY SOSHILOV: So I'm a senior
3 toxicologist at OEHHA. And today, I will present on the
4 use of computational toxicology and new approach
5 methodologies, or NAMs, at OEHHA.

6 [SLIDE CHANGE]

7 DR. ANATOLY SOSHILOV: In my talk, I will
8 describe new approach methodologies, or NAMs, and their
9 use in toxicology and risk assessment. Next, I will
10 summarize the NAMs-related activities at OEHHA, including
11 staff in the new NAMs section, academic collaborations on
12 NAMs-related projects, and creating an expert panel for
13 input to NAMs-related projects.

14 [SLIDE CHANGE]

15 DR. ANATOLY SOSHILOV: In contrast to traditional
16 approaches in toxicology, which analyze human
17 epidemiological and animal toxicological data, our new
18 approach methodologies, or NAMs, use in vitro data,
19 including information obtained from cell cultures, in
20 silico data such as predictions of binding chemicals to
21 macromolecular targets, and even some alternative animal
22 models, such as transgenic mice that are generated to
23 increase sensitivity in specific assays.

24 While traditional toxicological approaches employ
25 an animal's duration -- employ an animal's mimic duration

1 and route of exposure to humans and therefore require a
2 significant number of animals, NAMs are developed with the
3 goal to reduce and replace animal use in chemical risk
4 assessments.

5 [SLIDE CHANGE]

6 DR. ANATOLY SOSHILOV: NAMs is an umbrella term
7 that includes a variety of different approaches and
8 methods. And this is a rather busy slide. That's -- I'll
9 just spend some time here.

10 This chemical computational modeling and
11 read-across approaches in which Quantitative Structure
12 Activity Relationship Models, or QSARs, as well as
13 physiologically kinetic, or PBK, and other types of models
14 can be developed. Our computational methods can include
15 machine learning and read-across approaches, which utilize
16 toxicity data for source of various chemicals predict
17 effects for target or data-poor chemicals.

18 A lot of NAMs work is done with cells in vitro in
19 the form of 2-D or 3-D cell cultures. And it can be
20 engineered into microphysiological systems, such as
21 organoids or organ-on-a-chip. This one -- I don't know if
22 you can see my pointer. This is an organ-on-a-chip
23 actually. Multiple cell lines combined on a single chip
24 with -- connected with the flows.

25 Cell cultures are ideal analytes with high

1 through-put screening methods that can include different
2 or mixed approaches, such as genomics, transcriptomics,
3 proteomics, and different advanced imaging techniques.
4 The goal of NAMs implementation is to reduce and replace
5 vertebrate animal use. And some alternative species, such
6 as fish, were proposed for studies as a replacement, while
7 genetic mouse models were developed to increase
8 sensitivity, and therefore to reduce the overall number of
9 animals in experiments.

10 Next, I'm going to describe two examples of NAMs
11 used in risk assessment.

12 [SLIDE CHANGE]

13 DR. ANATOLY SOSHILOV: Our first example is
14 read-across. Read-across is an approach in which toxicity
15 for a target or data-poor chemical is predicted based on
16 similarity with a structurally related source chemical or
17 chemicals. The similarity can also be based on
18 toxicokinetic or mechanistic information that can be
19 obtained from NAMs. In this particular approach in this
20 read-across framework, the formulation of the initial
21 read-across hypothesis identification and evaluation of
22 the source chemical and refinement of read-across
23 hypothesis, with the help of NAMs occur iterative manner,
24 where newly required NAMs data may further inform the
25 read-across hypothesis. NAMs data in this approach can

1 in vivo dose responses produced that can be used for
2 derivation of reference dose. Of course, this method
3 comes with certain limitations that need to be carefully
4 considered on a case-by-case basis.

