CALIFORNIA ENVIRONMENTAL CONTAMINANT BIOMONITORING PROGRAM

(BIOMONITORING CALIFORNIA)

SCIENTIFIC GUIDANCE PANEL MEETING

CONVENED BY:

OFFICE OF ENVIRONMENTAL HEALTH HAZARD ASSESSMENT

CALIFORNIA DEPARTMENT OF PUBLIC HEALTH

STATE OF CALIFORNIA

CALEPA BUILDING

SIERRA HEARING ROOM

1001 I STREET

SACRAMENTO, CALIFORNIA

WEDNESDAY, MARCH 4, 2020

10:00 A.M.

JAMES F. PETERS, CSR
CERTIFIED SHORTHAND REPORTER
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A P P E A R A N C E S

PANEL MEMBERS:

Megan R. Schwarzman, M.D., M.P.H., Chair

Carl Cranor, Ph.D., M.S.L.

Oliver Fiehn, Ph.D.

Eunha Hoh, Ph.D., M.S.E.S.
(via teleconference)

Ulrike Luderer, M.D., Ph.D.

Thomas McKone, Ph.D.

Penelope (Jenny) Quintana, Ph.D., M.P.H.
(via teleconference)

José Suárez, M.D., Ph.D., M.P.H.

Veena Singla, Ph.D.

OFFICE OF ENVIRONMENTAL HEALTH HAZARD ASSESSMENT:

Lauren Zeise, Ph.D., Director

Carl DeNigris, Senior Attorney

Sara Hoover, M.S., Chief, Safer Alternatives Assessment and Biomonitoring Section, Reproductive and Cancer Hazard Assessment Branch

Shoba Iyer, Ph.D., Staff Toxicologist, Safer Alternatives Assessment and Biomonitoring Section, Reproductive and Cancer Hazard Assessment Branch

Duyen Kauffman, Health Program Specialist, Safer Alternatives Assessment and Biomonitoring Section, Reproductive and Cancer Hazard Assessment Branch

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

CALIFORNIA DEPARTMENT OF PUBLIC HEALTH:

Kathleen Attfield, Sc.D., Research Scientist III, Exposure Assessment Section, Environmental Health Investigations Branch

Bob Harrison, M.D., Ph.D., Chief, Occupational Health Surveillance and Evaluation Program, Occupational Health Branch

Nerissa Wu, Ph.D., Chief, Exposure Assessment Section, Environmental Health Investigations Branch

CALIFORNIA DEPARTMENT OF TOXIC SUBSTANCES CONTROL:

Anne Cooper Doherty, Ph.D.

PRESENTERS:

Terry Hrubec, D.V.M, Ph.D., Professor of Anatomy and Embryology, Edward Via College of Osteopathic Medicine, Virginia

Lipin Xu, Ph.D., Assistant Professor, Department of Medicinal Chemistry, School of Pharmacy, University of Washington

ALSO PRESENT:

Taylor Bradley, American Cleaning Institute

Emily Bryson, M.P.H., Senior Environmental Scientist, California Department of Pesticide Regulation

Sandipan Datta, Ph.D., University of California, Davis

Keith Hostetler, Ph.D., Toxicology Regulatory Services, Inc.

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

ALSO PRESENT:

Tom Osimitz, Ph.D., Science Strategies, LLC

Andrew Rubin, Ph.D., DABT, California Department of Pesticide Regulation

I N D E X

I N D E X C O N T I N U E D

P R O C E E D I N G S

MS. KAUFFMAN: Good morning, everyone. I'm Duyen Kauffman from the Office of Environmental Health Hazard Assessment. I'd like to invite you all to take your seats, please. If everyone could gather, we will begin the meeting -- yeah, we will begin the meeting promptly at 10:00 a.m.

So before we start promptly at 10:00, I do have a few housekeeping items. Today's meeting is available via webcast. Please speak directly into the microphone and introduce yourself before speaking. This is for the benefit of the people participating via the webcast and for the transcriber.

Copies of the meeting materials are available at the table near the door. We will break at 12:25 p.m. for lunch. And the restrooms are located through the doors that you entered through -- down the hall and to your left past all of the rest of the hearing rooms.

And in the event of an emergency, there are emergency exits at the back of the room marked and -- well, the front of the room and the back. So please use those to evacuate the room, if needed.

