VIDEOCONFERENCE MEETING

STATE OF CALIFORNIA

ENVIRONMENTAL PROTECTION AGENCY

AIR RESOURCES BOARD

SCIENTIFIC REVIEW PANEL

ON TOXIC AIR CONTAMINANTS

ZOOM PLATFORM

FRIDAY, MAY 7, 2021

9:30 A.M.

JAMES F. PETERS, CSR
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APPEARANCES

PANEL MEMBERS:

Cort Anastasio, Ph.D., Chairperson

Ahmad Besaratinia, Ph.D.

Paul D. Blanc, M.D.

S. Katharine Hammond, Ph.D.

Michael T. Kleinman, Ph.D.

Joseph R. Landolph, Jr., Ph.D.

Karen Messer, Ph.D.

Lisa A. Miller, Ph.D.

Beate R. Ritz, M.D., Ph.D., M.P.H.

REPRESENTING THE AIR RESOURCES BOARD:

Patrick Gaffney, Staff Air Pollution Specialist, Criteria Pollutant and Air Toxics Reporting Section, Greenhouse Gas and Toxics Emission Inventory Branch, Air Quality Planning and Science Division

Anne Klein, Air Pollution Specialist, Toxics Inventory and Special Projects Section, Air Quality Planning & Science Division

Lori Miyasato, Ph.D., Panel Liaison

REPRESENTING THE OFFICE OF ENVIRONMENTAL HEALTH HAZARD ASSESSMENT:

John Budroe, Ph.D., Chief, Air Toxicology and Risk Assessment Section

Rona Silva, Ph.D., Staff Toxicologist, Air Toxicology and Risk Assessment Section

APPEARANCES CONTINUED

ALSO PRESENT:

Stanton Glantz, Ph.D.

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PROCEEDINGS

CHAIRPERSON ANASTASIO: All right. Good morning, everyone and welcome to the May 2021 meeting of the Scientific Review Panel on toxic air contaminants. I'm Cort Anastasio, Chair of the Panel. And it's my pleasure to be call the meeting to order.

First, I'd like to welcome everyone to this webcast and just note that the webcast will be recorded. Anne Klein and Patrick Gaffney will be overseeing technical operations. And Patrick and Anne, would you like to give us any instructions at this point?

MR. GAFFNEY: I think you're all set, yeah, to get it done.

CHAIRPERSON ANASTASIO: Okay. Fantastic.

So then we're going to do Panel introductions. So I'd like to start with our newest member, Dr. Karen Messer. So, Karen, if you could just introduce yourself briefly, where you are, what kind of work you do.

PANEL MEMBER MESSER: Yeah. Good morning. I'm professor of biostatistics at University of California, San Diego. I'm the Director of Biostatistics Moores Cancer Center. I do a lot of cancer related statistics familiar with drug development studies, toxicology studies, mechanism of action, clinical trials, and the epidemiology of tobacco control.

CHAIRPERSON ANASTASIO: Excellent. Thank you, Karen. It's a pleasure to have you join the Panel.

Next, we'll just have each Panel member briefly essentially say that they're here, who they are, where they work. And I'm just going to go in the order I have on my sheet. We're going to start with Beate, who I'm happy to say was just reappointed as the epidemiology representative to the Panel. Beate.

PANEL MEMBER RITZ: Right. So, yeah, I'm an epidemiologist. But I'm actually MD, PhD, so I also have some clinical background. I'm a COEH member at UCLA, so the Center for Occupational and Environmental Health. And my main job is to ensure environmental and occupational health is being researched in the state, as well as provide service and teaching.

CHAIRPERSON ANASTASIO: Great. Thank you, Beate.

Next, Ahmad.

PANEL MEMBER BESARATINIA: Good morning. I'm Ahmad Besaratinia. I'm a professor of preventive medicine at Keck School of Medicine of University of Southern California. I'm a cancer biologist by training. And most of our research are on environmental carcinogenesis with a focus on tobacco-related cancers.

CHAIRPERSON ANASTASIO: And Ahmad, do you have any professional news you'd like to share with the Panel,

any good news recently occurred.

PANEL MEMBER BESARATINIA: Recently, well, I was promoted to full professor. And I recently got a new award actually from TRDRP.

CHAIRPERSON ANASTASIO: Awesome. Congratulations Ahmad on both of those good news pieces.

Next, Paul.

PANEL MEMBER BLANC: You're assuming I would be proficient at unmuting myself. But I like to be like those, you know, report -- those people being interviewed on MSNBC who always mess up the unmute.

I'm Paul Blanc. I'm at the University of California, San Francisco. And I'm Chief of the Division of Occupational and Environmental Medicine there and I am the State Senate appointee specifically in regard to occupational health. My areas of research include the epidemiology of lung disease and related conditions, as well as disability from occupational conditions.

CHAIRPERSON ANASTASIO: Great. Thank you, Paul.

Next, Joseph.

Sorry, Joe, you're muted.

PANEL MEMBER LANDOLPH: The same troubles as Paul. So I'm associate professor of molecular microbiology and immunology and pathology and a member of the USC Norris Comprehensive Cancer Center at the Keck

School of Medicine of the University of Southern California in Los Angeles, California. And my laboratory studies molecular carcinogenesis. And we're interested in mecha -- molecular mechanisms of carcinogenesis by chromium, nickel, arsenic, and polycyclic aromatic hydrocarbons. And I teach courses in that same area. And I've been appointed by Speaker the Honorable Anthony Rendon, Speaker of the California Assembly to the SRP.

CHAIRPERSON ANASTASIO: Great. Thank you, Joe.

Kathy.

PANEL MEMBER HAMMOND: I'm Kathy Hammond, a professor of environmental health sciences at the University of California, Berkeley's School of Public Health. And my research is in exposure assessment, occupational and environmental, and secondhand smoke. And often a lot of it is exposure assessment for epidemiology studies, but can also be just directly.

CHAIRPERSON ANASTASIO: Great. Thank you, Kathy.

Lisa.

PANEL MEMBER MILLER: There we go. Good morning, everybody. I'm Lisa Miller. I'm a professor in the Department of Anatomy, Physiology, and Cell Biology at the UC Davis School of Veterinary Medicine. And I'm also the Associate Director of Research at the California National Primate Research Center. So I specialist in large animal

models. My expertise is in respiratory immunology, that's my training. And my research program is focused on the pathological effects of environmental exposures on development of chronic respiratory disease, such as asthma.

CHAIRPERSON ANASTASIO: Great. Thank you, Lisa.

Mike.

PANEL MEMBER KLEINMAN: Good morning. I'm Mike Kleinman. I am a professor in the Department of Environmental and Occupational Health. I'm an inhalation toxicologist. And I direct the Air Pollution Health Effects Lab at UCI and primarily study the health effects of ambient air pollutants and products from electronic nicotine delivery systems, e-cigarettes, and hookahs.

And I was just reappointed by Speak Rendon, so I appreciate that and I'm happy to be part of the Panel again.

CHAIRPERSON ANASTASIO: Excellent. Thank you, Mike. It's good to have you join us again. That's great. So finally, me. I'm a professor in the Department of Land, Air, and Water Resources at UC Davis. And I study atmospheric chemistry.

So for today's meeting, we have two agenda items. The first we will be honoring Stan Glantz and talking about the Senate resolution he recently received. And

then the second item is from OEHHA. It's a review of chromium(III) water-soluble reference exposure level document.

We had originally thought we might do an AB 2588 item today, but we will not be doing that. So if you are interested in that item, we're hoping -- well, we're planning to do it at a future meeting, which we hope will be our October 15th meeting.

Okay. So with that, I'd like to move on to our first agenda item, the California Senate resolution for Dr. Stan Glantz.

Stan retired from the SRP in 2020. And he was part of the Panel for 34 years, which I'm guessing is a record, but I don't know for sure. So that's fantastic, Stan. Thank you for all your service.

The California Senate appointed him to the biostatistics position in 1986 and has recognized his achievements in a Members Resolution RN2150783, which reads as follows:

So Members Resolution by the Honorable Scott D. Wiener, 11th Senatorial District relative to commending Stanton A. Glantz, PhD.

"Whereas, Dr. Stanton A. Glantz, a professor at the University of California, San Francisco, School of Medicine is retiring after 34 years of dedicated service

to 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 1986 by the Senate Committee on Rules, Stanton Glantz has held continuous membership with the organizational body charged with evaluating the risk assessments of substances proposed for identification as toxic air contaminants by the California Air Resources Board, the Office of Environmental Health Hazard Assessment, and the Department of Pesticide Regulation, as well as the review of guidelines prepared by OEHHA, and;

"Whereas, having earned widespread recognition for his contributions to tobacco control policy development, evaluation, and implementation stemming from his research into the health impacts from tobacco smoke, Stan served as program director of the UCSF Center for Tobacco Control Research and Education Postdoctoral Training Program, supervising close to 100 fellows and graduate students over the course of his career and he has published more than 250 peer-reviewed articlesI and 40 editorials in his field of study, and;

"Whereas, additionally, Stan played a major role in the Scientific Review Panel's identification of

environmental tobacco smoke as a toxic air contaminant and the revisiting of environmental tobacco smoke in efforts to further reduce public exposure, which garnered international recognition and contributed to tobacco control policies across the globe, and;

"Whereas, furthermore, Stan contributed to the identification of particulate emissions from diesel fuel engines as a toxic air contaminant, which led to development of the Diesel Risk Reduction Plan by CARB to limit public exposure to particles emitted by diesel trucks and other diesel sources, and;

"Whereas, as the lead reviewer of numerous health risk assessment guideline documents drafted by OEHHA, Stan helped facilitate the establishment of hundreds of health values used in the preparation of health risk assessments for residents living near facilities emitting air toxics, and;

"Whereas, Californians across the state have greatly benefited from living in communities with significantly reduced concentrations of toxic air contaminants and Stanton Glantz has played an integral role in the evolution and implementation of California's Air Toxics Program;

"Now, therefore, be it resolved by Senator Scott D. Wiener that he commends Dr. Stanton A. Glantz for his

long and distinguished career of professional service and extends sincere best wishes for a rewarding and gratifying retirement".

Dated this 17th of day of March, 2021. Honorable Scott D. Wiener, 11th Senatorial District.

So, congratulations, Stan, and thank you very much for your service. Would you like to say a few words?

DR. GLANTZ: Sure. I mean, I have to say that being on the Committee was probably of all the public service I've done and committees I've been involved in has been, you know, probably the most gratifying. That's why I was willing to hang around for 34 years. And I think not only has the Committee, you know, done very important work and continues to do important work, but the people on the Committee have just been of uniform high quality. I've -- every single meeting I attended, I learned something.

And the people from the agencies from CARB and OEHHA, and, you know, at least in the last few years, the Department of Pesticide Regulation have been, you know, doing just first class work and being very responsive to the Committee. And it's just been a fantastic experience, you know. But I do think 34 years was enough.

The -- I mean, if there's anything that comes up that I can be of any help on, I'm happy to do that. I'm

glad to see that Karen Messer was appointed. I know Karen. She's does a great job. And I just hope the Committee continues its history of being a strong independent scientific voice in the deliberations over toxic air contaminants and the other issues that come before the Committee.

You know, one thing that's really impressed me over the life of the Committee is its independence. And the fact that during some administrations, there were political pressures brought to bear. I can remember specifically on lead and diesel. And the Committee was able to actually keep the process moving and prevent the politicization of some of these reports that come through the Committee.

And, you know, especially in -- you know, having lived through the Trump administration, the contrast between what the SRP was able to accomplish and what was going on at places like the federal EPA was quite dramatic.

So, you know, I thank you, you know, for all the time and all the things I've learned. And, you know, I'm very, very proud of the work, you know, that I've been able to contribute to working with the rest of the Committee. So keep up the good work.

CHAIRPERSON ANASTASIO: That's great. Thank you,

Stan. Would anybody like to say anything to Stan or about Stan?

I guess I'll start. I just -- Stan, I've always been so impressed with your work on the Panel in terms of our ability to get to really the heart of the matter it seemed like in every health guidance document we had. So I'd like to thank you for that and you definitely improved the Panel's work.

Kathy, would you like to say something?

PANEL MEMBER HAMMOND: Yes. Thank you, Stan. I have been so impressed with your work over the last few decades. Some of the time that we've been able to work together and I -- it's been an honor to serve on the Panel with you. And your service to the State through your SRP, but also to the entire global community through both the tobacco work, but the diesel work, is extraordinary. And I'm extremely grateful for both the work you've done and the path that you've laid for the rest of us.

Thank you.

CHAIRPERSON ANASTASIO: Thank you, Kathy.

Paul.

PANEL MEMBER BLANC: Yes, I did that.

Stan, obviously, you'll be sorely missed. And I also want to take this opportunity to mention the -- not just your work solo, but also your -- the dynamic duo of

you and John Froines often delivering the one-two punch, and provided me with a lot of cover to be -- to not seem too outrageous, because I had the two of you alongside.

CHAIRPERSON ANASTASIO: Great. Thank you, Paul.

Mike.

PANEL MEMBER KLEINMAN: Yes. Thank you.

Stan, when I came onto the Panel and I tried very insufficiently to take the role that John Froines left, who had been chairing, and I was sort of thrown into the deep end as the Chair of SRP for a while. And I really learned so much from working with you, and your advice, and also Paul's, keeping me on track, and getting me oriented into SRP and the great work that we do. So I really wanted to say how much I appreciated everything you've done and the sense of history that you bring, or brought, probably will still bring to the way our Committee has functioned and the kinds of results that we're able to provide.

So thank you.

CHAIRPERSON ANASTASIO: Thank you, Mike.

Karen.

PANEL MEMBER MESSER: I just want to thank Stan for his words of confidence. And I appreciate the huge gap that his absence is going to leave on this Panel and also the long history and the importance, and the good

work. And I just want to say I'll do my best to fulfill the biostatistician role, but -- I'll do my best.

And I know Stan's work. It seems like he's -- has a big footprint wherever he goes, because he's a leader in tobacco control and I know his work well from there.

So, Stan, thank you for your confidence and I'll do my best.

CHAIRPERSON ANASTASIO: Thank you, Karen.

We're looking forward to getting 34 years out of you as well. So I don't know if they told you that during your appointment.

Stan, could you show us the framed Senate Resolution that you received?

DR. GLANTZ: Yes, it's very big.

CHAIRPERSON ANASTASIO: It's beautiful. Yeah, that's fantastic. I'd like to thank Lori for really spearheading getting that done.

Yeah. Well, thank you very much, Stan. You are welcome to stay on and hear the discussion of chromium(III), but as a retired Panel member now, you're also welcome to turn off Zoom and go about your day. So congratulations

DR. GLANTZ: Yeah. Well, I've signed up to go help out at a food bank, so I'm going to -- since I didn't

read the chromium report, I think I'll leave you guys to your own devices. But again, I really -- I think the most important thing about the Panel has been, you know, the commitment to science, the commitment to staying above politics.

And, I mean, one last thing, and this is sort of for Karen's benefit, because she's a newbie, I think one of the real -- when I was first appointed to the Panel, you know, back in the Pliocene age, I was very frustrated that there was this firewall between the risk assessment and the risk management. It seemed to me, you know, frustrating that, well, gee, we're evaluating these compounds to see how dangerous they are or if they're dangerous, and why can't we say something about what to then do about the risks that we identified.