5 [SLIDE CHANGE]

6 DR. ANATOLY SOSHILOV: The need for NAMs in
7 toxicology is increasing. This is because we are exposed
8 to increasingly more chemicals that lack health
9 assessments. We also become aware that we are exposed to
10 more chemicals, when new detection methods are used to
11 detection limits of existing methods are lowered. Our new
12 chemical alternatives are proposed that lack health data
13 and require assessments as well. Some examples, in this
14 case, a novel PFAS, and disinfectant quaternary ammonium
15 compounds, or QACs.

16 Finally, several initiatives at the federal and
17 international levels are now underway that aim to reduce
18 and replace animal use in toxicological studies. In this
19 situation, NAMs are the main available method that can
20 help with the health assessments of chemicals that lack
21 regular toxicity data.

22 [SLIDE CHANGE]

23 DR. ANATOLY SOSHILOV: Contrary to the possible
24 perception that NAMs are a new and untried approach in
25 chemical risk assessment, several agencies have been using

1 NAMs data in routine assessments. For example, in
2 monographs by International Agency for Research on Cancer,
3 or IARC, NAMs made part of the mechanistic evidence
4 stream, which is organized according to the key
5 characteristics of carcinogens framework. Together, with
6 human and animal evidence streams, the mechanistic
7 evidence stream informs the carcinogen classification of
8 the chemical of interest.

9 U.S. EPA uses a read-across approach in
10 developing provisional peer-reviewed toxicity values, or
11 PPRTVs. This read-across method relies on three
12 similarity domains for the target and source chemicals,
13 including structural/physiochemical similarity,
14 metabolic/toxicokinetic similarity, and toxicodynamic or
15 mode-of-action similarity.

16 [SLIDE CHANGE]

17 DR. ANATOLY SOSHILOV: To address the increasing
18 need for NAMs in toxicology, in 2023 OEHHA created a New
19 Toxicology Evaluation Sections, or NTES. This section
20 works with our CalEPA BDOs, academics partners, and other
21 stakeholders on assessments of data-poor chemicals. This
22 section includes five newly hired staff with two
23 toxicologists, two chemicals scientists, and one
24 bioinformatic scientist.

25 [SLIDE CHANGE]

1 DR. ANATOLY SOSHILOV: Our academic partnerships
2 on new assessment methodologies include one contract with
3 UC Berkeley that focuses on predictive methods in
4 carcinogenesis, one contract with UC Davis that compares
5 in vitro and in vivo effects for emergent pollutants, and
6 three contracts with UC San Francisco that develop
7 alternative methods in assessing developmental toxicity,
8 as well as one contract with Texas A&M University that
9 focuses on toxicokinetic and transcriptomic studies.

10 [SLIDE CHANGE]

11 DR. ANATOLY SOSHILOV: As part of proposed NAMs
12 activities, NTES in cooperation with TAMU organized two
13 toxicokinetic workshops that included presentations by
14 academia industry and government agencies followed by
15 discussion of case studies relevant to our chemicals of
16 interest. The first workshop focused on toxicokinetic
17 tools in decision-making, and the second workshop focused
18 more narrowly on NAMs tools and inhalation toxicology.

19 [SLIDE CHANGE]

20 DR. ANATOLY SOSHILOV: Part of the proposed NAMs
21 work at NTES is creating a NAMs expert panel, or EPERA,
22 which stands for Expert Panel on Emerging Risk Assessment
23 Approaches. This panel includes experts in relevant
24 scientific fields who will provide expert advice and
25 feedback to activities on NAMs. The current plan for the

1 panel is to meet twice a year. It is not a mandated
2 committee like SRP or SAP and its input is not a
3 substitute for peer review process. First EPERA meeting
4 is planned for fall 2024.

5 [SLIDE CHANGE]

6 DR. ANATOLY SOSHILOV: And to conclude, our new
7 approach methodologies, or NAMs, are becoming part of
8 landscape of tools for informed decision-making for
9 data-poor chemicals. And OEHHA efforts in NAMs space
10 include creating new toxicology evaluation sections,
11 fostering academic collaborations, and assembling an
12 expert panel.