And now, I'd like to introduce Lauren Zeise, Director of the Office of Environmental Health Hazard Assessment, also known as OEHHA.

DIRECTOR ZEISE: Thank you, Duyen. So I'd like to welcome everyone on this beautiful spring -- early spring day to the meeting of the Scientific Guidance Panel for the California Environmental Contaminant Biomonitoring Program, also known as Biomonitoring California. So thank you, Panel and audience, both in the room and on the web for participating and sharing your expertise.

So just a brief recap of the November 6th, 2019 meeting. After the Program update, the morning session focused on reviewing initial findings from the California Regional Exposures Study in Los Angeles, also known as CARE-LA. We also have results posted on the web. And also, we heard on the initial findings for the East Bay Diesel Exposure Project. So -- and analyses of the -- these studies are ongoing and you'll hear more about the CARE study this morning.

In the afternoon, staff from the California Air Resources Board provided an update on the Community Air Protection Program, which was established as part of implementing AB 617, and two of the AB 617 communities were profiled. The morning and afternoon presentations informed the discussion -- the session exploring the next steps for biomonitoring in 617 communities.

Some of the recommendations from this discussion with the Panel, guest speakers, and audience were to

recruit pregnant women and children, as particularly vulnerable subpopulations in AB 617 communities, design intervention studies to examine the effectiveness of emissions and exposure reduction efforts, and inform regulatory policy, and continue the Program's community engagement work as a crucial element for the successful implementation of targeted biomonitoring studies.

So a summary of input from the November meeting, along with the complete transcript is posted on the November SGP meeting page on biomonitoring.ca.gov.

So I'd like to take the opportunity this morning to acknowledge Tom McKone for his Lifetime Achievement Award, a recognition bestowed by the Director of the Lawrence Berkeley National Laboratory. Tom has had a very distinguished career of more than 30 years in exposure science. He's come to provide us advice at OEHHA on many an occasion. And he has helped develop the exposure science field. And he's a world-renowned expert. So we're truly fortunate to benefit from Tom's expertise on the SGP as a member and we'd like to congratulate Tom.

(Applause.)

DIRECTOR ZEISE: And now I'll hand off to our SGP care -- Chair, Meg Schwarzman, who will provide more details about today's meeting.

CHAIRPERSON SCHWARZMAN: Great. Thank you so

much, Lauren.

Is that okay?

Yeah.

So I want to, now that Lauren has reviewed the last meeting, announce the goals for this meeting. In the morning session, we're going to receive a Program update, which will include a summary of recent activities of the CARE study, the California Regional Exposure Study. And the remainder of the meeting we'll focus on the Panel's consideration of quaternary ammonium compounds, which we'll refer to as QACs, or often they're called quats, as potential designated chemicals. We'll hear from OEHHA several presentations. One is an overview on the document on the QACs that OEHHA has prepared. We'll see -- have presentations by two guest speakers and we'll have remarks from a guest discussant and comments from Program stakeholders.

There will be plenty of time for Panel discussion, as well as comments from guest speakers and the audience, and additional public comment, and time for the Panel's deliberations on the recommendation for this class of chemicals.

If you wish to speak during the Program update public comment period, or the afternoon discussion, or comment periods, please fill out a comment card. They're

available at the table near the door and from Duyen Kauffman. For the question periods, please come to the podium here and -- or raise your hand, and I'll call on you at the appropriate moment. For the benefit of our transcriber, please clearly identify yourself, and -- before providing your comment and write your name and affiliation on the sign-in sheet for reference.

If you are joining the meeting via webinar, you can also provide public comments via email. The email address is on the webcast there. Its's biomonitoring@oehha.ca.gov. We will read aloud relevant comment and paraphrase them as necessary in the relevant time periods. Please keep your comments brief and focused on the items under discussion. And depending on how many comments there are, we'll impose time limits, but we'll see how that goes.

Two of our Panel members are joining the meeting remotely, Eunha Hoh and Jenny Quintana are connected by teleconference line and we'll work to integrate them into the discussion.

And before we go to our first presentation, I want to invite Veena Singla to announce her new position.

PANEL MEMBER SINGLA: Good morning. Thank you, Meg. I'm now a Senior Scientist with the Natural Resources Defense Council on my third day.

(Laughter.)

PANEL MEMBER SINGLA: So I don't have any email yet. It's wonderful.