And the law really separates that from the risk management phase. And the thing I've really come to learn, especially in comparing what we do with comparable groups at the EP -- federal EPA is that separation really helps to de-politicize the communication.

And I recall a meeting that John Froines and I had with the Diesel Manufacturers Association when diesel was being considered, and their lawyers -- and they -- you know, they went on and on about how, you know, listing diesel as a toxic air contaminant would destroy the

California economy.

And what John said to them was, you know, that's not our problem. You know, our problem is to give the State the best assessment we can of the science and then let the -- you know, the decision of what to do with that is a political decision. And that's something that's up to the regulators. And so, you know, we -- you're really talking to the wrong people. And I think that separation is one of the really strong elements of the law and I think has led to some very, you know, important developments. I mean, diesel.

Another one was chlorpyrifos which we just finished dealing with a few months ago. And I just hope that the Panel will maintain -- I guess one other quick story. I think it was lead where a massive report came forward. I was one of the leads on that, I think. And the Panel approved almost the entire report, except for a couple of items and sent it back to the agency to deal with and then it just vanished. And it turns out that there was political pressure coming down from I believe it was Governor Wilson. And the Committee actually held a meeting, even though no report had been delivered. And the question to the Acting Director of OEHHA was where is the damn report?

And that forced it out into the open. And then I

remember making like an hour-long resolution, basically specifying that editing of the report to put it back to the way we had approved it, and, you know, except for the couple of things that had been updated.

And I think that that strength of the Committee, and the independence, and the willingness to stand up to the politicians and sometimes to bureaucracy has, you know, really contributed to the quality of the work that came out and the health of the people in California. And again, that's why I was willing to stay on it for so many years.

I have to say that I actually tried to retire three years earlier right after Trump got elected. And Lauren Zeise and Gina Solomon called me up and said are you crazy? Look who just got elected President.

And I agreed to stay another term. And I'm glad that they -- that they got me to do it, because it gave me the opportunity to contribute to the chlorpyrifos report, which I think was one of the most important things the Committee has done.

And again, for Karen's benefit, DPR came forward using one endpoint, where there was a lot of data. And we -- the Committee really pushed them to change the endpoint, even though there was less data, but it was more modern data and resulted in the acceptable exposure level

being cut by I believe it was a factor of 300, which eventually led to the decision to end its use in California.

And so this Committee has a lot of power. And it comes I think from the quality of the people on it and the commitment to, you know, just focusing on the science. So I, you know, commend everyone for that and I just hope you continue doing it. It's very, very important work, I think.

So with that, I'll go load food into bags and you can deal with the next report. And, you know, thank you all for inviting me to this meeting.

CHAIRPERSON ANASTASIO: Well, thanks, Stan. Again, really appreciate your 34 years of service. And I think what you've been talking about in terms of the history of the Panel and the strengths of the Panel is important for us to remember going forward, so we can continue to have the Panel be a vital part of science-based rulemaking in the state. Yeah.

Well, enjoy bagging food and --

DR. GLANTZ: Okay.

CHAIRPERSON ANASTASIO: -- we look forward to seeing you again.

DR. GLANTZ: Okay. Take care and have a good rest of the meeting.

CHAIRPERSON ANASTASIO: All right. Thanks, Stan.

DR. GLANTZ: Bye-bye

CHAIRPERSON ANASTASIO: Bye.

Okay. So that was our first agenda item.

Our second agenda item is a review of the OEHHA reference exposure level report for chromium trivalent (inorganic water-soluble compounds). Let's just call it water-soluble chromium(III). And this document is from OEHHA. It was released for public review and comment on January 8th, 2021. The document was then revised. And the Scientific Review Panel draft, dated April 2021, was sent to the full Panel for review and was also posted on OEHHA's website for the public.

Today, we'll hear a presentation from OEHHA staff on the proposed reference exposure levels for water-soluble chromium(III) and then we'll take a short break and then we'll have a Panel discussion about the document.

So I'd like to now introduce Dr. John Budroe, Chief of the OEHHA's Air Toxicology and Risk Assessment Section.

John.

(Thereupon a slide presentation.)

DR. BUDROE: Good morning. I, in turn, would like to introduce Dr. Rona Silva. She's the lead on the

trivalent chromium inorganic water-soluble compounds reference exposure levels document. She'll be making a presentation on the document and on the associated response to comments. And I'd like to note that her laptop doesn't have a working webcam, but her audio -- she will be presenting this slides and you will hear her audio.

Dr. Silva.

DR. SILVA: Hi. Sorry. Please let me know if you can see my screen. I'm sharing it now.

CHAIRPERSON ANASTASIO: Yes, we can see that, Rona.

DR. SILVA: Okay. Thank you.

Sorry. I'm having some trouble with my view here.

Okay. Good morning and welcome. My name is Rona Silva and I am a staff toxicologist in OEHHA's Air Toxics and Risk Assessment Section.

Chromium is one of the most common elements in the earth's crust and seawater. It's a naturally occurring heavy metal that can exist in oxidation states from negative two to positive six. However, chromium(III) is generally the most thermodynamically stable and prevalent state in the environment. Atmospheric chromium(III) can result from activities like mining and

refinement of ores, production of tanned leather or chrome plated materials, and conversion of airborne chromium(VI) species emitted during industrial processes.

Slide two.

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DR. SILVA: In the draft REL document posted online, we specified that chromium(III) compounds with a solubility greater than 100 milligrams per liter at 20 degrees Celsius were considered water soluble. Examples of water-soluble chromium(III) compounds include, but are not limited to, chromic chloride hexahydrate and basic chromium sulfate, both of which are used in leather tanning and chrome plating solutions.

Chromic chloride and basic chromium sulfate are general chemical names used to describe different chemicals with varying physical chemical characteristics.

Slide three.

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DR. SILVA: In this table, there are two examples of chromic chloride and four examples of basic chromium sulfate. Despite that some of these chemicals share a common name, they have different molecular formulas, molecular weights, solubilities, and identification numbers in the Chemical Abstract Service or CAS database.

Slide four.

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DR. SILVA: OEHHA is developing RELs for chromium(III), because it's sometimes used as a replacement for hexavalent chromium in chrome plating processes. There is potential for inhalation exposure to airborne chromium(III) among community members and off-site workers. There are currently no RELs for chromium(III). And chromium(III) inhalation toxicity data are available for REL development.

Slide five.

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DR. SILVA: Toxicokinetics of inhaled chromium(III) compounds are variable and influenced in part by aerosol characteristics like size and water solubility, as well as exposure parameters like inhaled dose rates. For water-soluble chromium(III) species, absorption of particles greater than five microns in diameter may occur as a result of deposition in the head or conducting airways with dissolution and translocation to blood through the mucus lining. Absorption of water-soluble particles less than five microns would likely be the result of deposition in the gas exchange region of the lungs, protein binding, and translocation, which could occur rapidly or after some time of retention in the pulmonary tissues.

Slide six.

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DR. SILVA: Upon absorption into blood, chromium(III) tends to partition into plasma versus the cells at a ratio of two to one and distribute to tissues, including the gastrointestinal tract, bones, kidneys, and liver within the first 24 hours.

In terms of metabolism: binding to biomolecules generally excludes chromium(III) from the intracellular space; cellular entry occurs via phagocytic or non-specific diffusion mechanisms; and three, intracellular chromium(III) can produce reactive oxygen species, which may decrease antioxidant capabilities and/or produce toxic responses.

Slide seven.

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DR. SILVA: Approximately 50 percent of the absorbed chromium is excreted in urine, five percent is excreted in feces, and the rest is deposited in deep body compartments like bone and soft tissue. Elimination is biphasic and occurs in a rapid phase representing clearance from blood and a slower phase representing clearance from tissues. Occupational exposure studies suggest that renal excretion of approximately half of the absorbed exposure dose takes less than 12 hours.

Slide eight.

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DR. SILVA: The 1979 study by Henderson et al., was used as the basis of the acute REL. Acute RELs are air concentrations at or below which infrequent one-hour exposures are not expected to result in adverse non-cancer health effects. In the Henderson study, Syrian hamsters were exposed via nose only inhalation to chromium(III) at 0, 0.55, or 15 milligrams per cubic meter as nebulized chromic chloride hexahydrate aerosol at 0, 2.8, or 77 milligrams per cubic meter for 30 minutes. There were four hamsters per sex treatment group and necropsy time point.

Slide nine.

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DR. SILVA: Necropsies occurred at two hours or 1, 7, or 21 days post-exposure. At these time points, lung tissue and bronchoalveolar lavage fluid, or BALF, were obtained for analysis of histopathology and quantification of inflammatory biomarkers.

No statistically significant differences were observed between the controls and the groups exposed at 0.55 milligrams of chromium(III) per cubic meter of air. Thus, we considered this concentration to be the no observable adverse effect level, or NOAEL.

Four critical effects were observed between the controls and the 15 milligrams of chromium(III) per cubic meter high exposure groups. First, on post-exposure day one, there was a statistically significant 75 percent increase in tissue acid phosphatase, or AP, activity, and, on slide 10 --

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DR. SILVA: -- bullet two, an increase of unstated magnitude in beta-glucuronidase activity. The AP and beta-glucuronidase enzymes are released by macrophages and inflammatory polymorphonuclear cells, like neutrophils. Enzyme release occurs during phagocytosis when cell membranes are damaged or when the cells are undergoing necrotic cell death.

In the Henderson study, the AP levels in the high exposure groups returned to near control levels on days seven and 21.

Bullet three. On post-exposure day 21, there was a doubling of tissue alkaline phosphatase, or ALP, activity. ALP is a general marker of lung tissue damage and alveolar type II cell proliferation and has been shown to control chemotaxis of inflammatory polymorphonuclear cells. Alveolar type II cells secrete poly -- excuse me -- pulmonary surfactant essential for proper lung function, and they proliferate when alveolar tissues are

damaged.

Bullet four, similar to what was observed in the tissues, there were statistically significant increase in -- increases in BALF AP activity at days 1, 7, and 21 post-exposure with variable levels of BALF ALP activity at days 1 and 12.

Slide 11.

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DR. SILVA: This is the start of our acute REL derivation. Using Haber's Law, we calculated a time-adjusted exposure, or (K), down here at the bottom. This -- in this equation, the multiplicancy, or concentration, is raised to the Nth power. We use a default N value of 1 to indicate equal dependence on concentration and duration of exposure for pulmonary effects. This first term C to the Nth power is multiplied by a second term T, representing the ratio of the study duration to one hour.

By using the 0.55 milligram per cubic meter chromium(III) concentration and the half hour duration from the Henderson study, we got a time-adjusted exposure concentration of 0.27 milligrams per cubic meter.

Slide 12.

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DR. SILVA: We determined a regional deposited

dose ratio, or RDDR, using the 1995 study by Jarabek. The RDDR is a ratio of fractional particle deposition in the lungs of animals to that in humans. The pulmonary RDDR of 0.35 indicates that humans would have greater pulmonary deposition than hamsters when breathing particles with the size distribution reported by Henderson et al.

By multiplying the RDDR by the time-adjusted exposure K from the previous slide, we calculated a human equivalent concentration, or HEC, of 0.10 milligrams per cubic meter. This was adjusted by a number of uncertainty factors to obtain the proposed acute REL. First, we used a lowest observable adverse effect level, or LOAEL, uncertainty factor of 1, since the point of departure is a NOAEL. The LOAEL uncertainty factor is abbreviated in the bottom of the slide as UFL.

Slide 13.

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DR. SILVA: We included an interspecies toxicokinetic uncertainty factor, or UFA-k, of 2 for residual toxicokinetic differences not addressed by the HEC approach and an interspecies toxicodynamic uncertainty factor, or UFA-d, of 3 for the lack of toxicodynamic data.

Slide 14.

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DR. SILVA: To address differences among humans,

we included an intraspecies toxicokinetic uncertainty factor, or UFH-k, of 3 for variability that may occur between human infants and adults, as well as an intraspecies toxicodynamic uncertainty factor, or UFH-d of 10 for the potentially increased sensitivity of children relative to adults.

In the study by Henderson et al., lung cell death and tissue damage were observed. Between infancy and adulthood, alveolar number, size, and complexity changed exponentially at times, so insults to the lungs during critical time frames can produce irrecoverable damage and stunted lung development. Potential for sensitization and asthma exacerbation were also considered in the designation of the UFH-d.

Slide 15 --

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DR. SILVA: -- shows a summary of our acute REL derivation starting at our point of departure up at the top, the NOAEL of 0.55 milligrams per cubic meter. The HEC was ultimately divided by a cumulative uncertainty factor of 200, shown closer to the bottom of the screen, and that was used to obtain the proposed REL -- acute REL of 0.48 micrograms per cubic meter.

Slide 16.

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DR. SILVA: This is the start of our discussion on the chronic and 8-hour RELs. The 1999 study by Derelanko et al., was used as the basis of the chronic and 8-hour RELs. Chronic RELs are air concentrations at or below which adverse noncancer health effects are unlikely to occur in the general human population exposed continuously over a lifetime. Eight-hour RELs are designed to protect against daily workweek exposures in off-site workers.

In the Derelanko study, rats were exposed via nose-only inhalation to air or chromium(III) at 0, 3, 10, or 30 milligrams per cubic meter as basic chromium(III) sulfate at 0, 17, 54, or 168 milligrams per cubic meter for six hours per day, five days per week, over a total of 13 weeks.

The pH of the basic chromium(III) sulfate was 2.8, and there were four to five rats per sex, treatment group, and necropsy time point.

Slide 17.

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DR. SILVA: Necropsies occurred immediately after the last exposure or 13 weeks post-exposure. At these time points, blood, BALF, urine, sperm, and various organ tissue samples were collected. OEHHA designated the 3 milligram per cubic meter chromium(III) concentration as

the LOAEL.

Critical effects included increased lung weight relative to body weight in males due to granulomatous inflammation, type II cell hyperplasia, and histiocytosis or excessive tissue macrophages in lymphoid tissues.

Slide 18.

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DR. SILVA: Here, you can see that we actually looked at multiple different endpoints with the United States Environmental Protectioncy -- Protection Agency's Benchmark Dose Software. The viable benchmark dose, or BMD, results for male rat lung weights are highlighted at the top of the table in blue with the benchmark dose response, or BMR, of 0.869 milligrams per cubic meter, and it's 95 percent lower confidence interval, or BMCLSD of 0.656 milligrams per cubic meter.

The BMR is one standard deviation from the control mean. And for public health protection OEHHA used the BMCLSD as the point of departure for the chronic and 8-hour REL derivations.

Slide 19.

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DR. SILVA: This slide shows the model that we obtained from the BMD analysis. The BMR and BMCLSD are shown as yellow and green vertical lines respectively at

the left side of the graph. And the dose response data points that we used are shown along the blue curve here.

Slide 20.

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DR. SILVA: This is the start of our chronic REL derivation. This time our time-adjusted exposure, or C average, shown at the bottom -- the bottom slide here, was calculated by multiplying the BMCLSD by 6 out of 24 hours and five out of seven days. These latter two terms represent the number of hours in a day and days in a week that rats were exposed in the Derelanko study. C average was calculated at 0.117 milligrams per cubic meter.