13 Thank you.

14 CHAIR ANASTASIO: That's great. Thank you very
15 much, Anatoly.

16 Panel, comments?

17 Okay. I'll -- oh, Karen, go ahead.

18 PANEL MEMBER MESSER: Yeah. Very nice to see
19 these new technologies brought into this area. These are
20 technologies that we see in drug development in cancer.
21 I'm familiar with a lot of them in that context, high
22 throughput screening, and computational biology, and these
23 rapidly developing models, organoid models that are in
24 use. And it's a very exciting area. A lot going on.
25 Rapidly developing. And I'm sure that there will be use

1 cases that will come out of your work that will be very,
2 very helpful. So just a vote of enthusiasm for the
3 effort.

4 And then just a comment that where I'm familiar
5 with using these technologies, drug development, their
6 pre-clinical work, and then it goes into progressively
7 into animal models for confirmation and finally into human
8 studies for confirmation. So just pointing out that
9 that's the context in which we're used to seeing this kind
10 of work. So that will be our natural inclination to call
11 for validation studies, you know, if there's a
12 computational prediction. So just setting that up is what
13 someone like me would expect to see.

14 And then another comment that it seems like a
15 particularly fruitful area might be in prioritization of
16 this long list of chemicals. That that's something that
17 has come up before on this Panel, that there are so many
18 chemicals out there, how are they being prioritized for
19 study? And it seems to me that's an area where there
20 might be a big impact from some of these technologies.
21 And then they would feed naturally into more, either
22 future animal studies or epidemiologic studies that can
23 have a confirmatory nature.

24 So thank you.

25 DR. ANATOLY SOSHILOV: Thank you for the comment.

1 CHAIR ANASTASIO: Thank you, Karen.

2 Beate.

3 PANEL MEMBER RITZ: Yeah. Generally, I really,
4 you know, enjoy what is coming out of these technologies
5 and all these data streams. And in epidemiologic
6 research, I've been more and more using, you know, Omics
7 tools. So I think they're very useful. But recently, EPA
8 is reassessing several OP pesticides and has been using
9 NAMs to excuse all epi studies, and more or less, you
10 know, invalidate what they've been showing in terms of
11 neurodevelopment in children, and has -- they have also
12 been used to replace some of the more -- the older
13 toxicology assessments. And I don't think they should be
14 used in this way, but I don't know how we can guard
15 against that, because they seem like such shiny beautiful
16 tools. And, you know, they can be very convincing in some
17 way but they should not replace the real model, which is
18 human data, and certainly not the traditional animal
19 studies.

20 CHAIR ANASTASIO: Yeah. I think that points out
21 the importance of validation, as Karen mentioned.

22 DR. ANATOLY SOSHILOV: I also would like to point
23 out that we -- in any study or health assessment that we
24 would develop that's applicable to air pollutants would
25 eventually come up in front of this Panel. So this would

1 be the discussion where applicability of this method would
2 be relevant.

3 CHAIR ANASTASIO: Yeah, that's a good point.

4 Other Panel comments?

5 I would just like to echo what Karen said and I
6 know I've said this at prior meetings as well, that I
7 really think this is an enormously important effort, given
8 that we have, I believe, hundreds of toxic chemicals
9 listed on Appendix E for the Hot Spots, and we can get
10 through maybe two a year. So, we need a new approach that
11 really gives us at least, you know, rough estimates of
12 health guidance values, so that we can then maybe focus
13 the animal studies on the most important chemicals that
14 are identified using NAMs. So, yeah, I think this is
15 really important.

16 I did have one question for you, Anatoly. Can
17 you talk a little bit about the timeline? When do you
18 expect to start having health guidance values, some
19 initial ones that can be validated?

