MEETING

STATE OF CALIFORNIA

ENVIRONMENTAL PROTECTION AGENCY

AIR RESOURCES BOARD

SCIENTIFIC REVIEW PANEL

ON TOXIC AIR CONTAMINANTS

ZOOM PLATFORM

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PROCEEDINGS

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

Arash, you want to say that now.

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

Thank you, Cort.

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

Joe, you're muted.

PANEL MEMBER LANDOLPH: Did that do it?

CHAIR ANASTASIO: Yep.

PANEL MEMBER LANDOLPH: Okay. Sorry. Thank you.

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

CHAIR ANASTASIO: Thank you, Joe.

Paul.

PANEL MEMBER BLANC: Me?

CHAIR ANASTASIO: You.

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

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

PANEL MEMBER BLANC: Yeah.

CHAIR ANASTASIO: Thank you, Paul.

Karen.

PANEL MEMBER MESSER: Good morning. I'm Karen

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

CHAIR ANASTASIO: Thank you, Karen.

Ahmad.

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

CHAIR ANASTASIO: Thank you, Ahmad.

Mike.

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

CHAIR ANASTASIO: Nice. Thank you, Mike.

Beate.

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

CHAIR ANASTASIO: Thank you, Beate.

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

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

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

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

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

All right. So move to the first item, the isoprene cancer inhalation unit risk factor. So the staff from the Office of Environmental Health Hazard Assessment, OEHHA are going to present a draft document summarizing the development of a cancer potency factor and 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 Programs, which is part of 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 of 2024. No public comments were received. More information regarding the document can be found at a long website, HTTPS -- I'm not going to read the whole thing. It's on the OEHHA website under isoprene.

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

(Thereupon a slide presentation).

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

Okay. Next slide.

[SLIDE CHANGE]

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

[SLIDE CHANGE]

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

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

[SLIDE CHANGE]

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

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

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

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

[SLIDE CHANGE]

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

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

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

[SLIDE CHANGE]

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

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

[SLIDE CHANGE]

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

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

[SLIDE CHANGE]

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

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

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

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

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

[SLIDE CHANGE]

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

[SLIDE CHANGE]

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

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

a chemical, the combined benign and malignant tumors.

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

[SLIDE CHANGE]

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

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

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

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

[SLIDE CHANGE]

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

[SLIDE CHANGE]

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

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

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

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

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

[SLIDE CHANGE]

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

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

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

[SLIDE CHANGE]

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

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

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

Next slide.

[SLIDE CHANGE]

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

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

[SLIDE CHANGE]

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

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

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

[SLIDE CHANGE]

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

[SLIDE CHANGE]

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

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

[SLIDE CHANGE]

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

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

[SLIDE CHANGE]

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

gland adenomas, both individually and combined. However, we did not use the female mice information to determine a final cancer slope factor, because only adenomas were increased in female mice, in other words benign tumors.

In the NTP study in male and female rats, in the male rats we looked at the cancer slope factors or calculated cancer slope factors for kidney, mammary gland, and testes individually and combined using the multi-site model. For female rats, there was only one tumor site and this was mammary gland and only fibroadenomas were increased. Since these were benign tumors, we did not go any further in terms of calculating cancer slope factors with that information.

[SLIDE CHANGE]

DR. DARYN DODGE: So this is the graphical output of the Benchmark Dose Software. In this graph, we show the renal tubule adenoma and carcinoma combined in male rats from the NTP study. So along the bottom row, or the X axis, that is the lifetime average daily dose in milligrams per kilogram day. Now, along the Y axis on the left side, that's the tumor incidence. The orange triangles is the incidence data. And the Benchmark Dose Software draws a line to this data. And that's the blue curved -- slightly curved line.

The benchmark dose, five percent above control,

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

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

[SLIDE CHANGE]

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

[SLIDE CHANGE]

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

of almost 100 percent.

[SLIDE CHANGE]

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

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

[SLIDE CHANGE]

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

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

[SLIDE CHANGE]

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

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

[SLIDE CHANGE]

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

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

[SLIDE CHANGE]

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

And that concludes my presentation.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

And just a couple of minor comments. I think it

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

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

And that's all I have. Thank you.