Slide 21.

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DR. SILVA: An RDDR of 0.3 shown at the top of the slide was determined using a multiple path particle dosimetry model. We multiplied this by C average to get a HEC of 0.04 milligrams per cubic meter. And as with the acute REL derivation, the HEC was adjusted by several uncertainty factors to obtain the proposed chronic REL.

First, a LOAEL uncertainty factor of one was used because our point of departure, or POD, was a BMCLSD. A subchronic uncertainty factor, or UFs, of three was also used to account for the 13-week study duration.

Slide 22.

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DR. SILVA: We included an interspecies toxicokinetic uncertainty factor, or UFA-k, of 2 for residual toxicokinetic differences not addressed by the HEC approach, and an interspecies toxicodynamic uncertainty factor of 3 for the lack of toxicodynamic data.

Slide 23.

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DR. SILVA: To address differences among humans, we included an intraspecies toxicokinetic uncertainty factor, or UFH-k, of 3 for variability that may occur between human infants and adults, as well as an intraspecies toxicodynamic uncertainty factor of 10 for the potentially increased sensitivity of children relative to adults and possible asthma exacerbation.

Slide 24.

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DR. SILVA: This shows a summary of our chronic REL derivation starting at our point of departure, which was the benchmark concentration of 0.656 milligrams per cubic meter. Our HEC was ultimately divided by a cumulative uncertainty factor of 600 to derive the proposed chronic REL of 0.6 micrograms per cubic meter shown at the bottom of the slide.

Slide 25.

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DR. SILVA: The chronic and 8-hour REL derivations are mostly the same, except for the C average concentration that's shown in the middle of the slide. The 8-hour calculations are shown on the right-hand side and the 8-hour REL calculation of C average, there is another multiplier of 20 over 10. And this is based on the assumption that half of the 20 cubic meters of air breathed in any 24-hour period is breathed while active at work.

Inclusion of this multiplier brings the 8-hour C average to 0.234 milligrams per cubic meter, the HEC to 0.07 milligrams per cubic meter, and the proposed 8-hour REL to 0.12 micrograms per cubic meter.

Slide 26.

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DR. SILVA: This is a summary of our 8-hour REL derivation in which the HEC of 0.07 milligrams per cubic meter is adjusted by a cumulative uncertainty factor of 600 to achieve the proposed REL of 0.12 micrograms per cubic meter.

Slide 27.

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DR. SILVA: OEHHA found no studies concerning the

effects of chromium(III) exposure in children. However, it is likely children would experience similar health effects as adults possibly to greater severity. In view of, one, the potential of chromium(III) to produce immune sensitization and allergic asthma, and two, the higher susceptibility of children to these impacts, especially during critical windows of development, OEHHA considers chromium(III) to be a toxic contaminant that may disproportionately impact children.

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DR. SILVA: Slide 28, shows a summary of all of our proposed RELs: the acute REL of 0.48 micrograms per cubic meter; the 8-hour REL of 0.12 micrograms per cubic meter; and the chronic REL of 0.06 micrograms per cubic meter.

So slide 29

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DR. SILVA: At this point in the presentation, if there are any questions on the REL derivation, we can take those now.

CHAIRPERSON ANASTASIO: So we're going to hold the main Panel discussion for after a short break, but are there any kind of specific questions about anything that Rona said in her presentation?

Thank you, by the way, Rona, for your

presentation. Appreciate that.

DR. SILVA: Thank you.

CHAIRPERSON ANASTASIO: Okay. I don't see any kind of small-scale questions. So what we're going to do we're going to take a 10-minute break. I've got 10:23 on my computer. So let's reassemble at 10:33 and then we'll start with the leads asking questions of OEHHA and then we'll go through the rest of the Panel. Okay. So --

PANEL MEMBER BLANC: Cort --

CHAIRPERSON ANASTASIO: Yes, Paul.

PANEL MEMBER BLANC: -- just one quick process question. Normally, at this point, the OEHHA presenter would say something about their response to public documents --

CHAIRPERSON ANASTASIO: Good point, right.

PANEL MEMBER BLANC: -- comments. Wouldn't that make sense to cover now rather than --

CHAIRPERSON ANASTASIO: Yes. That's a very good point. Rona, do you have a response to the set of comments you received?

DR. SILVA: We do. We had set up the presentation so that we could include comments at this part of questions. But I am -- I'm ready to go on with the responses -- the comments and responses now, if the Panel wants me to do that.

CHAIRPERSON ANASTASIO: Yeah. Let's do that, so that we can consider that in our Panel discussion later as well. Okay. So cancel the break. Sorry, everybody.

(Laughter.)

CHAIRPERSON ANASTASIO: Sit back down. Coffee is going to have to wait. Rona, if you could please tell us the comments you received and OEHHA's response to them.

DR. SILVA: Okay. Sure.

So slide 30.

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DR. SILVA: During the public comment period, OEHHA received comments from the Specialty Steel Industry of North America, or SSINA, regarding the draft REL document, or document hereafter, that was released on January 8th, 2021. Those comments are addressed in the subsequent slides.

Slide 31.

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DR. SILVA: Comment one. The proposed draft RELs are inapplicable to insoluble elemental chromium(III). OEHHA must revise the scope of the draft RELs accordingly.

Response one. OEHHA has added to the document an explicit statement that the RELs are not applicable to water-insoluble chromium(III) compounds or elemental metallic chromium, also known as Chromium(0). OEHHA

further states the chromium, or Cr(III) abbreviation, sorry, used in the draft is meant to represent bound and unbound forms of trivalent chromium as the RELs are applicable to the chromium(III) ion.

Slide 32.

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DR. SILVA: Comment two. The allergic sensitization and asthma risk evaluation is based on studies that:

One, involved individuals first sensitized by exposure to chromium(VI) before being exposed to chromium(III); and two, were performed several decades ago when study methodologies were significantly less rigorous and there was much more widespread environmental exposure to chromium(VI).

The relevance of these studies to a current risk evaluation for chromium(III) is questionable.

Additionally, nickel is a known sensitizer mostly not discussed in the document. The patient in the study by Novey et al., 1983, exhibited an acute drop in spirometric values and exacerbation of symptoms upon inhaling fumes from a nickel sulfate versus control solution.

Slide 33.

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DR. SILVA: Response two. In the later studies by Novey et al., 1983, and Park et al., 1994, it is not at all clear which chromium species caused the initial sensitization in the human subjects. With regard to nickel exposure, human and guinea pig studies failed to find cross-reactivity reactions between chromium and nickel. Concomitant allergies to chromium and nickel could be explained by their co-occurrence during the sensitizing exposures.

Control and comprehensive guinea pig studies by Gross et al., in 1968 clearly showed in at least five different experiments that allergic sensitization to a water soluble chromium(III) compound can occur independent of prior exposure to chromium(VI) species. This was especially true if skin permeability is increased by physical or chemical means prior to contact.

Slide 34.

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DR. SILVA: Comment three. The estimated prevalence of chromium(VI) allergy in the California population is based on studies that are outdated, involve small cohorts, and/or reflect unfounded assumptions. OEHHA incorrectly states a prevalence of 0.08 percent would account for approximately 316,456 Californians based upon the most recent California populous -- population

estimate of 39,557,045 than the U.S. Census Bureau. The math is incorrect. A prevalence of 0.08 percent equates to approximately 31,646 Californians.

Slide 35.

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DR. SILVA: Response 3. The 2012 ATSDR toxicological profile for chromium provided the estimate of 0.08 percent to seven percent for chromium sensitivity in the general U.S. population. It's the most recent prevalence estimate found by OEHHA and it did not cite the source of this information.

Therefore, OEHHA summarized studies which may have been used to derive the prevalence estimate. Given chromium(VI) to chromium(III) cross reactivity, the 0.08 percent to seven percent range was used by OEHHA to calculate a worst-case estimate of the chromium(III) allergy prevalence in California.

We thank the SSINA for the math correction. The revised document reflects the corrected lower-bound prevalence estimate of 31,646 Californians.

Slide 36.

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DR. SILVA: Comment 4. The rodent toxicity studies have significant methodological problems and OEHHA conflates insoluble elemental chromium(III) results with

findings relevant to water-soluble chromium(III) compounds only.

In the 1979 study by Henderson et al., nebulized chromic chloride hexahydrate aerosol concentrations of 0, 2.8, or 77 milligrams per cubic meter were used. OEHHA identifies the LOAEL at 77 milligrams per cubic meter, then uses the next lowest dose, 2.8 milligrams per cubic meter, as the NOAEL. However, the NOAEL may be substantially higher, given the significant differences in dose.

Further, OEHHA applies the results of this study to insoluble chromium(III), though the study was conducted on soluble chromic chloride hexahydrate. In the 1999 study by Derelanko et al., some of the effects may have been related to the acidity of the tested chromium(III) salt.

Slide 37.

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DR. SILVA: Response 4. The RELs do not apply to insoluble chromium(III) compounds, as mentioned in OEHHA's response to comment 1. With regard to the Henderson et al., 1979 study, there are no data indicating the 2.8 milligram per cubic meter concentration should not be considered as the NOAEL. Use of a NOAEL is preferable to use of a LOAEL when deriving a REL. The 2.8 milligram per

cubic meter NOAEL is an appropriate point of departure for derivation of the acute chromium(III) REL. Calculations performed with the 2.8 milligram per cubic meter NOAEL resulted in a more health protective draft acute REL value of 2.5 micrograms per cubic meter. Calculations performed with the 77 milligram per cubic meter LOAEL, the same time-adjusted exposure and HEC adjustments and all of the same uncertainty factors, except for the LOAEL uncertainty factor would yield an acute REL of 11 micrograms per cubic meter.

Slide 38.

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DR. SILVA: OEHHA has revised its public comment calculation of the acute REL to account for the percentage of chromium(III) in the aerosol.

The chromic chloride hexahydrate concentrations of 0, 2.8, or 77 milligrams per cubic meter were converted by OEHHA to chromium(III) equivalent concentrations of approximately 0, 0.55, or 15 milligrams per cubic meter, which accounted for the 28 percent fraction of chromium. Use of metal equivalent concentrations is supported by OEHHA's 2012 REL for nickel and the recent 2020 cancer evaluation for cobalt.

Use of the 0.55 milligram of chromium(III) per cubic meter concentration as the NOAEL, along with all of

the adjustments entailed in the document, yielded a rise -- yielded a revised acute REL of 0.48 micrograms per cubic meter.

Slide 39.

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DR. SILVA: With regard to the Derelanko et al., 1999 study used to derive the draft chronic and 8-hour RELs, the true impact of the aerosol pH is unknown to OEHHA and the study authors due to factors such as the relative concentration of acidic sulfate and ammonia, which were mentioned in section 6.3 of the document but not mentioned in -- or measured in the study.

OEHHA does not believe use of basic chromium sulfate by Derelanko et al., in their 1999 study, represents a methodological problem. Rather, the observed responses to basic chromium sulfate are representative of some of the more severe health impacts possible with repeated exposure to inorganic water-soluble chromium(III) compounds.

As stated in the document, basic chromium sulfate has been found in chrome plating bath solutions. It is also used by leather tanning and khaki clothes dyeing operations and used to produce other chromic compounds.

Slide 40.

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DR. SILVA: Resulting air emissions of basic chromium sulfate from such operations are relevant to the Hot Spots Program, especially since chromium(III) has already been identified as a toxic air contaminant through the listing of chromium and chromium compounds as hazardous air pollutants.

It should be noted that the chronic and 8-hour draft RELs have been recalculated based upon new BMDS modeling using the chromium(III) concentration equivalents of 0, 3, 10, and 30 milligrams per cubic meter from the Derelanko et al. study.

Slide 41.

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DR. SILVA: Comment 5. The derived RELs are based on inaccurate selection of a LOAEL. Erroneous application of results from water-soluble chromium(III) compounds to insoluble elemental chromium(III), and inappropriate uncertainty factors.

Response 5. Most of this comment was addressed in OEHHA's responses to comments 1 and 4 above. The uncertainty factors assessed in the draft RELs were based upon guidance from OEHHA's 2008 technical support document, or TSD, and are in alignment with previously published RELs and data available at this time.

With regard to the acute REL, first, a LOAEL

uncertainty factor, or UFL of 1, was chosen due to the mild effect, which produced no statistically significant changes in enzyme levels at 0.55 milligrams of chromium(III) per cubic meter. And it was consistent with the severity level of 0 to 1. This is the lowest UFL that can be assigned.

Slide 42.

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DR. SILVA: Bullet 2. A toxicokinetic interspecies uncertainty factor, or UFA-k, of 2 was used to account for any residual toxicokinetic differences between the non-primate animal model and humans that were not addressed by the HEC approach.

According to OEHHA's 2018 TSD, the HEC accounts for only a portion of the UFA-k, leaving a residual value of 2 that should be assessed. A UFA-k of 2 is the lowest value that can be assigned.

Bullet 3. A toxicodynamic interspecies uncertainty factor, or UFA-d, value of 3 was assigned to account for the lack of data on toxicodynamic interspecies differences between the hamster model and humans. A UFA-d of 3 is the default when using the HEC approach.

Slide 43.

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DR. SILVA: Bullet 4. A toxicokinetic

intraspecies uncertainty factor, or UFH-k, of 3 was included to account for variability that may occur due to lower protein binding; hepatic and renal clearance; and metabolic enzyme activity abundance; and expression in infants versus adults.

Bullet 5. A toxicodynamic intraspecies uncertainty factor, or UFH-d, of 10 was added in consideration of potentially increased sensitivity of children relative to adults during critical developmental windows. Potential for sensitization and exacerbation of asthma were also considered in designation of the UFH-d. The uncertainty factors were mostly the same in the acute, chronic, and 8-hour REL derivations apart from the inclusion of a subchronic uncertainty factor or UFs of 3 in the latter two. The UFs of 3 was assessed according to OEHHA's 2008 guidelines to account for the 13-week study duration, which was approximately 12 percent of the estimate lifetime of a rat.

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DR. SILVA: Slide 44 marks the end of our presentation. We thank you for your attention and welcome your comments at this time.

CHAIRPERSON ANASTASIO: Thank you very much, Rona.

So now we'll take our 10-minute break and then we

will reconvene and do the Panel discussion. So I have 10:38. So we'll reconvene at 10:48.

Thank you, everyone.

DR. SILVA: Thank you.

(Off record: 10:38 a.m.)

(Thereupon a recess was taken.)

(On record: 10:51 a.m.)

CHAIRPERSON ANASTASIO: Welcome back, everyone, from our short break. We'll now go to Panel discussion of the water-soluble inorganic chromium(III) reference exposure level document. And the leads for this were Joe Landolph and Paul Blanc, so we'll start with them. Joe, would you like to begin.

PANEL MEMBER LANDOLPH: Yeah. First off, thank you for letting me review this document. It came out on the authority of the Director Lauren Zeise and the author Dr. Silva, and the technical reviewers Daryn Dodge, John Budroe, and David Siegel. And John is Chairman of Air Toxics and Risk Assessment.