(Laughter.)

CHAIRPERSON SCHWARZMAN: Great. Thank you.

Okay. Next, I want to introduce Nerissa Wu. She is Chief of the Exposure Assessment Section in the Environmental Health Investigations Branch at the California Department of Public Health. And she's overall lead for Biomonitoring California. She'll provide an update on current Program activities.

(Thereupon an overhead presentation was presented as follows.)

DR. WU: Got it. Okay. There we go. Hi, everyone. Thanks for joining us. Welcome. Particularly if you're coming from some distance, I really appreciate you making the trip here. I know it's not the easiest time to travel. I am going to be giving an overview of our Program activities over the last few months, particularly focusing on CARE, but I do want to spend a little time talking first about the East Bay Diesel, which --

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DR. WU: -- the East Bay Diesel Exposure Project, which you heard about in our last session. Last time we

met, you had just heard that results had been given back to participants, and that includes both the 1-NP, 1-nitropyrene, metabolites in urine, as well as the environmental information in dust and air. So all 40 of the households that participated in EBDEP were sent their results.

Most recently, there was just a community meeting held at the AB 617 steering committee meeting in West Oakland and that was in mid-February. It was well attended. We had EBDEP staff there answering questions that came up during the meeting. And the staff is now currently tentatively planning to meet with another community, the 617 steering committee for the Richmond-San Pablo community. And both at the SGP meeting and at the screening meetings preliminary data analyses are being presented.

But there is quite a bit more data analysis to come, as the EBDEP collected many, many facets of data, many different things to look at, including traffic, and other diesel exhaust exposures sources, time at home and participant activities, and also weather conditions. So all that will be modeled and we'll have more to present on this project in the future.

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DR. WU: Related to EBDEP, we have the AB 617

activities, which again you also heard a little bit about at our last meeting. OEHHA is leading the work, working with the Community Air Protection Program, which was established by the California Air Resources Board. So there's coordination with CARB. There's engagement with the AB 617 communities and local air districts. And they're working to get contract funds out to scope and design these three targeted biomonitoring studies in AB 617 communities in Northern, Central, and Southern California.

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DR. WU: So now I'm going to turn to the CARE study, the California Regional Exposure Study, which is our statewide surveillance. And I know most of you have heard this. But for those of you tuning in for the first time, let me give you a quick overview of what the study looks like.

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DR. WU: Statewide surveillance. We've divided California up into eight regions, based on the geography and population. We're currently on pace to biomonitor in one region per year, enrolling 300 to 500 participants per region. And any participant in our biomonitoring studies is biomonitored for metals and for per- and polyfluoroalkyl substances, or the PFASs. And then as

possible, we add on some additional chemical panels.

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DR. WU: This is an overview of the different regions where we've been in the past few years. CARE-LA was our first region, which we biomonitored in 2018. We were able to get results back and we're now in the phase of more in-depth data analysis. CARE-2, which is San Bernardino, Riverside, Inyo, Mono, and Imperial counties, we finished our field work in 2019 and we were -- we returned results in February. And we are now in the field for CARE-3. So we have three active CARE regions going on.

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DR. WU: CARE-3 is San Diego and Orange counties. And you see here a map which depicts the zones. As per our usual protocol, we've taken the region and divided it into these geographic subzones so that we can look at demographics and come up with sampling goals across the region. It's roughly evenly split population-wide between San Diego and Orange County. And so our sampling goals reflect that.

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DR. WU: We have gotten our field offices open. In Orange County, we're at the Regional Transportation Center at Santa Ana. In San Diego, we have an office at

the Collective Impact Center. These are both very centrally located with good parking and public access. And so we hope that makes it easy for our participants to get to.

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DR. WU: And our recruitment postcard, which I'm now realizing I forgot to bring a copy of, it's a similar postcard to what went out last year. It went out to 65,000 households that were in randomly selected carrier routes. So that went out to those households in early February. We typically see a little bump in people responding to our -- we have an online form, where people can come and say I'm interested in being part of this -- of this study, so we can screen their eligibility, get some information on their demographics. And we usually see a surge in interest about a week after the postcard goes out.

And so by February 20th, we're able to do a round of selection, where we go through eligible participants and pick the people that we're going to invite. This was only the first round. We usually do two or three more rounds of selection. So if you live in San Diego or Orange County and haven't gotten your invitation yet, don't despair, there's still time to get on our list.