CHAIR ANASTASIO: Thank you, Ahmad.

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

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

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

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

Does that help?

CHAIR ANASTASIO: Yeah, that's great.

PANEL MEMBER BESARATINIA: Great. Thanks.

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

CHAIR ANASTASIO: Sure.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

DR. DARYN DODGE: Yes. Yes.

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

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

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

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

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

Joe, any comments from you?

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

went into it.

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

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

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

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

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

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

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

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

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

that into consideration.

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

Joe, any other comments?

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

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

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

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

CHAIR ANASTASIO: Yeah.

THE WITNESS: High the Dr.

DR. RIMA WOODS: Hi. This is Dr. Rima Woods. I'm the Chief of the Air Toxicology and Risk Assessment Section. And we work closely with CARB on the Hot Spots Program. And typically our top priorities are set in conjunction with CARB. So it's a combination of high emission compounds that CARB is seeing and then we combine that with information from what we know about toxicity. So there are a few chemicals that we are working on currently.

Am I allowed to say them? No.

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

Okay. Great. Just wanted confirmation.

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

PANEL MEMBER LANDOLPH: Thank you very much.

CHAIR ANASTASIO: Thank you, Joe.

Paul, comments.

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

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

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

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

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

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

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

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

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

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

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

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

PANEL MEMBER BLANC: Yeah.

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

PANEL MEMBER BLANC: Yeah.

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

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

DR. DARYN DODGE: In the male mice?

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

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

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

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

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

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

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

PANEL MEMBER BLANC: Right.

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

PANEL MEMBER BLANC: Right.

DR. DARYN DODGE: -- epoxides that could be

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

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

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

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

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

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

DR. KEN KLOC: Yes.

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

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

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

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

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

mean anthropogenic other than industrial?

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

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

DR. DARYN DODGE: Um-hmm.

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

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

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

DR. DARYN DODGE: Okay. We can --

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

DR. DARYN DODGE: Okay.

PANEL MEMBER BLANC: -- if I were you.

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

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

DR. DARYN DODGE: Um-hmm.

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

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

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

CHAIR ANASTASIO: Great. Thank you, Paul.

Karen, comments.

PANEL MEMBER MESSER: Yeah. Thank you.

My comments are similar to those of my

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

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

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

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

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

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

PANEL MEMBER MESSER: Yeah, that would be super,

super helpful.

CHAIR ANASTASIO: Great. Thank you, Karen.

Beate.

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

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

of it. That's basically it.

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

Okay. Thank you, Beate.

Last, but not least, Dr. Mike Kleinman.

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

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

(Laughter).

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

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

CHAIR ANASTASIO: Okay. Thank you, Mike.

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

PANEL MEMBER KLEINMAN: Oh, excuse me, Cort.

CHAIR ANASTASIO: Yes.

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

CHAIR ANASTASIO: Ah, okay.

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

CHAIR ANASTASIO: Perfect.

Karen, you have a comment.

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

And if those are the major exposure sources, then

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

CHAIR ANASTASIO: Thank you, Karen.

Sorry, Joe, did you have your land up for a second?

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

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

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

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

DR. RIMA WOODS: Yes. We do have that list. It's on our website, but we can also send you a copy of

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

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

DR. RIMA WOODS: Yes. Yeah.

PANEL MEMBER LANDOLPH: Do you know the website?

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

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

DR. RIMA WOODS: Sure.

CHAIR ANASTASIO: Okay. Any other Panel comments?

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

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

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

(Thereupon a recess was taken).

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

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

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

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

(Ayes).

(Hands raised).

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

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

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

(Hands raised).

CHAIR ANASTASIO: Okay. We've got --

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

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

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

PANEL MEMBER BESARATINIA: Okay. Great.

CHAIR ANASTASIO: Which is very helpful.

PANEL MEMBER BESARATINIA: Thank you.

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

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

(Hands raised).

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

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

CHAIR ANASTASIO: Thank you.

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

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

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

Welcome, Anatoly.

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

(Thereupon a slide presentation).

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

CHAIR ANASTASIO: Yes, looks like.

PANEL MEMBER LANDOLPH: Yeah.