And it's clear a lot effort went into this document. It's a very thick document, but it's concisely written. And I appreciated that. So I thought it was a very well researched and well written document. It covered the necessary scientific literature in the field on water-soluble trivalent chromium compounds.

To discuss, the whole document is appropriately complete and critical and the document was written in a very clear manner. It's also organized very well. And the summary was written in a very clear manner, appropriately concise, lays out why the document was created due to a statutory requirement that describes the methodology for deriving acute, chronic, and 8-hour reference levels in this case for water-soluble chromium(III) compounds. And sticking with the water soluble, it was very smart on OEHHA's part and the author's part. And it described the RELs and valence states of chromium and everything, so it's very complete.

And they say that potential cancer impacts of chromium were not explored -- chromium(III) were not explored in the present document and OEHHA has not developed unit risk of cancer potency factors for chromium(III) compounds and that's because IARC classified chromium(III) compounds as Group 3 agents, i.e., not classifiable as to the carcinogenicity in humans due to inadequate evidence of carcinogenicity. And this is appropriate.

And I've also read the criticisms of this document on RELs from the company SSINA, the Specialty Steels Industry and I found the answers and rebuttals from OEHHA to these agency's comments and criticisms were very

appropriate.

The Director of OEHHA, Lauren Zeise, the author, Rona M. Silva, and the technical reviewers should all be congratulated on the production of this comprehensive and critical document, which is overall of high quality, both in the scientific matters considered in the inhalation of soluble chromium(III) compounds and the excellent and clear manner in which the document was written and led to the derivation of the soluble chromium -- insoluble -- soluble chromium(III) compounds.

The authors came to a number of conclusions with the RELs that Dr. Silva listed. And I thought that the methodology by which they arrived at that was correct and I had no criticisms of that.

Specific comments. I read through every section, at least three times and I like the sections on physical and chemical properties, production, major uses, measurements, and occurrence, production, major uses, measurement of airborne chromium, and there are about ten more sections. And I thought the derivation of the chromium acute reference exposure levels was straightforward as presented here and by Dr. Silva on her slides.

I asked them to please state what the abbreviation of RDDR stands for in the document, which is

the regional deposited dose ratio and explain it briefly. Otherwise, the derivation of the uncertainty factors, plus the calculation of the REL for soluble chromium(III) compounds, plus the derivation of the uncertainty factors measuring 200 for the acute and 600 for the other two RELs straightforward as presented. Let' see. And what else do I have to say.

And I looked through the principal studies that they used. And those were appropriate to use as NOEL. That was all fine.

And critique overall, the document is well written, clearly written, takes proper account of the literature on the toxicology of water-soluble chromium(III) compounds and reviews the literature critically indicating whether chromium(III) is a required essential nutrient and handles this latter issue carefully and appropriately as it deserves, since the issue is not completely settled.

All the methods used to generate the RELs in this document appear appropriate as the choice for uncertainty factors, resulting in appropriate cumulative uncertainty factors, and therefore appropriate RELs, which should be health protective.

The authors, and the reviewers, and the Director of OEHHA are all to be congratulated on a thorough job,

well done in composing this document.

And so it's unusual that I get a document that I don't put a lot of red on, but this one was pretty clean, so I didn't have to do that. I congratulate the author, the Director, and Dr. Budroe, the Chief of Air Toxic and Risk Assessment, and the other reviewers on a pretty good document. It looks pretty solid to me. And I work in the area of chromium(VI) and chromium(III), so I know this literature pretty well.

CHAIRPERSON ANASTASIO: Great. Thank you very much, Joe.

Paul, comments.

PANEL MEMBER BLANC: I want to start off with a question to the leadership. As Joe said, the introduction states their regulatory requirement to derive these documents essentially for anything which is a toxic air contaminant. But since we've spent so much time on this Panel discussing priorities, I'm wondering why this document was a priority.

DR. BUDROE: Can I answer that question, Dr. Blanc?

PANEL MEMBER BLANC: Yeah, I think you're the right person to answer it.

DR. BUDROE: Okay. This -- trivalent chromium was picked as a priority because California Air Resources

Board has been suggesting to -- and the various California air districts have been suggesting to chrome plating facilities, that where possible, they move from using hexavalent chromium with its associated cancer risk, moving from hexavalent chromium in chrome plating facilities to trivalent chromium. And that's a good move, but we want to have some kind of at least non-cancer health values available for the districts to use to be able to put into place for doing hot spots facility health risk assessments.

And we didn't want to suggest that they switch over from hexavalent chromium to trivalent chromium without having any kind of idea of what the toxicity of trivalent chromium was.

PANEL MEMBER BLANC: Would it not be possible to state that in the overview or the introduction in some way that would not be regulatorily compromised or politically compromised? It seems -- it would have been helpful for me to see that stated more explicitly, because to tell you the truth, I couldn't figure out why this was a priority.

DR. BUDROE: Okay. We could add that to the introduction of the document.

PANEL MEMBER BLANC: But if you're going to do that, I would also think you would want to say something about nonchromium-dependent plating options or anodizing

options, let's just say. There's a nice document that you don't cite, which was a U.S. Army public health center toxicologic review from 2000. Did you happen to see that? It's easily accessible on the Internet. And it's relevant, because it has a nice discussion of trivalent chromium and why despite the -- one of these major methods, which is a sulfuric acid, tartaric acid anodizing method is chromium(VI) free, there are post-treatment sealants that have chromium(III) in them.

So just be -- and so that would serve two purposes. That's a product that's probably going to come into more use and would be -- should be described specifically I think in your industrial uses section specific to chromium(III).

DR. BUDROE: Okay. We can get that document and look at it and see what would be appropriate to add.

PANEL MEMBER BLANC: It's easy -- it's easy to find it. If you -- if you took -- and if you don't -- if you have problems, send me an email.

DR. BUDROE: Okay. We'll do that.

PANEL MEMBER BLANC: But this sealant is called Chemeon, C-h-e-m-e-o-n.

DR. BUDROE: Okay. We will look at that.

PANEL MEMBER BLANC: Yeah. The other thing I might say just in a more global sense is the title of this

document, which is chromium tri -- comma trivalent parentheses inorganic water-soluble compounds. You know, you've done that explicitly to make clear that you're not talking about insoluble compounds, right? That's why it's titled the way it is.

DR. BUDROE: Also, that it's distinction from hexavalent chromium.

PANEL MEMBER BLANC: Well, yeah, I know. That --

DR. BUDROE: And so we're being consistent with the listing for hexavalent chromium also. We're kind of trying to not -- we're trying to stay in synch with the way we've described hexavalent chromium.

PANEL MEMBER BLANC: Well, the -- why? Hexavalent chromium is water soluble. Is there an insoluble form of hexavalent chromium? Does that have the paren -- parenthetic statement in it?

I'm talking about the --

DR. BUDROE: I'd have to --

PANEL MEMBER BLANC: I'm talking about the parenthetic title comment, because my only -- my only comment would be that the naive person reading that title would think that what you're saying is that what's in parentheses is a synonym for chromium trivalent, but it's a subset of chromium trivalent. In other words, this document is chromium trivalent, but inorganic water

soluble compounds only.

DR. BUDROE: Okay. Well, the listing is designed to be similar to past listings that we've done where solubility -- compound solubility has been an issue, this is the way we've done it.

PANEL MEMBER BLANC: With a parenthetic?

DR. BUDROE: Right? So the listing (inaudible) is consistent.

PANEL MEMBER BLANC: Okay. So you -- what you might want to do is also think about making sure that in your summary -- introduction summary, which starts off the document the summary, you know, starting on page -- Appendix D1 -- I'm sorry Appendix I, page I. Just in there you also -- where you do say you're going to be talking about soluble compounds that, you know, you make -- if there's a way making clear that -- what that parenthetic means that I just suggest it.

I also suggest in the -- in the summary that you make clear that chromium(III) is chromium plus, plus, plus, you do that later in the document. But again, I know you're so knee deep in this, it's hard to believe that anybody would be confused on that matter.

DR. BUDROE: Okay.

PANEL MEMBER BLANC: Because I made a note to myself, as I read it, just to make sure that that is what

we're talking about.

DR. BUDROE: Okay. We'll clarify that.

PANEL MEMBER BLANC: And frankly, somewhere else I wouldn't clutter the summary with it, it wouldn't be so bad to have a figure -- this should warm Joe's heart. He always likes figures that just shows the back and forth between oxidized and reduced chrome(III) and chrome(VI) showing that, for example, heat or in the presence of oxygen drives chromium(III) to chromium(VI). You don't actually ever explicitly show what it is that reduces chrome(VI) to chrome(III). You say it happens atmospherically, but you don't say explicitly why it happens. Is it just an equilibrium or is there something about sunlight or -- I mean, that's a major point in where exposure occurs, right, if there's chrome(VI) in the atmosphere and it gets converted to chromium(III) in the atmosphere.

DR. BUDROE: Okay. Well, we can -- we can clarify that in the document. I mean, you know, the real point of the listing is for exposure to the community or off-site workers of compounds that are deliberately -- that are inherently trivalent chromium compounds. So it would have less to do with atmospheric transformation of say a hexavalent chrome -- chromium compound to trivalent chromium compound.

PANEL MEMBER BLANC: Why would that be, because wouldn't it be -- the exposure to the population would be by either source.

DR. BUDROE: Because -- the methodology that's used to model the exposures and produce the risk estimates doesn't include that, so it's outside the scope of the methodology.

PANEL MEMBER BLANC: Joe, could you -- maybe could you comment here?

You're muted, Joe.

You're muted.

PANEL MEMBER LANDOLPH: Yeah, sorry. What did you want about the atmospheric reduction? Was that what you --

PANEL MEMBER BLANC: Yeah, and the idea that it would be helpful to show a little figure showing the back and forth between oxidized and reduced, if that's critical to a lot of the discussion.

PANEL MEMBER LANDOLPH: Yeah. I think it is important. I can make -- I'm going to make two suggestions when I send me handout back to John and Lori. The first one is it might be worth citing a paper that came out of our lab years ago, where for mutagenesis and toxicity, the chromium(VI) goes like this on a log scale. And for toxicity in chromium(III) is like a thousandfold

less toxic. And the same thing for it's a thousandfold less mutagenic.

The other thing is I was a little bit confused about chromium(III) and radic -- oxygen radical generation that was mentioned in the document. Maybe that's something new. It was from a paper you guys cited by John Wise, I think. So I'm very familiar with, you know, chromium(VI) going to (V), to (IV), to (III). And (III) interestingly makes a coordinate covalent complex with DNA and then that has to get repaired and you get mutagenesis during the misrepair.

And then you also get some chromium(VI) and (V), you get a generation of an electron which goes to oxygen, which makes superoxide, two of those make hydrogen peroxide. That oxidizes DNA and gets misrepaired. And then you also get the reduction of hydrogen peroxide which turns it into hydroxyl radical and hydroxyl ion and that oxidizes DNA basis. So I'm very familiar with that for chromium(VI).

I guess for chromium(III) I'm wondering if the instances you referred to were (III) getting oxidized up to (V) or (VI), and then doing this thing. Do you have a comment on that, John.

DR. BUDROE: I do not. I'd have to go back and look at the citation.

PANEL MEMBER LANDOLPH: Okay.

DR. BUDROE: Rona.

DR. SILVA: Yeah. So that citation by Wise et al. was actually a book. And they had a section that was on -- that discussed the Haber-Weiss reactions of chromium(VI) and chromium(III). But I can go through and look at that to see if whether there's anything further that I can add to the document to clarify how those reactions take place, intracellularly.

PANEL MEMBER LANDOLPH: Yeah, that would be good, because I'm used to thinking of chromium(III) thermodynamically dead-end product which will bind to DNA, but extracellularly is not important, because it just comes out in the urine. Intracellularly, it's important, because it binds to DNA, but I've not heard about it generating oxygen radicals before, whereas (VI) is well, well known to do that.

DR. SILVA: Right. There actually quite a few studies that were done in vitro that looked at oxidant generation -- sorry, reactive oxygen species generation by chromium(III), and also the associated toxic responses. I didn't kind of go into that, but, yeah, I'll take your point and revise that section a little bit more to make it clearer.

PANEL MEMBER LANDOLPH: And I'll put my comments

into my review and send them to you also, so you'll have it.

DR. SILVA: Thank you.

PANEL MEMBER LANDOLPH: My pleasure.

PANEL MEMBER KLEINMAN: This is Mike. I just wanted to point out with regard to the atmospheric reactions, it's actually in the document in the section on measurement of airborne chromium. But chromium(VI) reacts with organic molecules, including diesel particulates that have organic coatings and secondary organic aerosols. And the chromium is a strong oxidizer. It oxidizes these compounds and in the process becomes reduced. So that's sort of the transport. So chromium(VI) does reduce to chromium(III). And then in the presence of free radicals, chromium(III) can be oxidized up.

The thing with chromium(VI) is that it's in anionic form and it can enter through cell membranes and nuclear membranes. So chromium -- hexavalent chrome can penetrate through the nuclear membrane. And then the hexavalent is reduced internally in the nucleus to chrome(III) and then goes on to react with DNA.

So that's partially, yeah, the rationale for the carcinogenicity of chrome(VI). And chrome(III) does not have the ability to go across, because it's cationic. It doesn't cross the cell membrane directly and that's why it

ends up being excreted more readily.

PANEL MEMBER BLANC: So I would say -- to me, that's just a further argument for the potential utility of such a figurative display of the pathways of oxidation and reduction. And it's a good segue also to another general point, so this isn't textual, per se, except that I think it could be better stated in the summary -- the two-page summary at the beginning -- the two-page narrative summary, which is the sort of elephant in the room of sensitization to chromium(VI) and cross-reactivity with chromium(III).

So it's stated in the summary, chromium(III) can cause sensitization and induction of asthma de novo, that people who have asthma -- allergic asthma with coughing, wheezing, difficulty breathing, and decrements -- with short-term exposure, I was completely unclear what the point of separating number one and number two. And it would seem to me that the point you're -- the document is more convincing on is that persons who have been sensitized to either chromium(VI) or chromium(III), the former being very well documented and inarguable, and sensitization to chromium(III) -- initial sensitization to chromium(III) being hard to prove, but it's very -- I think you establish it well that there would be anticipated responses to someone -- cross-sensitivity to

chromium(VI), if somebody's exposed to chromium(III).

And then you -- but you -- then you go on to say this document however is not going to -- realizes that it's not going to be looking at standards which are protective against asthmatic responses in people who are sensitized.

So those things in combination are -- present the possibility for confusion in the reader as to what is really meant and what the purpose of this is.

But let me ask the first part first. Do you disagree with the statement that it's, I think, convincing that there is enough cross-sensitivity that if you challenge someone who had asthma to chromium(VI), they would be likely to respond to chromium(III), but that you don't really have data showing anybody gets sensitized to chromium(III) or do you think your data support -- that strongly support sensitization to chrome -- primary, original sensitization to chromium(III)?

From a public health point of view, I actually don't think you have to show that, if people are going to respond to chromium(III) if they've been sensitized to chromium(VI). But I'm just wondering what you think you've shown in the document.