20 DR. ANATOLY SOSHILOV: We are currently working
21 on one chemical to supplement assessment that's been
22 performed in water. And so, our original strategy is to
23 develop assessments in parallel as a means to validate the
24 approach, and not necessarily as our -- well, definitely
25 not as our proposed free-standing reference value. So we

1 do pay validate -- a lot of attention to validation part.
2 And that assessment should be coming out within a year, I
3 would imagine. So that would be the first example where
4 we actually producing something that goes into an existing
5 regulatory document.

6 CHAIR ANASTASIO: That's great.

7 PANEL MEMBER BLANC: Is that chemical is --
8 Anatoly, what is that chemical?

9 DR. ANATOLY SOSHILOV: I don't think I can say
10 that. It's one their chemicals that Water Board requested
11 to develop a notification level for.

12 PANEL MEMBER BLANC: Can you give us a chemical
13 category? Is it organochlorine?

14 DR. ANATOLY SOSHILOV: It's a PFAS. So all the
15 chemicals that have been recently requested by Water Board
16 belong to the PFAS class.

17 PANEL MEMBER BLANC: A PFAS. Thank you.

18 DR. ANATOLY SOSHILOV: It's one of the chemicals
19 where there is some data, but it definitely helps to
20 provide -- to analyze all available data to strengthen the
21 assessment.

22 CHAIR ANASTASIO: Yeah. Great.

23 Karen.

24 PANEL MEMBER MESSER: Yeah. You know, NAMs is
25 such a broad term that there are lots of different ways it

1 could be -- it could be useful. And some of them are very
2 different. So I imagine you can really help with insights
3 in the mechanism of action that can then give a sharper
4 idea of risk, either from the step from one species to
5 another, or in different exposure levels, or of related
6 compounds. And those are sort of specific studies, like
7 you're describing here. And I think very targeted studies
8 that you could do could be very useful and fill in gaps.
9 That's the kind of application that I think many of us, if
10 we saw the details, would be fairly comfortable with. I
11 think what might -- what we would be less comfortable with
12 is sort of a de novo study that stands in for any animal
13 studies.

14 And then the idea of ranking these chemicals or
15 doing -- having a risk scoring system somehow for the long
16 list of chemicals that's available, that's kind of a
17 different animal or a different project. So just
18 encouraging your group to put some thought into that kind
19 of project sort of a broad risk assessment, or
20 prioritization, or scoring study.

21 DR. ANATOLY SOSHILOV: Noted.

22 CHAIR ANASTASIO: Yeah, that's a very good point.

23 Yeah. Any other comments from the panel?

24 Mike.

25 PANEL MEMBER KLEINMAN: Yeah. I think I want to,

1 you know, amplify the idea of the validation. And that
2 might be one of the first tasks your expert panel could
3 take on is identifying some compounds wherein you have
4 enough data from the traditional toxicology and the new
5 methods to actually do a good validation to -- you know,
6 that will provide a lot more competence in the
7 applicability of the method. I see this as being
8 extremely useful in enabling us to fill out sort of the
9 adverse outcome pathway for giving chemicals starting with
10 molecular mechanisms and working our way through to
11 natural organ effects in multiple species.

12 The other comment I wanted to make is that
13 despite the fact that it's very easy to look at one
14 chemical at a time, they're all exposed to mixtures. And
15 I think some effort should be go into evaluating how
16 mixtures would play out in this framework.

17 Thank you.

18 DR. ANATOLY SOSHILOV: I agree a hundred percent.
19 And then there is just no chance that we would get all the
20 toxicity studies for mixtures. So once you start
21 approaching make analysis of mixtures, you need to
22 understand what is happening, what's the mechanism, so
23 NAMs again help. They even help us with traditional
24 toxicity methods providing better sort of understanding of
25 the mechanism that can inform assessments.