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

[SLIDE CHANGE]

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

[SLIDE CHANGE]

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

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

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

[SLIDE CHANGE]

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

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

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

Cell cultures are ideal analytes with high

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

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

[SLIDE CHANGE]

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

also provide toxicokinetic and toxicodynamic insights.

The next step in this framework is uncertainty assessment. And in the end, the overall approach allows for data gap filling in the risk assessment of the target data-poor chemical.

[SLIDE CHANGE]

DR. ANATOLY SOSHILOV: Our second example is in vitro to in vivo extrapolation or IVIVE method. Sometimes when no in vivo toxicity data is available for the chemical of interest, in vitro data, such as derived from cell culture, can provide dose response information on the relevant endpoint or combination of endpoints. The question becomes how do we extrapolate the in vitro point of departure - in this case it's AC, active concentration - to an in vivo equivalent? To do so, we assume that the observed concentration or equivalent adjusted for cell culture effects represents blood or organ concentration.

Next, this assumed metric is converted to apply dose using a physiologically based kinetic model, with an example here. Such models imagine the body as a number of interconnected compartments. And typically, model absorption, distribution, and elimination of target chemicals as precise flows in and out of the system and between the compartments. In the end, the equivalent of

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

[SLIDE CHANGE]

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

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

[SLIDE CHANGE]

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

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

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

[SLIDE CHANGE]

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

[SLIDE CHANGE]

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

[SLIDE CHANGE]

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

[SLIDE CHANGE]

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

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

[SLIDE CHANGE]

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

Thank you.

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

Panel, comments?

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

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

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

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

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

So thank you.

DR. ANATOLY SOSHILOV: Thank you for the comment.

CHAIR ANASTASIO: Thank you, Karen.

Beate.

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

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

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

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

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

Other Panel comments?

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

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

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

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

CHAIR ANASTASIO: That's great.

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

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

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

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

PANEL MEMBER BLANC: A PFAS. Thank you.

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

CHAIR ANASTASIO: Yeah. Great.

Karen.

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

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

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

DR. ANATOLY SOSHILOV: Noted.

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

Yeah. Any other comments from the panel?

Mike.

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

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

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

Thank you.

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

CHAIR ANASTASIO: Yeah, that's great.

Any other Panel comments?

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

DR. ANATOLY SOSHILOV: Thank you.

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

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

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

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

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

Yes. Sorry, Paul.

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

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

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

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

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

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

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

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

Whereas, first appointed to the Scientific Review

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

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

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

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

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

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

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

reduced concentrations of toxic air contaminants.

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

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

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

(Applause).

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

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

(Laughter).

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

CHAIR ANASTASIO: All has been forgiven.

PANEL MEMBER BLANC: And just a brief moment to

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

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

PANEL MEMBER BLANC: You're most welcome.

CHAIR ANASTASIO: Anyone else want to roast Paul?

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

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

PANEL MEMBER BLANC: Yeah. Yeah.

CHAIR ANASTASIO: Mike.

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

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

CHAIR ANASTASIO: Ahmad.

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

PANEL MEMBER BLANC: You're welcome.

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

(Laughter).

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

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

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

Thank you.

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

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

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

Okay. Great.

PANEL MEMBER BLANC: Thank you.

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

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

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

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

PANEL MEMBER KLEINMAN: So moved.

PANEL MEMBER BLANC: So moved.

CHAIR ANASTASIO: Excellent. Second.

PANEL MEMBER BESARATINIA: Second.

CHAIR ANASTASIO: All in favor?

(Hands raised)

CHAIR ANASTASIO: Mike, you want to keep going? No.

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

PANEL MEMBER BLANC: You're welcome.

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

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

CERTIFICATE OF REPORTER

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

That I am a disinterested person herein; that the foregoing California Air Resources Board, Scientific Review Panel meeting was reported in shorthand by me, James F. Peters, a Certified Shorthand Reporter of the State of California;

That the said proceedings was taken before me, in shorthand writing, and was thereafter transcribed, under my direction, by computer-assisted transcription.

I further certify that I am not of counsel or attorney for any of the parties to said meeting nor in any way interested in the outcome of said meeting.

IN WITNESS WHEREOF, I have hereunto set my hand this 20th day of August, 2024.

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