DR. SILVA: I think -- do you mind just pointing me to where --

PANEL MEMBER BLANC: I'm looking at --

DR. SILVA: I think --

PANEL MEMBER BLANC: I'm looking at summary page ii.

DR. SILVA: Okay.

PANEL MEMBER BLANC: And where it says, "Inhalation exposure to water-soluble chromium(III) compounds has been shown to cause adverse respiratory effects in animals and humans, including but not limited to sensitization and induction of asthma with repeated exposure; allergic asthma with coughing, wheezing, difficulty breathing; and decrements in lung function with short-term exposure", and then 3, the tox effects that actually generate your exposure limits, your RELs.

DR. SILVA: And so --

PANEL MEMBER BLANC: One and two have no impact on your RELs whatsoever, except in one way I'm going to come back to in a minute.

And so two things. One, I don't understand what the difference is between inducing asthma and then having an asthmatic effect, numbers one and two. Those are related to the same thing.

DR. SILVA: Okay.

PANEL MEMBER BLANC: But what are the studies that you believe show that chromium(III) specifically

induces asthma? You've shown that you -- that the people who are sensitized presumably to chromium(VI) have responded to challenges with chromium(III) in the one study where it's actually been done.

DR. SILVA: Yeah, I think that -- is my -- I'm hearing a little bit of feedback. Am I sounding okay to you guys?

DR. BUDROE: Yes.

PANEL MEMBER BLANC: You sound okay to me.

DR. SILVA: Okay. So I think that part of the issue is that we had initially included another study that we took out at a later date, because it was -- it was sort of deemed to be inethical[SIC]. And I think that this port of the -- I probably forgot to revise this part of the REL document when we took that out.

But in answer to your question, so some of the studies, the earlier studies, and this is what I had responded to in the -- to the SSINA. While some of the studies do require that chromium(VI) exposure happened before sensitization, there are the two studies the Novey and Park studies where we're not sure whether chromium(VI) was what caused sensitization.

And you're right, I agree, we don't have a study that conclusively shows that chromium(III) causes sensitivity in humans, but there are those comprehensive

guinea pig studies that were done by Gross where they do show -- I know that in the document there's a really long set of results shown in a table where chromium(III) exposure causes sensitization to both chromium(III) and chromium(VI). So that's sort of the strongest -- I guess, the strongest evidence that we have.

PANEL MEMBER BLANC: Which can you refer me to the page and the study, the table?

DR. SILVA: It's Gross et al. is the study. Let me try and do a search. So Section 5.2 discusses chromium(III) to chromium(VI) cross-reactivity in guinea pigs.

PANEL MEMBER BLANC: Yeah.

DR. SILVA: So that's page 55 if you're looking at the hard copy.

PANEL MEMBER BLANC: Yeah, hold on.

DR. SILVA: And then let me try and find the table.

PANEL MEMBER BLANC: You're saying it's Gross?

DR. SILVA: It's Gross, et al., yeah. It's Table 6.

PANEL MEMBER BLANC: Yeah.

DR. SILVA: And that's on page 57.

PANEL MEMBER BLANC: It's 19 -- the 1968.

DR. SILVA: Right. Right. So it is an older

study. So pages 56 to 57, 57 being the pages where chromium(III) was used as the sensitizer.

PANEL MEMBER BLANC: Okay. Well, you -- so I'd say two things.

DR. SILVA: Okay.

PANEL MEMBER BLANC: One is I would be more specific in your language then. And I would actually in your text make a bit more of that, since it completely was lost on me in the table. I mean, you say there's -- there is one study that you can cite, which shows sensitization with chromium(III) as is possible in an animal model. And you -- you know, and I'm assuming you've looked at that closely, so you know that it was -- you know, they used chromium -- trivalent chromium without any hexavalent chromium contamination, that was -- as far as technically could be done. And then in terms of humans, you have no such data.

DR. SILVA: Okay.

PANEL MEMBER BLANC: It is strong, but you certainly can say that humans who are sensitized with chromium(VI) can cross-respond to chromium(III) in the one inhalation study that you have that did that, right?

DR. SILVA: Okay. And you want that in the -- in the summary section to clarify on page ii?

PANEL MEMBER BLANC: I would clarify there and I

would --

DR. SILVA: Okay.

PANEL MEMBER BLANC: -- clarify later in your text, if you feel you haven't sufficiently brought that point home --

DR. SILVA: Okay. Okay. I can do that.

PANEL MEMBER BLANC: -- because it's -- and then I think the other thing -- and, John, maybe you want to comment, but I think the other thing you want to do in this overview introduction is say that although you're not using this as a basis for an R -- for the source study of the REL, you are taking this into account in your adjusting factors --

DR. SILVA: Okay.

PANEL MEMBER BLANC: -- since in the presentation you said that one of your reasons for using an intraspecies in humans uncertainty factor was because of asthmatic responses in children.

DR. SILVA: Okay.

PANEL MEMBER BLANC: You said that, right, in the text and in your presentation?

DR. BUDROE: Yes.

DR. SILVA: Yes.

PANEL MEMBER BLANC: Which is a different argument than the argument about children have developing

alveoli, and therefore they may be more sensitive. That's a separate --

DR. SILVA: Okay.

PANEL MEMBER BLANC: -- and equal argument. But if you're going to say that it's because of asthma, then you can't say you're not considering asthma at all. You're considering it, but only insofar as you're going to use it in your uncertainty factor considerations. And I would say that --

DR. SILVA: Okay.

PANEL MEMBER BLANC: -- up front here, because otherwise somebody reads this and they say, well, you said you weren't going to use asthma.

DR. SILVA: Okay.

PANEL MEMBER BLANC: And that also, by the way, justifies, in a sense, spending as much time as you do on cross-reactivity.

DR. SILVA: Okay.

DR. BUDROE: We could do.

PANEL MEMBER BLANC: Does that make sense?

DR. SILVA: Yes.

DR. BUDROE: Yes.

PANEL MEMBER BLANC: And I think it would strengthen what you're talking about. I think that in the sections where you talk about production and uses of

chromium(III), obviously a big challenge in all of this is where chromium(VI) is used in addition to chromium(III), or where chromium(VI) may get converted to chromium(III) and all of that. But I did find that somehow the presence of chromium in cement manufacturing, and in concrete applications, and concrete finishing was present in only a very fleeting way.

And I'm not saying there should be a whole new section on that, but I'm -- I think part of the problem is that most of that literature is concerned with chromium(VI), but there certainly have been people who have gotten asthma from working with cement. And those people are sensitive to chromium(VI), and therefore could be sensitive to chromium(III), but -- so that's relevant from that point of view, but that also some of this concrete dust becomes atmospheric, I suppose. Well, I know cement manufacturing. So I'm assuming that's a big point -- source point of chromium(VI) if you did a hot spot -- when you did your hot spots. And therefore, that all gets converted to chromium(III) much of it, even though that's not your concern here with the studies that you use.

But in the parts that talk about sources and uses, I just thought that it was I expected to find more about cement and concrete there than was. It was very

fleeting.

DR. SILVA: And so just to clarify, how you would want that section revised. Are you wanting more information about specific studies -- study summaries or just --

PANEL MEMBER BLANC: No. No.

DR. SILVA: Okay.

PANEL MEMBER BLANC: You can just say, you know, we also recognize that chromium(VI) is a major issue in concrete and cement, but we will not be alluding to it further -- and even in sensitization, but we won't be covering it more here or whatever you -- whatever caveat you want.

DR. SILVA: Okay. Yeah, it was kind of a difficult needle to thread in that --

PANEL MEMBER BLANC: Oh, yeah.

DR. SILVA: -- I do know the studies that you're talking about. I have seen those, but, you know, in trying to focus on chromium(III), we excluded a lot of the studies in which the exposures were dual chromium(VI) and (III), but I can do what you're saying.

PANEL MEMBER BLANC: Yeah.

DR. SILVA: I understand what you're saying and I can do that, yeah.

PANEL MEMBER BLANC: Because otherwise, it makes

it sound like you did -- you're not aware of that --

DR. SILVA: Yeah, no I understand.

PANEL MEMBER BLANC: Right. And can you say a little bit about what the ethical considerations were that made you exclude an otherwise relevant study to chromium(III) sensitization?

DR. SILVA: It was -- so this was a very old study that was performed in primarily African-American prisoners. And it was performed before IRB considerations were in place. And maybe that's something that John can talk more about. There was some discussion within OEHHA and we decided to exclude it.

PANEL MEMBER BLANC: And what did it -- what was the exposure to? They did chromium(III) specific?

DR. SILVA: They were chromium(III) sensitization studies, yes. Walnut studies, but experiments within one study. I can share the -- I can share the -- the publication with you via email, if you want.

PANEL MEMBER BLANC: Yeah, sure. I'd be curious to see it.

DR. SILVA: Okay.

PANEL MEMBER BLANC: I mean, it's not the first time that that kind of issue has come up. So I'd be curious to hear.

But in any event, I think I made my point

sufficiently about the sort of overview. And you really almost can't give too much consideration to those sorts of things, because it's setting up the whole thing.

And the -- of course, the other -- the other issue that John had already alluded to and also Mike, you know, the issue with -- it's almost -- it's not semantic, but a lot of what we think of as chromium(VI) issues are chromium(III) issues, right, because it gets into the body and then it acts as chromium(III).

So you might want to also say that as a caveat. It's not like we're ignoring -- it's not that we're not aware that chromium(VI)'s affects are once it gets reduced to chromium(III), but that's beyond the scope of this document or however you want to say it.

DR. SILVA: Okay. I can do that.

DR. BUDROE: Yeah, we can clarify that.

PANEL MEMBER BLANC: Add also, can you say something about the chromium content of secondhand cigarette smoke and what form that's in? That must be chromium(VI), because of the heat.

DR. SILVA: That was not something that I found in my research for chromium(III). I don't know. Is that something that one of the Panel members might know about?

PANEL MEMBER BLANC: Karen. Karen, do you have any comment? There is chromium in cigarettes, right,

cigarette smoke?

DR. SILVA: Do you know on that --

CHAIRPERSON ANASTASIO: I think, Ahmad, do you want to say something about that.

DR. SILVA: Oh, sorry. Sorry.

CHAIRPERSON ANASTASIO: Ahmad, you're muted.

Ahmad, you're muted.

PANEL MEMBER BESARATINIA: Okay. Yeah, I just want to add that a significant, but relatively newer source of chromium exposure is electronic cigarette use or vaping, which is not covered in this report. And that is important, given the increasing popularity of vaping, especially among adolescent and young adults. And the fact that vaping occurs in many public places, so the source of exposure seems quite important for public health and also relevant for regulatory purposes concerning the vaping industry and product manufactured.

It is now established that chromium and other heavy metals can leak from the metal coil in cigarette devices into the liquid. And after vaporization, they can get inhaled by the e-cigarette users. And there have been quite a wide ideal of literature available showing detectable levels of chromium and other heavy metals in various tissues and organs of electronic cigarette users. And they have also been linked to adverse biological

effects, some of which have been mentioned in this report.

There is also -- I have come across quite a few reports where were chromium and other toxic metals have been measured and detected in the ambient air of people who wait, which may constitute a source of secondhand exposure for bystanders. And as I said, the literature is growing on this considering the fact that e-cigarette is a relatively newer technology.

As for the point that Paul just mentioned, the concentration of many of these heavy metals in e-cigarette vapor is either comparable, but in some instances even higher than those in smoke from tobacco cigarettes and that has been shown by analytical chemistry. And I'm wondering what the Panel, and John and Rona think about this.

PANEL MEMBER BLANC: Well, is that Chromium(VI) or chromium -- trivalent chromium.

PANEL MEMBER BESARATINIA: Well, I am not sure about it. But I can go back through the literature. I think there have been quite a few studies by NIH inter -- NIH internal labs in mid-2000 -- I think 2015, 2014. And I think that would be published in different tobacco research and chemical research toxicology journals, if I remember correctly.

DR. SILVA: I can look through that as well. I

know that chromium, in general, tends to accumulate in the lungs over time with age. And some of that has been associated with exposure to cigarette smoke, but I didn't find anything that was specific to chromium(III). A lot of the studies that I found during my literature review were studies in which they did not actually speciate the chromium. But I'll look into that, because I do understand that it's an important consideration, the vaping and cigarette smoke.

CHAIRPERSON ANASTASIO: Thank you, Rona.

Mike, did you want to follow up and then we'll go to Joe?

PANEL MEMBER KLEINMAN: Yeah. Thank you.

Yeah. On the vaping, the coils that they use are stainless steel and nickel chromium alloys, for the most part. And there is transport -- you know, leakage from the coils into the vaping fluid. And then it gets aerosolized when you heat the vapor -- you know, the liquid up. So the cloud does contain small amounts of chromium.

But all of the data that I've seen is related to total chromium, because the samples are just analyzed by ICP-MS. And I think that leads us to a -- you know, one of the things that mentioned in the document, they talk about the really arduous ways you have to use to get real

measurements of chromium(III). And these are not things that you would formally do analytically. So we take our -- you know, generally the best approach is collect the sample and they use ion chromatography with a reactor to isolate out the chromium(VI). And then you measure total chromium with something like atomic absorption or ICP-MS and then you subtract those two numbers to get chromium(III). So our knowledge for the most part of environmental levels of chromium(III) are really subject to large uncertainties.

CHAIRPERSON ANASTASIO: All right. Thank you, Mike.

Joe, did you have a comment?

PANEL MEMBER LANDOLPH: Yes. Just a brief one. It was a question Paul had asked of John. And it was about are there insoluble chromium -- hexavalent chromium compounds and the answer is, of course, yeah, there are. Lead chromate is one we've worked with extensively. It used to be used to paint airplanes, because it stops the corrosion of iron and the chromium instead gets reduced.

And then that was replaced by strontium chromate because lead chromate was too carcinogenic, too toxic. And then that was replaced by barium chromate. And strontium chromate and barium chromate are less insoluble. They're very slightly soluble. And you can actually watch

some of the particles dissolve as a function of time. So kinetically they become soluble over time. So that's just to clear up the question about chromium.

PANEL MEMBER BLANC: Thanks.

CHAIRPERSON ANASTASIO: All right. Thank you, Joe.

Go ahead, Paul.

PANEL MEMBER BLANC: That reminds me of when I was doing a summer internship with Shell Oil. And that one of my tasks was to track down some information on material and safety data sheets at the time. And their proprietary yellow paint was strontium chromate. And so I called the manufacturer and said, you know, your material safety data sheet doesn't say anything about, you know, carcinogenesis of chromium(VI). And they said -- the guy said, well, it's just like all that talk about lead being toxic.

(Laughter.)

PANEL MEMBER BLANC: Anyway. Let me -- I'm sorry.

CHAIRPERSON ANASTASIO: Sorry, Paul, before you get going, Kathy had her hand up.

PANEL MEMBER BLANC: Oh, sorry.

CHAIRPERSON ANASTASIO: Kathy, did you want to make a comment on something?

PANEL MEMBER HAMMOND: Sure. I did -- don't mean to interrupt Paul, if he wants to finish though.

PANEL MEMBER BLANC: No, go ahead.