1 CHAIR ANASTASIO: Yeah, that's great.

2 Any other Panel comments?

3 Okay. If not, thank you very much, Anatoly. We
4 appreciate your presentation.

5 DR. ANATOLY SOSHILOV: Thank you.

6 CHAIR ANASTASIO: The final agenda item is
7 consideration of administrative matters. First, look
8 ahead to our next meeting. We're going to have two items
9 soon, hopefully before the end of this year. The first
10 item is Blueprint 2.0 from OCAP and CARB, where we've
11 received an informational presentation on that at our
12 prior meeting. And then we're going to have a health
13 guidance value on 1,4-dichlorobenzene from OEHHA.

14 It's possible that hybrid meetings, such as this
15 one, where we all get to stay at home, might not be
16 allowed next year. So, we're going to try to schedule the
17 next SRP meeting before the December vacations. So Arash
18 is going to be reaching out to folks with the Panel as
19 soon as we can get that on our calendars.

20 Next informational item. I just want to
21 acknowledge again that we have four Panel members who have
22 ended their terms. Really appreciate your many years of
23 service and I really, really appreciate your continued
24 service on the Panel as we wait for replacement members.

25 So, you know, we need a quorum to have an

1 official meeting. That's five members. And with four
2 retired members out of nine, it doesn't give us any
3 leeway. So I really appreciate the Panel members whose
4 terms have officially expired continuing to serve on the
5 Panel.

6 Yes. Sorry, Paul.

7 PANEL MEMBER BLANC: I think you may want to ask
8 guidance on the minutes how the minutes should reflect
9 that wording, because if you say our service has expired,
10 we actually have no we shouldn't even be here. So I think
11 what you want to say is that our term would have lapsed
12 save for our continued participation, or whatever the
13 technical term is.

14 CHAIR ANASTASIO: Yes. Good point. I should
15 have spoken a little more precisely. The terms are
16 officially over, but your -- you can continue to serve
17 officially until a replacement has been named. So you're
18 still officially members of the Panel, although your
19 nominal term is over. So I appreciate your service.

20 The last thing -- oh, sorry, one more just note
21 about that. So the process has started in terms of
22 identifying new members, but no one has yet been selected,
23 so we don't have replacements yet.

24 The last item of business is a tribute to Paul.
25 So it looks like he may be trapped in a one room cell, but

1 I'm sure he's got some retirement location that we don't
2 know about. So I'm going to read a statement from the
3 Legislature acknowledging Paul's many decades of service
4 to the State and service on the Panel.

5 So CARB staff have come up with a resolution that
6 was supported by two Assembly members and one State
7 Senator that I'm going to read now. So sit back, get a
8 beverage, maybe some snacks, as I read this epic poem to
9 Paul Blanc. Okay. Here we go.

10 So this is dated August 9th, 2024. This is a
11 Members' resolution by the Honorable Scott Wiener B, 11th
12 Senatorial District, the Honorable Matt Haney, 17th
13 Assembly District, and the Honorable Philip Y. Ting, 19th
14 Assembly District relative to commending Paul D. Blanc,
15 MD.

16 Whereas, the Dr. Paul D. Blanc, Professor and
17 Endowed Chair in Occupational and Environmental Medicine
18 at the University of California, San Francisco, School of
19 Medicine will be concluding his remarkable 26th year
20 tenure on the Scientific Review Panel on Toxic Air
21 Contaminants. And it is appropriate at this time to
22 highlight his many achievements and extend to him special
23 public recognition and commendations for his professional
24 leadership, and;

25 Whereas, first appointed to the Scientific Review

1 Panel in 1997 by the Senate Committee on Rules, Dr. Paul
2 Blanc has held continuous membership on the Panel, which
3 is charged with evaluating substances proposed for
4 identification as toxic air contaminants by the California
5 Air Resources Board in coordination with the Office of
6 Environmental Health Hazard Assessment and the Department
7 of Pesticide Regulation, and for 26 years he has provided
8 his expertise in reviewing risk assessments, guidelines,
9 and other documents to better characterize and reduce the
10 risks of toxic air contaminants, and;