PANEL MEMBER HAMMOND: So thank you very much for the document. I was surprised. Normally, we see a lot more information about air concentrations and airborne concentrations, because that's kind of the focus of this. And most of the discussion was about occupational exposures. And I understand that -- the issues about the valences, the different valences and the uncertainty and all of that.

But if there's no other information available, I do think total chromium should be reported, because obviously chrome -- chromium(III) will be something less than all of chromium. And certainly, the other issue is that, in general, every time we talk about chromium(VI), they say, well, the total chromium is always all chromium(III).

So I think what we need to -- it would be good to be -- to discuss then what the chromium if (III) and/or chromium total concentrations are airborne to be part of a hot spot kind of discussion.

DR. SILVA: I can do that.

PANEL MEMBER HAMMOND: Because I think that's a critical piece of this. And then I sent some small minor

corrections to John that -- to take care of.

DR. SILVA: Okay. Thank you.

PANEL MEMBER HAMMOND: Okay. Thank you,

CHAIRPERSON ANASTASIO: Thank you, Kathy.

DR. SILVA: Thank you.

CHAIRPERSON ANASTASIO: Okay. Paul, back to you.

PANEL MEMBER BLANC: Yeah. So I mean clearly a big part of the setup is the discussion of cross-reactivity between -- the cross-sensitization. If you're sensitized to chromium(VI), are you sensitized to chromium(III)? And I thought the -- I thought in summary that that was convincing, which is why I would put that more clearly in the general summary.

But I did come across a paper, which I thought was quite relevant to your argument and supportive, but it's not cited. And it's by Lindemann, L-i-n-d-e-m-a-n-n, first initial M on a detection of chromium allergy by cellular in vitro methods. And its one of the few papers that specifically cross-compares the in vitro response to trivalent chromium and hexavalent chromium.

So -- and it shows that there's almost complete in vitro cross-responsiveness, but that -- and there's a dose response, but that the response to trivalent chromium is far, far less per weight. And they speculate it's because it binds almost immediately to proteins.

DR. SILVA: Okay. Thank you.

PANEL MEMBER BLANC: So I would suggest that you cite that paper, which is --

DR. SILVA: Okay.

PANEL MEMBER BLANC: -- from 2008, so it's not an old, old paper.

DR. SILVA: Thank you.

PANEL MEMBER BLANC: Because I think the argument is quite important later on.

Can I ask, on a completely unrelated front, on Table 4, on page 33, which is tissue deposition, which has the GI tract in general, but doesn't have deposition in the pancreas in that summary. I don't know if that's because it wasn't in the paper or you just didn't include that as a row. And I wonder if there's any data you came across on depo -- pancreatic deposition, per se.

DR. SILVA: No. This -- I -- if I found anything on the pancreas, it would definitely be in the paper. This table was -- so all of the tissues shown in the table are tissues that were reported. There's nothing that I excluded, even though some of the calculations were done by OEHHA. We had to have the first column, fraction of total body deposition, that part was reported by Henderson. So, yeah, I didn't have pancreas information.

PANEL MEMBER BLANC: And is there -- was there

any from any other study?

DR. SILVA: Not that I know of. Not for inhalation, anyway.

PANEL MEMBER BLANC: Okay. Because you had the earlier discussion as to whether or not chromium was, in fact, an essential nutrient.

DR. SILVA: Right. That brief section, yeah, sentence.

PANEL MEMBER BLANC: Yeah. And it -- I mean, it's always been my understanding that chromium is, in fact, a necessary enzymatic co-factor in certain enzymatic functions, is that not the case?

DR. SILVA: I'll have to look at that information again. I can't remember what the dispute was exactly as to why some people were thinking it was a non-essential nutrient. I recall very vaguely discussions about lipid metabolism and -- in chromium(III), so it may have something to do with that, but I'll have to look specifically at those -- at those studies again.

And I think Dr. Landolph has something to say.

PANEL MEMBER LANDOLPH: Yeah. There was a dispute. The original investigators determined some kind of a chromium complex they thought. But Max Costa and his colleagues went back and redid those experiments and they claim that it's not a -- it's not a serious complex. So

it's been in dispute for years. And I think Rona and her colleagues answered it -- you know, stated it precisely. It's still a controversial aspect and more experiments need to be done to prove it or disprove it. So Costa's camp is firmly against that discovery for various technical reasons. And the other --

PANEL MEMBER BLANC: You mean, that chromium is an enzyme -- in enzyme complexes?

PANEL MEMBER LANDOLPH: No. That it's a -- that it's an essential nutrient.

PANEL MEMBER BLANC: But is there any debate as to whether or not chromium is a metal which is -- partakes of human enzymatic function? Is that the debate?

PANEL MEMBER LANDOLPH: It's a debate that it's, in the form that the original authors published it, that it was actually a complex that functioned as an essential biochemical function. That seem to still be in dispute between these two camps.

PANEL MEMBER BLANC: Interesting.

PANEL MEMBER LANDOLPH: And now they have taken that and they're using mega doses of chromium(III) and --

PANEL MEMBER BLANC: No, I -- okay.

PANEL MEMBER LANDOLPH: -- diabetes and --

PANEL MEMBER BLANC: Curious. All right. That was my question on that.

So I want to just then go forward to the actual calculations and the uncertainty factors. By the way, I also want to echo Kathy's very good point about the importance of saying something about air levels. And, you know, if Kathy is saying this is all occupational, where is the air pollution, you know that you've got an issue, right? Because usually it's she and me that are saying where is the occupational data or you've ignored the occupational data.

So my question has to do with the mathematics of the calculation for the acute REL. And it's based on an assumption that since you do a benchmark approach with the chronic and 8-hour, that that benchmark statistical approach takes into account the size of the individual groups of animals.

So maybe that's a false assumption, but let's assume that's correct. For the acute REL, where it's not a benchmark approach, are you -- do you have enough uncertainty reflected given the fact that this is all based on four animals in each of the exposure groups? And I also take great exception to when you said the reason why the 55 or the lowest dose was a no-effect dose is because there was no statistical difference in certain of the outcomes.

I mean, it's amazing that there was any

statistical difference in any of the pairwise comparisons with four animals. You don't actually say what the difference was that wasn't statistically significant. So if you told me that the difference was trivial and not significant, that's one thing. But since you don't say what the differences are, I can't really tell. So those are two separate points.

DR. SILVA: Okay. I can -- so first point was that you -- would you -- are you requesting the exact P values that are -- that were associated, is that helpful?

PANEL MEMBER BLANC: I think the P values are meaningless. I think it's -- I mean, on that front, it's not what the P value was. Although, if you told me the P value was 0.10, I'd say, well, with four animals in each group, it was probably a pretty darn big difference. But I guess is it a trivial -- is the observed difference trivial? Let's leave the statistics aside -- out of the point of four animals in each of the two groups.

But with that limitation, the second part of my question is is your uncertainty factor -- do you need an added uncertainty factor, given how small your groups are?

DR. SILVA: To account for the potentially insufficient power statistically is what you're saying?

PANEL MEMBER BLANC: Yeah.

DR. SILVA: So I am not sure if I can add

additional -- which uncertainty factor are you thinking of specifically? Because a lot of the ones that I assigned were --

PANEL MEMBER BLANC: They were boilerplate.

DR. SILVA: Yeah.

PANEL MEMBER BLANC: But you can always add an extra uncertainty factor, which we've done, if the --

DR. SILVA: Okay.

PANEL MEMBER BLANC: -- if the database is really not very sufficient and robust.

DR. SILVA: Okay.

PANEL MEMBER BLANC: We have good precedent for doing that. And so there are two parts to my question. One -- and your argument that this is -- the no effect level is perhaps even more important. Is this really a no effect level or not? How sure are you of that? So the questions are interrelated, right, if everybody follows my gist. And since Karen has inherited Stan's role, I think maybe you should -- you have your hand up. I'd love you to comment on this.

PANEL MEMBER MESSER: I actually had somewhat the same question. And I want to -- you know, I'm new to this, so I'm mostly sitting and listening. And I do want to echo the first reviewer's compliments about how well written this report was, because I felt -- after I read it

a few times, I felt like I pretty much understood what was going on, which is a challenge on your first go-round.

But I did have --

DR. SILVA: Thank you.

PANEL MEMBER MESSER: -- the -- and our presentation, by the way, I thought it was clear and very helpful. I learned more from the oral presentation.

But I did have somewhat the same question that Dr. Blanc is raising right now on that one calculation, that it -- four animals per group is very small. And the fact that no adverse effect level was on the basis of lack of statistical significance raised the same question in my mind, what was the observed difference.

So I didn't look up the paper, which I think is the next step, to see if they present the actual data in that paper and perhaps that would be convincing. You know, if you look at the data and you see a huge effect at the next dose up and then a pretty small effect at the no adverse effects level, then you have more confidence in it.

I think the uncertainty factor would be the one associated with the -- if I'm remembering all this correctly, would be the one associated with the no adverse effect level, which right now is one, so that you could raise that to a two maybe to represent that there's

perhaps still some uncertainty or whatever the next appropriate level would be. But I think that's where it would be -- the uncertainty factor would be, if I'm following the methodology, at this point.

DR. SILVA: Okay. I can -- I can look more at the study again to see how much detail they provided. And then I can also talk with John to see how much leeway we have in terms of adjusting some of the different uncertainty factors with regard to your comments on the animal number and the potential lack of statistical power.

PANEL MEMBER MESSER: And again, I don't know what your standard practice is yet --

DR. BUDROE: Right.

PANEL MEMBER MESSER: -- just looking at this for the first time. So I wouldn't be arguing to go outside your standard practice, I guess --

DR. BUDROE: Right. Well, one, if we were to do that to essentially change the uncertainty factor in this instance, we would need to have an idea of how -- what order of magnitude change we'd want to do. If we raise it from one to two, what would be our justification quantitatively for doing that?

PANEL MEMBER BLANC: Well, I think you -- first of all, maybe you want take a Bayesian approach to the data that you do have. And if there were not four

animals, but there were 40 animals, would the difference you're seeing be statistically significant, if that's your argument.

But as Karen said, I think you need to look what is the difference? For example, if the difference is negative, if the -- you know, if the endpoints that you use in the higher dose -- in the lower dose, in fact, were lower than the control animals, then it's not -- it's much less an issue of, you know, okay, maybe it is by chance, but it's not blatantly. Yeah, there's the difference -- there's an effect here. It's just with four animals you could never show it statistically of an effect that would be consistent with the slope of a linear line going to zero from 15, right? Because you're arguing it's no effect. It's a no effect level and your argument is because there's not a statistical difference in pairwise comparisons between these outcomes, like the alkaline phosphatase, I suppose.

DR. SILVA: Just for kind of as a clarifying point from -- for me, would it matter whether we also saw tissue damage?

PANEL MEMBER MESSER: Yes.

DR. SILVA: This is something -- you know, I mean, if we have no statistical differences in our measurable endpoints, our quantified endpoints, and also

no changes in the lung tissue upon histopathology, we wouldn't necessarily be able to add an extra uncertainty factor, correct?

PANEL MEMBER BLANC: No, you're not correct, because one would expect that the enzymatic measurements or the biochemical measurements might be the only thing that you would see at the level. So you're arguing that there's no effect. Certainly, the reverse is true.

DR. SILVA: Okay.

PANEL MEMBER BLANC: If you say tissue damage, but no enzymatic damage --

DR. SILVA: Right.

PANEL MEMBER BLANC: -- that was statistically significant, you had a qualitative measure that's suggested something was going on, then that adds more fuel to the fire.

DR. SILVA: Okay.

PANEL MEMBER BLANC: But the reverse, I would not say is true.

DR. SILVA: Okay. Right. Because the enzyme levels are the more sensitive endpoint. Okay.

PANEL MEMBER BLANC: Yeah.

CHAIRPERSON ANASTASIO: Karen, did you want to follow up?

PANEL MEMBER MESSER: Yeah. I guess, maybe I'm

not quite following that last discussion. So you have several endpoints. You have enzymatic endpoints and then you have this alveolar damage. Is that a histopathology endpoint? I don't quite remember clearly.

DR. SILVA: Yes, that's correct.

PANEL MEMBER MESSER: Okay. And in the -- and you're seeing no effect across these multiple endpoints, is that -- is that correct, no statistically significant effect?

DR. SILVA: So the histopathology is not usually quantified. It's just a visual examination of changes in the tissue relative to the control.

You know, sometimes maybe they'll just see accumulations of chromium, sometimes they'll see inflammatory cells in the area, and sometimes in really bad cases - this is not necessarily for chromium - you might see sloughing of tissues maybe in the bronchiolar -- the bronchioles.

PANEL MEMBER MESSER: And you're saying --

DR. SILVA: So, yeah, those are not usually quantified, or they can be, not often quantified.

PANEL MEMBER MESSER: Okay. And so you're seeing nothing on the histopathology, but that's a subjective measure. And then across the quantitative measures, you have several of those and you're not seeing anything

that's significant across several measures, is that right?

DR. SILVA: I believe that's the case. I can look up the table now to be sure. And also, I can also later on look at the paper to see if I can glean anymore from the details. But I just wanted to clarify that for myself, whether adding additional uncertainty factors would still be possible, if I didn't see any changes in the histopathology. But that makes sense what Dr. Blanc was saying that the enzymatic changes -- the changes in the bronchial, alveolar, lavage also are sometimes seen before you actually have tissue damage. So potentially, you know, I think we could add an uncertainty factor.

PANEL MEMBER BLANC: Well, there's two ways -- there's two ways you'd have to handle -- you have two choices --

PANEL MEMBER MESSER: But if I could just --

PANEL MEMBER BLANC: Oh, yeah. Sorry.

PANEL MEMBER MESSER: Sorry. If I could just finish that train of thought. I do think it's an accumulating level of evidence however, if you have multiple quantitative measures, none of which show a significant effect, and also, you can see that none of them -- I think there possibly should be an informal power analysis done, you know. With four animals across those measures, do you expect to see a signal if there really is

one? That's where you might sharpen your argument for the --

DR. SILVA: Okay.

PANEL MEMBER MESSER: -- (inaudible) the evidence. And also to look at the magnitude of the changes. If the magnitude of the changes is small across all of those measures, then I think even though we might not formalize it with this sort of Bayesian argument, I think the weight of the evidence accumulates that it's a confident no adverse effect level. So it's part of a whole -- incorporating all those measures together might strengthen the argument or conversely let you know that maybe it's less certain than you think.

DR. SILVA: Okay.

PANEL MEMBER BLANC: And just to build on that, I'd say you have two approaches. One is to stick with this as a no effect level. I think no matter what the endpoint of your decision about that is, I think you should strongly consider a little bit more uncertainty. But if you believe it's not a no effect level, then you're going to have to treat it as a low effect level and do your calculations on that basis.

DR. SILVA: Correct.

PANEL MEMBER BLANC: So if you have enough uncertainty to reject calling it a no effect level, then

it's a low effect level and you have to proceed accordingly, because I actually don't remember a recent example where we had, you know, this few test animals per group. And I think the reason obviously is that you have so little data altogether for your -- you know, to make your conclusions, it's not your fault. It's just that the literature has, you know, kind of let you down on this one.

I see Mike has a question, as I have one last comment about the other -- the other calculations.