11 Whereas, throughout his academic career, Dr.
12 Blanc has demonstrated extensive accomplishments in
13 research and contributed significantly to studying asthma
14 and chronic obstructive pulmonary disease in relation to
15 workplace and environmental factors, and he has published
16 more than 400 peer-reviewed articles, authored two books,
17 and served as editor-in-chief of the Journal of
18 Occupational Medicine and Toxicology, in addition to
19 serving as Chief of Occupational And Environmental
20 Medicine at UCSF, and;

21 Whereas, honored with many accolades and awards,
22 Dr. Blanc has received the Jaroslav Teisinger Medal from
23 the Society of Occupational Medicine of the Czech Medical
24 Association, Excellence in Education or Research in
25 Occupational and Environmental Medicine Award from the

1 American College of Occupational and Environmental
2 Medicine, and Excellence in Interprofessional Teaching
3 Award from the UCSF Program for Interprofessional Practice
4 and Education, and;

5 Whereas, contributing to research programs and
6 policies in the United States and around the world, Dr.
7 Blanc has served on multiple national and international
8 panels, including the United States Environmental
9 Protection Agency Clean Air Scientific Advisory
10 Committee's Carbon Monoxide Review Panel, and the Danish
11 Working Environment Research Fund's Occupation in Chronic
12 Obstructive Pulmonary Disease Expert Review Panel, among
13 others, and;

14 Whereas, as the lead reviewer of numerous health
15 risk assessment guideline documents, Dr. Blanc helped to
16 facilitate the establishment of many health values using
17 the preparation of health risk assessments and
18 identification of toxic air contaminants, such as
19 chloropicrin and diesel particulate matter that led to
20 efforts to protect public health, and;

21 Whereas, having served on the Scientific Review
22 Panel for 26 years, Dr. Paul Blanc has played an integral
23 role in the evolution and implementation of California's
24 Air Toxics Program, which has given Californians the
25 opportunity to live in communities with significantly

1 reduced concentrations of toxic air contaminants.

2 Now, therefore be it resolved, by Senator Scott
3 D. Wiener and Asseblymembers Matt Haney and Philip Y.
4 Ting, that Dr. Paul D Blanc be honored for his extensive
5 contributions to the Scientific Review Panel on Toxic Air
6 Contaminants and extend its sincere best wishes for
7 success in the future.

8 Dated this 16th day of August 2024. The
9 Honorable Scott D. Wiener, 11th Senatorial District,
10 Honorable Matt Haney, 17th Assembly District, and
11 Honorable Philip Ting, 19th Assembly District.

12 So with that, Paul, thank you very much for your
13 26 years of impressive service and we will miss you on the
14 Panel.

15 (Applause).

16 CHAIR ANASTASIO: You can now have a rebuttal, if
17 you would like.

18 PANEL MEMBER BLANC: Well, I'm glad that the --
19 nobody from OEHHA said anything about making them cry in
20 the past.

21 (Laughter).

22 PANEL MEMBER BLANC: I haven't done that awhile,
23 so --

24 CHAIR ANASTASIO: All has been forgiven.

25 PANEL MEMBER BLANC: And just a brief moment to

1 think fondly of Dr. John Froines, who was my mentor and
2 friend, and whose memory will be a blessing.

3 CHAIR ANASTASIO: Yeah. Well, thank you very
4 much for all your work over these decades, Paul. We
5 really appreciate your input and the State of California
6 really appreciates your help.

7 PANEL MEMBER BLANC: You're most welcome.

8 CHAIR ANASTASIO: Anyone else want to roast Paul?

9 DR. ARASH MOHEGH: I just want to mention that
10 this is maybe why we can't replace Panel members, because
11 how we could find someone like Paul.