PANEL MEMBER KLEINMAN: Yeah. I just wanted to point out that in terms of, you know, are the numbers relatively consistent when you look across the RELs that are calculated? So we've got the acute 1-hour REL is about 48 micrograms -- pico -- nano -- 480 nanograms, 0.48 micrograms per cubic meter. You look at the 8-hour, it's 0.12 micrograms per cubic meter. And if you use the dose -- you know, the time concentration profile and back calculate from eight hours to one, you'd end up with a 0.96, and then add in an uncertainty for that.

So the number we're getting where one approach was a benchmark dose approach and the other is -- or at least I think the eight hour is benchmark.

PANEL MEMBER BLANC: Yes, I think it was.

DR. SILVA: That's correct.

DR. BUDROE: That's correct.

PANEL MEMBER KLEINMAN: And then the other where you use the -- just the NOEL use that as a departure point, you know, the fact that they're that close, it kind of gives me confidence that we're in a, you know, pretty good ballpark for this.

And the other point I wanted to make, I looked up some ambient air data. And when you look at ambient -- and this was, I guess, a study done using ARB analytical methods, and they found that it looks like, you know, on the average, more than 90 percent of the ambient chromium is chromium(III), where they looked at total chromium and chromium(VI) and subtracted to get the chromium(III) amount.

So, you know, for all practical purposes, you know, if we were to -- you know, I think the numbers that have been derived are in a relatively good ballpark, but, you know, we did have in, I think, at least in one of the other RELs we looked at, we also put in a -- an additional uncertainty for the quality of the database. And I think having these small numbers of animals would certainly qualify as, you know, an additional level of uncertainty that we might want to consider.

DR. BUDROE: Okay.

DR. SILVA: Are you suggesting, Dr. Kleinman, to

go that route irrespective of whether our -- the suggested power analysis and/or Bayesian analysis suggests that we should do that or are you just saying, you know, based upon historical REL documents, we sort of have this set precedence where we use this additional uncertainty factor because there's a smaller number of animals?

PANEL MEMBER KLEINMAN: I would not say don't do the more rigorous power calculation or Bayesian approach and that may give you, you know, much more justifiable numbers.

DR. SILVA: Okay.

PANEL MEMBER KLEINMAN: I'm just suggesting as an alternative that there is also this other route that one could take.

DR. SILVA: Oh. Okay. Thank you. That's helpful.

PANEL MEMBER BLANC: I'll yield my final comments to hear first from Beate.

PANEL MEMBER RITZ: I just have one comment about -- because Kathy mentioned the ambient levels. And we currently have a paper in review that should come out really soon where we did a whole monitoring campaign across LA in two seasons with 20 Harvard impactors and chromium is one of the elements that was measured. So you can actually get that paper and cite it and it will give

your urban background, as well as roadside measures for chromium or for particulate matter 2.5, et cetera.

I can give you --

DR. SILVA: Thank you.

PANEL MEMBER RITZ: I can give you the citation.

DR. SILVA: Okay. Thank you.

CHAIRPERSON ANASTASIO: Thank you, Beate.

PANEL MEMBER BLANC: So --

CHAIRPERSON ANASTASIO: Paul, did you have additional comments?

PANEL MEMBER BLANC: Yeah, I have a final comment on the process on the other RELs.

Table 18, for example, has a column with Akaike information criterion values. But I don't believe you explicitly alluded to those in your -- as support of your model choice or did I miss that text?

CHAIRPERSON ANASTASIO: Paul, which page are you on?

PANEL MEMBER BLANC: It's page 94 for example.

DR. SILVA: Right. So if you're looking at the hard copy, it's page 94. If you're in adobe, it's page 105.

I see what you're talking about and I thought that I talked about -- okay. So the AIC value was something that I talked about in a footnote on page 93,

the page right before the table.

PANEL MEMBER BLANC: Well, I guess it's not -- a footnote isn't on my -- on my hard copy.

DR. SILVA: Oh. Oh, interesting.

PANEL MEMBER BLANC: -- or maybe it's just how it printed out.

DR. SILVA: Okay.

PANEL MEMBER BLANC: But there's a lot of footnotes to the table.

DR. SILVA: Right. Yeah. So this is a footnote to the text on page 93 or page 104, if you're in the -- in the adobe version.

PANEL MEMBER BLANC: Oh, wait. I see it. I'm sorry. I'm sorry. I see it, yeah.

DR. SILVA: So it's possible that the AIC actually didn't play a role in my choosing of that model, because it's only usable when you're talking about data from the same data set.

PANEL MEMBER BLANC: But these aren't from the -- aren't these four models you ran on the same data set?

DR. SILVA: No. So one is, you know, females for one day, females for 13 weeks post-exposure, it's -- they're all -- all of the four --

PANEL MEMBER BLANC: Oh, I see. I see. Yes, yes, yes, yes. And the model that you chose in the end

was, remind us again which row?

DR. SILVA: The first row.

PANEL MEMBER BLANC: The first row, which even though you can't use the AIC by far has the lowest AIC.

DR. SILVA: Right. Right.

PANEL MEMBER BLANC: Well, I guess that makes me -- okay. I understand better now. I guess my question would be if you can't use the AIC, why are you showing it or if you aren't in the -- or if some people wouldn't recommend using it, but you have it, you know, is it worthy of comment, again with a bit of a caveat, even though strictly speaking we wouldn't use this when we're not comparing models with exactly the same data set. Clearly, the AIC is much lower for this model as well, lending further support, whatever the caveat is, because it's rather -- you can see why I'm confused.

DR. SILVA: Yes. And I can either -- I did include it, because it's something that we normally include in our summary tables for the BMD analysis, but I understand what you're saying about it being confusing. And I don't have a problem taking it out or adding clarification in the text, either way.

PANEL MEMBER BLANC: I would add clarification in the text. I'd say --

DR. SILVA: Okay.

PANEL MEMBER BLANC: -- you know, strictly speaking, it -- it shouldn't form the basis of choosing one over the other, because these aren't exactly the same -- exact same data sets --

DR. SILVA: Um-hmm.

PANEL MEMBER BLANC: -- but it certainly is consistent with a better model.

DR. SILVA: Okay.

PANEL MEMBER BLANC: Something like that.

DR. SILVA: Okay. Yeah, I can do that.

PANEL MEMBER BLANC: Because the numbers are the same. I mean, they're close enough that it must have some relevance.

And just to circle back to our discussion on the other -- the other data set that you were forced to use with the four animals in each of the groups. Using the benchmark calculation does take into account to an extent the size of the study groups, right? I mean, that -- that's where the confidence bounds are driven in part by that.

DR. BUDROE: Right. I believe that that's it.

PANEL MEMBER BLANC: So just to reassure ourselves. And I realize why the other study with the just two levels you can't do a benchmark on that one, I'm assuming. Well, three levels you have zero. But in any

event, just to put it in context.

That's it. Those are my -- that's my shtick.

CHAIRPERSON BLANC: Okay. Thank you, Paul.

DR. SILVA: Thank you.

CHAIRPERSON ANASTASIO: I open it up to other Panel members now, other comments, items that have not been discussed?

All right. Let's see, we've heard from Joe, heard from Paul. Lisa, anything from your end?

PANEL MEMBER MILLER: Well, I had the same concerns that Paul had, in terms of the sensitization issues. And I don't want to, you know, beat a dead horse here, but certainly I have a lot of concerns about the use of the single study to establish the acute RELs. And I -- and again, I understand this is what you have to work with, right?

As an immunologist, when I see words like "phagocytosis" and "sensitization", the implication is reprogramming and you -- so these sorts of studies, particularly studies that were done in the 70s and the 60s, and not that they're not relevant and helpful, it's just that they're not designed to detect -- they don't have the methodologies to detect this sort of response. That's a sensitization response, which would be an adverse effect. So I think that's an important caveat to

emphasize as you establish these -- as you establish an acute REL. And it goes back to setting up these uncertainty factors.

One quick comment that would be helpful for me and perhaps the readers also going back to the cross-reactivity studies in guinea pigs. I wasn't able to look this up -- study up, but this in my read of it, it looks like the challenge studies were done using a dermal challenge as opposed to an inhalation challenge, is that correct?

DR. SILVA: Correct.

PANEL MEMBER MILLER: Okay. Because I think that would be helpful to clarify, because in my first read, I had assumed it was inhalation. But, in fact, as I read through it again, it -- I thought that it was dermal. So I think that's an important clarification that should be emphasized, because that's -- you're talking about --

DR. SILVA: Okay. I can do that up front and at the table, again, yeah. Thank you.

PANEL MEMBER MILLER: Great. Thank you.

So that's all I have.

CHAIRPERSON ANASTASIO: Thank you, Lisa.

Mike.

PANEL MEMBER KLEINMAN: Yeah. This is quite minor, but just for consistency, you go back and forth in

the write-up and the discussion between using the square root of 10 or the number 3, which are essentially equivalent. I think to avoid confusion, it might be easier to just pick one and use that throughout the document.

DR. SILVA: Yeah. I was thinking about that as I was doing my presentation today and saying 3 and looking at the root 10, so I'll do that. Thank you.

PANEL MEMBER KLEINMAN: Okay. The other comment I wanted to make is that on your slide 5, where you talk about particles depositing in the tracheobronchial airways and then dissolving and going into the bloodstream, it would be worthwhile mentioning that most of the stuff on the tracheobronchial airway will clear very rapidly through mucociliary clearance and then enter through the GI tract.

DR. SILVA: Okay. Yeah, I do talk about that in the paper, but I'll make that more clear --

PANEL MEMBER KLEINMAN: Great.

DR. SILVA: -- about the proportion. Yeah, that's important. I agree.

CHAIRPERSON ANASTASIO: Okay. Thank you, Mike.

PANEL MEMBER KLEINMAN: Thank you.

CHAIRPERSON ANASTASIO: Kathy.

PANEL MEMBER HAMMOND: Sure. These are just some

small comments, about I think they -- they're important to get.

CHAIRPERSON ANASTASIO: Sorry, Kathy, can you move your mic, so we can hear you better.

PANEL MEMBER HAMMOND: My apologies. Sorry.

Okay. On just a few -- a few points, but I think I'd just like to get these correct. On page 14, line 424, you talked about the workers wearing masks. And I would like to clarify whether that's masks or respirators. My guess is that that's respirators. And those are distinct and certainly these days we're making those distinctions.

DR. SILVA: I'm sorry. Can you clarify, is it page 14 on the hard copy?

PANEL MEMBER HAMMOND: Yes. I'm holding the hard copy. Sorry.

DR. SILVA: Oh, okay. Okay.

PANEL MEMBER HAMMOND: I'm sorry.

DR. SILVA: No, no. That's okay. I know you said the line number --

PANEL MEMBER HAMMOND: Sure.

DR. SILVA: -- but I stuck in my head page 14, so --

(Laughter.)

PANEL MEMBER HAMMOND: That's okay. No, no, no. My apologies.

Yeah.

DR. SILVA: I think -- so that terminology was something I used from the -- from the paper masks, so I don't know what they were actually.

PANEL MEMBER HAMMOND: Okay. I think it -- check it -- check it carefully to see if it could be respirators, because it's most --

DR. SILVA: Okay.

PANEL MEMBER HAMMOND: -- likely respirators.

DR. SILVA: Okay.

PANEL MEMBER HAMMOND: Usually, they don't use masks in a workplace, other than medical workplace.

On the same page, line 437, you say about 30 percent of dust particles were less than 5 micrometers in diameter. I think you don't mean 30 percent of the particles, but 30 percent of the mass. I haven't really checked, but that's an important distinction, whether it's --

DR. SILVA: I agree. I can -- I can clarify. I'll look at the text and clarify that.

PANEL MEMBER HAMMOND: Okay.

Then on page 15, lines 462, I don't understand what that means, "a monitor with a less than four millimeter size restriction". What monitor would that be?

DR. SILVA: So a sampler, I guess.

PANEL MEMBER HAMMOND: I think that this is incorrect. Okay.

DR. SILVA: Okay.

PANEL MEMBER HAMMOND: I'm almost certain it's incorrect. And there may be a size selective sampler ahead of it, and if so, it would not be that size.

DR. SILVA: Okay. I'll clarify the --

PANEL MEMBER HAMMOND: The size is wrong.

DR. SILVA: I'll look at it to make sure.

PANEL MEMBER HAMMOND: Right. Yeah. Yeah, because that should -- that should be in there correct. I didn't go back to the paper.

Then on page 16, lines 480 and 481, you say that respirable particles are particulate matter less than 10 micrometers in aerodynamic diameter that's PM10, that's incorrect. Respirable particles could be defined as PM4. Their 50 percent penetration is 4 micrometers, not 10.

DR. SILVA: Okay.

PANEL MEMBER HAMMOND: Ten would be what's called the thoracic dose.

DR. SILVA: Okay.

PANEL MEMBER HAMMOND: Oh, and then just as a small thing, but, you know, I think it's important. As examples, lines 539 and 541, but I request you actually do a search and replace, we're doing a scientific document.

And I don't think we should say, "OEHHA believes". We should just state this. Beliefs are not -- this is a scientific document. We're not talking belief systems.

DR. SILVA: Okay. So that was terminology that I used because we weren't sure exactly what they are --

PANEL MEMBER HAMMOND: I think that you should say --

DR. SILVA: -- based on the reporting.

PANEL MEMBER HAMMOND: I think you should say, "you think".

DR. SILVA: Oh, okay. Sure, I can use that instead.

PANEL MEMBER HAMMOND: Okay?

DR. SILVA: Yes. Thank you.

PANEL MEMBER HAMMOND: And just as an -- first of all, I did want to also note that for the very first time that I've been on this committee, I mean, I was the only woman for a long time and then was joined by -- you know, finally had two, and now we're almost half women. This is fabulous, but -- so this is great. But one small thing is that women tend to use the word "believe" when we should say "think" too often. And so I just want to encourage you to start --

DR. SILVA: I take your point.

PANEL MEMBER HAMMOND: Yep.

(Laughter.)

DR. SILVA: Thank you.

PANEL MEMBER HAMMOND: We just -- I do too and we just have to work on that, because we're --

PANEL MEMBER RITZ: Yeah. Wouldn't it even --

PANEL MEMBER HAMMOND: -- denigrating ourselves. Okay. Thank you.

PANEL MEMBER RITZ: Wouldn't it even be better to say "assume".

PANEL MEMBER HAMMOND: Yeah, that might be a better one, yes.

DR. SILVA: Okay.

PANEL MEMBER HAMMOND: I agree.

DR. SILVA: Thank you.

PANEL MEMBER HAMMOND: So thank you. And again, I encourage you to get more of the environmental -- there's a lot of environmental data out there and it should be included. Yeah.

DR. SILVA: Thank you.

CHAIRPERSON ANASTASIO: All right. Thank you, Kathy.

Karen.

PANEL MEMBER MESSER: Yeah, I just wanted to remark, I looked up the Derelanko paper. There's a nice data table there. So there's means and standard

deviations of the -- of the assays at the given doses. So there's a -- there will be a lot of information that could be included.

CHAIRPERSON ANASTASIO: Thank you, Karen.

Paul.

CHAIRPERSON ANASTASIO: Paul, you just muted yourself.

PANEL MEMBER BLANC: Karen, since you just looked at the paper, aside from the means and standard deviations, were there differences -- in other words, even if they weren't statistically significant was in general the measured outcomes higher in the -- compared to the reference -- or the controls?

PANEL MEMBER MESSER: It looks like there are differences. You know, this is by eyeball.

PANEL MEMBER BLANC: Yeah. Okay. Just curious.

PANEL MEMBER MESSER: But yes, there are differences. They are more modest than at higher doses. So it looks like there's a clear dose response relationship --

PANEL MEMBER BLANC: Yeah.

PANEL MEMBER MESSER: -- but we're already above --

PANEL MEMBER BLANC: Yeah.

PANEL MEMBER MESSER: -- consistently across

assays --

PANEL MEMBER BLANC: Okay.

PANEL MEMBER MESSER: -- above the controls. That's a quick look by eyeball.

PANEL MEMBER BLANC: Okay. Thanks.

PANEL MEMBER HAMMOND: But means it's a LOEL not a NOEL, right?

PANEL MEMBER BLANC: That might be the most conservative way of handling this problem.

PANEL MEMBER MESSER: Yeah. And again, I would -- I would ask that the agency go back and review that carefully and not take my word for it.

PANEL MEMBER BLANC: Yeah. Yeah. Yeah, yeah. And then in response to what Lisa had said, I would also say that because -- there actually is a robust literature on chromium(VI) allergy with positive inhalation challenges. The problem is that none of those studies ever did an inhalation challenge separately with trivalent chromium, probably because the options for soluble trivalent chromium are limited. That might be one of the reasons, but I -- I would say that if you still have the energy left, a single sentence that said that and gave those -- the three most recent papers with positive inhalation challenge would be useful to have. It sort of tells the reader, yeah, we're aware of this very

convincing literature. It's just that we can't do anything with -- else with what we've got, because nobody bothered to do those inhalation challenges with trivalent chromium.

DR. SILVA: Okay.

PANEL MEMBER BLANC: And that wouldn't take up a lot of space and it would just sort of underscore the thoroughness of the review of the literature. And then one final methodologic question I have for you and for OEHHA generally, obviously you -- you're very aggressive in using PubMed, and keyword searches, and probably -- and I assume going to TOXNET and some of the other databases.

But when you're in this -- sort of the final throes of this and you've got only one study to choose from for an acute REL and one study to choose from for the 8-hour and chronic REL, do you actually use a search engine that makes sure that you found anyone who's ever cited either of those two papers and why they were citing it?

DR. SILVA: I have not looked at the people that were citing or the numbers of citations the studies have received. But during my literature search, I am using multiple different databases --

PANEL MEMBER BLANC: Yeah.

DR. SILVA: -- so I have access to whatever is

available through UC Davis because I still work with UC Davis. All of, you know, Web of Science, all of the things that students would be -- all of the databases that students would be -- would have access to, their library, in addition to everything that OEHHA has. So I've pooled all of those resources in my searches, but I did -- that's not something that I looked at in terms of, you know, the citations like you're talking about.

PANEL MEMBER BLANC: Well, I wouldn't -- I mean, you'd drive yourself crazy if you did that too much, but one thing I would suggest as a -- as a double or triple check is on these two critical papers, which are driving so much of what you're doing, I would just use the citation function in Web of Science to make sure that you haven't missed a paper that has cited either of these, because they've also done something along the same lines.

DR. SILVA: That's a good idea. I'll do that.

CHAIRPERSON ANASTASIO: Yeah. Thank you, Paul. Good comment.

Any other comments from the Panel?

So my suggestion is often if -- you know, I think the modifications that OEHHA has to make to the document are generally minor, except for this question of the statistics, and the small animal number, and the possibility of increasing the uncertainty factor.

So my suggestion is that when we have a revised document, OEHHA sends it to Paul, and Karen, and me. And then Paul and Karen, maybe you could check the statistical issue. And then if you think that's okay, I can check the rest of the document for the other comments that people made today.

Does that sound acceptable to the Panel? People like that?

PANEL MEMBER HAMMOND: I have a comment on that, okay.

CHAIRPERSON ANASTASIO: Okay.

PANEL MEMBER HAMMOND: My only concern is that we should be looking at the ambient levels to compare what these proposals are to the ambient levels before we go forward.

CHAIRPERSON ANASTASIO: Yeah, I think there -- I believe Rona got that comment and she's going to add ambient concentrations.

PANEL MEMBER HAMMOND: But I think it's a critical piece of that. I mean, because if the ambient level are far above the suggestions, they just need to think about that. That's all.

CHAIRPERSON ANASTASIO: So I'm not quite sure what you're asking, Kathy. Are you saying you'd like to check the document to make sure ambient levels are in

there before we approve it?

PANEL MEMBER HAMMOND: Yeah. Yes.

CHAIRPERSON ANASTASIO: Okay. So I've got Kathy checking ambient levels and Karen and Paul checking the statistics. Okay.

PANEL MEMBER MESSER: Could I just venture a clarifying suggestion and Paul please comment on it. I just think it doesn't necessarily require a huge statistical project or a sophisticated statistical approach to answer our questions about the un -- the uncertainty of the small sample sizes, especially given that the means and standard deviations are there. Is that your feeling, Paul?

You're muted.

PANEL MEMBER BLANC: I think what Cort was referring to is when we have a major change to a document, typically there's a second look at it with that major change. So if the level goes down by a considerable factor, if they have to go with that value being a low effect level, so the Panel, or representatives of the Panel, should look at it. Then what Kathy is saying, and, Kathy, I hope I'm not putting words in your mouth, but what I hear her saying is not that she doesn't believe they'll put ambient data in the document. But if that ambient data shows that the current ambient levels would

be triggering the REL every day of the week, then that raises an issue that the Panel might want to consider, because they'll have to address that issue. Not they'll have to water down the REL, but they'll have to come up with language which says that we need additional speciated data, and, you know, whatever -- there -- you know, I think we faced this before with -- I forget if it was the value on acrolein or something, you know, where the level came out to be very close to what frequent ambient values are, but I -- Kathy, isn't that what you were kind of getting at?

PANEL MEMBER HAMMOND: Yes. And actually since you're a lead reviewer, I'd be happy to defer to you, you know, to look at those values, just to make it easier for -- but, yes, I agree. I agree. Yeah.

PANEL MEMBER BLANC: And I actually would --

PANEL MEMBER HAMMOND: I mean, it's not to water them down, but rather --

PANEL MEMBER BLANC: No, I know.

PANEL MEMBER HAMMOND: -- it's like we need to not put out a document where nobody says hey, hey, hey, you know, we're at ten times the levels or something.

PANEL MEMBER BLANC: Right. Well, I think that would also -- I would rely on the judgment of the Chair in terms of whether the --

PANEL MEMBER HAMMOND: Um-hmm.

PANEL MEMBER BLANC: -- the whole group needs to then --

PANEL MEMBER HAMMOND: Right.

PANEL MEMBER BLANC: -- have a follow-up discussion in our October meeting with this. And -- oh, that reminds me of one other thing I meant to say, which is I do think, Rona, there should be a sentence there which says even though this document only looked at the literature systematically through August of 2020, we did do a follow-up review just to make sure there we're no major papers since that time through, you know, April of 2021. Because now, we're nine months out, and so it looks -- you know, it looks a little odd. You don't have to say we went back to ground zero and did everything over, but we -- you know, we've --

DR. SILVA: Yeah.

PANEL MEMBER BLANC: -- reassured ourselves that there's nothing in the interim. One sentence like that.

DR. SILVA: Yeah, we can do that and we actually have done that, so --

(Laughter.)

PANEL MEMBER BLANC: Why not take credit for it.

DR. SILVA: Yeah. Yeah. Right, yes.

CHAIRPERSON ANASTASIO: Okay. So OEHHA -- oh,

sorry. Karen, go ahead.

PANEL MEMBER MESSER: Yeah, sorry to keep harping on this. So, thank you, Paul. I'm totally happen to review the document. I guess my comment was more I didn't want these comments to necessarily be interpreted that we're requiring a huge statistical modeling effort, if that's not required, to make the case. That was -- that was my comment. It's just we need a better look at this issue. And if the case can be made without a huge sophisticated statistical modeling effort, that's fine.

PANEL MEMBER BLANC: Yeah. I don't disagree with that. I do think that -- I think this will resonate with John, which is to whatever extent they can come up with a way of doing this in the systematic fashion, which they can then use the next time around, it will probably be something to have in their back pocket, right, John?

DR. BUDROE: That's what we'll try to do.

PANEL MEMBER MESSER: I agree. I agree.

CHAIRPERSON ANASTASIO: Thank you, Karen.

Beate, did you have a question or comment?

PANEL MEMBER RITZ: Yeah, just a comment. I looked at the table in our measurement and it looks darn close to your levels, if I interpret correctly, the microgram per cubic meter, on the Harvard impactors. But, of course, that was also chromium. So there's some, you

know, speculations probably to be made. But I think Kathy is right on, we need to at least be aware of it.

CHAIRPERSON ANASTASIO: Okay. Yeah. So I'll -- I will look at that. And then if the ambient levels are close to what the chronic REL ends up being, I'll contact the panel and see if we want to do anything differently.

Any other comments?

Okay. Seeing none, we'll put chromium(III) temporarily to rest. I'd like to thank Rona again for her document and her presentation and thank all of OEHHA for that input.

The last piece we have here is the catch-all consideration of administrative matters. And the only administrative matter we have is our next meeting. So, Lori, sent this out already, but make sure that it's on your calendar, please. Friday, October 15th, at 9:30 a.m. We expect we're going to have a full agenda then, so we'll go until 2:30-ish, so please block that out.

Any other administrative matters from anyone?

PANEL MEMBER BLANC: I mean, just an administrative matter is we still don't know whether -- do we still not know whether that meeting will be face-to-face or is the decision that we will no longer meet face-to-face no matter what happens?

CHAIRPERSON ANASTASIO: We've not --

PANEL MEMBER BLANC: And is there a date for when that piece of it will be decided?

CHAIRPERSON ANASTASIO: We have made no decision about moving to all remote meetings. But, Lori, any thoughts about whether we'll be able to meet in person or whether that will be remote?

PANEL LIAISON MIYASATO: I don't think we know yet, but I reserved a hearing room just in case. But it could go either way.

CHAIRPERSON ANASTASIO: I mean, I have to say this remote meeting is very convenient. So we should talk as a Panel. And I don't know if there are any requirements on the Panel that we meet in person, but maybe we move to a schedule where it's mostly remote or part-time remote. We could think about what works best for us.

And if -- you know, you certainly lose things, you lose some things when you meet remotely, but perhaps the incredible convenience is worth it. So that's something I can talk about with CalEPA.

PANEL MEMBER BLANC: Yeah, I mean, I think that legal should weigh in on that.

CHAIRPERSON ANASTASIO: Yeah.

PANEL MEMBER BLANC: There may be, in fact, a legal requirement that doesn't matter what we would prefer

once it's -- once we're over the emergency, we would have to meet in person.

CHAIRPERSON ANASTASIO: Yeah, right. That's something we'll check.

PANEL MEMBER HAMMOND: And another possibility is if it legal, following Paul's comment, we might still want to have one meeting a year that's in person. I mean, I think the -- there is the opportunity --

CHAIRPERSON ANASTASIO: Yeah, it's nice to see each other and see the agency people definitely.

PANEL MEMBER HAMMOND: Exactly. I think to see the agency people and for the public, if the public wants to actually see us too. All of that.

CHAIRPERSON ANASTASIO: Yeah.

PANEL MEMBER HAMMOND: Maybe once, if it's not required otherwise.

CHAIRPERSON ANASTASIO: Yeah.

PANEL MEMBER BLANC: Yeah. Actually, to follow up on that on the legal aspect, we have had -- what -- when we've had meetings where some participants participated remotely, those locations had to be public, right? So when I would join --

CHAIRPERSON ANASTASIO: Right.

PANEL MEMBER BLANC: -- Stan at his office, it was publicly announced where he and I were participating

from.

CHAIRPERSON ANASTASIO: Right. And the public could join you in that location.

PANEL MEMBER BLANC: That's right. Yeah.

CHAIRPERSON ANASTASIO: So I hope you can put on some coffee for them, Paul, when they come by your house.

(Laughter.)

PANEL MEMBER RITZ: So that means in October I can only participate if it's remote, because I'm going to be in Europe.

CHAIRPERSON ANASTASIO: Okay.

PANEL MEMBER RITZ: I can go to a library, but nobody probably will fly over there.

PANEL MEMBER BLANC: No, I think Beate, you're not correct. If it was in person and you could only participate remotely, you can do that --

CHAIRPERSON ANASTASIO: Yes.

PANEL MEMBER BLANC: -- I mean, historically. You'd have to say the library that you were doing it at. And if somebody wanted to show up there, theoretically they could, but otherwise, you can.

PANEL MEMBER KLEINMAN: But if we keep to a hybrid model, where non-panel members can just join by Zoom and the rest of us meet in person, we eliminate that problem, even for people who are going to be coming in

remotely. I think the way we did it today is perfect.

PANEL MEMBER BLANC: No, I think --

CHAIRPERSON ANASTASIO: You just muted yourself, Paul.

Paul, you were -- you started talking and then you muted.

Okay. You muted again.

You're too fast on the trigger.

You're muted.

PANEL MEMBER BLANC: Okay. So now I'm not muted.

Mike, I think that's not true based on these -- this experience I'm saying that it was -- there was an open meeting in person, but we -- I participated with Stan from UCSF and I think we had to say where we were, even though people could have gone to the meeting in Sacramento, I think. That's my memory. And maybe I'm --

CHAIRPERSON ANASTASIO: Yeah, that's correct. And, you know, even when we met in person, it's always been broadcast over the web.

PANEL MEMBER BLANC: Yeah.

CHAIRPERSON ANASTASIO: And people can comment over the web, so that's always been available to people.

So I'll talk with CalEPA, see what the legal or other requirements might be and then we can talk as a Panel once we understand the parameters, and talk about

what we would prefer, if we have some options.

Yeah. Okay. Any other administrative matters?

Okay. Seeing none, could I get a motion to adjourn?

PANEL MEMBER LANDOLPH: Hand raised.

PANEL MEMBER KLEINMAN: So moved.

CHAIRPERSON ANASTASIO: Okay. Can I get?

All in favor?

(Hands raised.)

CHAIRPERSON ANASTASIO: Ahmad, you want to keep going?

Oh, there we go.

(Laughter.)

CHAIRPERSON ANASTASIO: All right. He can't Get enough SRP. All right. Well, the meeting is therefore adjourned. Thank you, everyone. Appreciate your time and you intellectual prowess. And we will follow up on this document in the way that we discussed.

All right. Have a great weekend.

(Byes.)

(Thank yous.)

(Thereupon the California Air Resources Board, Scientific Review Panel adjourned at 12:40 p.m.)

CERTIFICATE OF REPORTER

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

That I am a disinterested person herein; that the foregoing California 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 12th day of May, 2020.

JAMES F. PETERS, CSR
Certified Shorthand Reporter
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