12 CHAIR ANASTASIO: That's a good point. You've
13 made yourself irreplaceable, Paul.

14 PANEL MEMBER BLANC: Yeah. Yeah.

15 CHAIR ANASTASIO: Mike.

16 PANEL MEMBER KLEINMAN: Yeah. I just want to
17 thank Paul, because over the years that I've served on the
18 Panel as co-panelist, I have learned so much from his
19 approach to toxicology and his extremely acute
20 understanding of how the mechanisms of various compounds
21 interact. I think it would be impossible to replace. So
22 I'd like to thank you for all the things you've taught me.

23 PANEL MEMBER BLANC: That's very kind. Very kind
24 of you.

25 CHAIR ANASTASIO: Ahmad.

1 PANEL MEMBER BESARATINIA: Yeah. I just want to
2 echo and thank Paul for his really lifetime contribution
3 to the Panel. And I want to just say that it has truly
4 been an honor to serve on the Panel with you and learn so
5 much from you, particularly the meticulous way of you
6 reviewing the documents and commenting on them. And it
7 has truly been educational, at least for me, and thank you
8 for that.

9 PANEL MEMBER BLANC: You're welcome.

10 CHAIR ANASTASIO: I think Rima would like to
11 address Paul making members of OEHHA cry.

12 (Laughter).

13 DR. RIMA WOODS: Well, I' knew here, so I haven't
14 seen anyone cry and I haven't heard the stories, but I
15 believe Dr. Krishnan would like to speak.

16 DR. KANNAN KRISHNAN: Yeah. Kannan Krishnan,
17 Assistant Deputy Director at OEHHA, Scientific Program.

18 I just want to thank you, Paul, for the wonderful
19 contributions over the years and your enthusiasm, passion,
20 rigor, and the guidance you have provided us over the
21 years. Now, I have had the opportunity to listen to you
22 during the last couple of years since I got on Board here
23 at OEHHA. Thank you on behalf of Lauren who has retired
24 now and on behalf all of us at OEHHA.

25 Thank you.

1 PANEL MEMBER BLANC: Thanks. I'd also like to
2 acknowledge our court reporter today and all of our court
3 reporters at all of these meetings and wishing that none
4 of them got carpal tunnel from what we've done to them,
5 but that may not be possible. I mean, it's possible for
6 me to thank them, but I don't know if it's possible for us
7 to have not caused that.

8 CHAIR ANASTASIO: Jim is very tough. I think
9 he's making it all work, but I second your thanks for the
10 court reporters and all their tireless work on this.

11 Okay. That then concludes our meeting, unless
12 there are any final thoughts or questions.

13 Okay. Great.

14 PANEL MEMBER BLANC: Thank you.

15 CHAIR ANASTASIO: So we do need a motion to
16 adjourn. But actually before we get to that, Paul. I
17 forgot to ask you, so you've officially retired, correct,
18 from UCSF?

19 PANEL MEMBER BLANC: Yeah. I'm doing a little
20 bit of call back. And I'm currently working on a book
21 project, which is why I'm calling in from the National
22 Library of Medicine.

23 CHAIR ANASTASIO: Ah, that's where you are.
24 Okay. Yeah. I knew you'd be busy. I just didn't know
25 with what. So good to hear.

1 Yeah. Okay. With that, I'm looking for a motion
2 to adjourn.

3 PANEL MEMBER KLEINMAN: So moved.

4 PANEL MEMBER BLANC: So moved.

5 CHAIR ANASTASIO: Excellent. Second.

6 PANEL MEMBER BESARATINIA: Second.

7 CHAIR ANASTASIO: All in favor?

8 (Hands raised)

9 CHAIR ANASTASIO: Mike, you want to keep going?

10 No.

11 Okay. We have unanimous. Thank you very much,
12 everyone. Thank you, Arash, for organizing. And Paul,
13 thanks and congratulations.

14 PANEL MEMBER BLANC: You're welcome.

15 CHAIR ANASTASIO: Yeah. All right. Have a great
16 weekend, everyone.

17 (Thereupon the California Air Resources Board,
18 Scientific Review Panel adjourned at 11:55 a.m.)

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