We were able to get our office opened and

operating February 26th and we had our first sample collected. That's very exciting. We will be in the field till the end of April, may go through till the beginning of May. We had a little delay in getting our office set up, some challenges getting that on the ground. So it may go a little later this year than it has in the past.

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DR. WU: So here's how we're doing in recruitment so far. We've had more than 700 people fill out the form saying I am interested in being part of this study. About a third of those came from the postcard. So we're on track for about the same kind of response rate of the postcard. We don't expect a ton of people to respond to it, but it's at a percentage high enough that we are getting about a third of our participants from that postcard.

We've invited 378 people to participate in the study so far. And 167 of them have already responded and participated to an extent. They've gotten their informed consent in or their survey, and 148 of those have scheduled their appointment.

So a couple things to note that some of the participants, about 85 percent of them, are participating online, which is quick, it's easy for us, and for the participants. But there is 15 percent of our participant

pool that wants a paper-mailed packet. So these numbers are going to change rapidly as those packets make their way to their address, get filled out, and sent back to us. There's always a little bit of a delay when people are filling it out on paper.

The other thing we see in this region, which is consistent with previous regions is that people aren't really getting stuck in the pipeline. If you enroll, you're typically going through and getting your appointment scheduled. People aren't dropping out at the informed consent or at the survey phase, which is good for us to know. It means that our survey is not -- we hope it means that it's not onerous and people aren't giving up part way through.

We did start sample collection, as I mentioned, and as of Monday, we had 13 samples. But I checked this morning and we're up to 21, so that's only 330 more to go.

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DR. WU: So moving on to CARE-2, as I mentioned, we did get our results back to participants within a year of starting field work in CARE-2, which is our goals as a Program to return results within a year, because people are often very anxious and asking why does it take so long to get my results. So we actually have that written into our IRB protocol that we will get results back to people

within the year, and we work very hard to meet that.

All of our 359 participants did give us a urine and a whole blood sample. We were missing a serum sample from one participant. And unfortunately, we did have two urine samples break during shipment. And so as I walk through the results, just note that the denominator is not the same for each of the analytes. We're missing a couple here and there.

You see here the breakdown of who got what results. We were able to do 1-nitropyrene analysis on 159 samples and phenols analysis on 150 samples. And we select those by, first of all, on the informed consent, people are able to opt to donate their samples for addition analyses, but also they need to have given us enough urine, particularly for 1-nitropyrene which -- for which we do need quite a large volume of urine and then we select the participants from the eligible pool.

So about a third of the participants got the baseline, metals and PFAS only. And most participants at least got one additional panel with 63 of our 359 participants getting all four analytical panels in their packet.

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DR. WU: So I'm going to walk through an overview of what the results from metals and PFAS look like. I

want to just state again that this is really preliminary. We haven't gotten to the point of data analysis looking at demographics and doing comparisons. So just keep that in mind as we walk through.

These are blood metals. And as you can see, the detection frequency is pretty similar to what we saw in CARE-LA, the geometric means are slightly lower.

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DR. WU: Also, for urinary metals, the detection frequencies again are very similar to what's found in CARE-LA, with the exception of mercury. There were some differences in minimum detect limits. So we'll be doing analysis to see how much that might have had a bearing on the detection frequency. And you do see that there are some lower geometric means in Region 2 as compared to Region 1. And this just to note it's creatinine adjusted, so it is adjusted for dilution.

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DR. WU: One of the ways we look at metals levels is looking at the number of exceedances, the number of participants who have a metals level over our observed level of concern. And we do have levels of concern for urinary and blood mercury, for inorganic arsenic, and lead, and cadmium.

And so the table here shows the number and

proportion of participants who are showing an exceedance of an LOC. And we see that for mercury and for blood mercury. And for inorganic arsenic, CARE-LA had larger proportion of participants exceed the LOC. But as I think was reported out in our last meeting, in CARE-2, we did have somebody with a very elevated level of urinary mercury, which is something that we did not see in CARE-LA. And we did have some more lead exceedances in CARE-2 compared with CARE-LA.

So again, we will be going back and looking at the demographics, looking at some of the exposure parameters to see what we can learn about people in the this exceedance category and what predicts that level of exposure.

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DR. WU: Now, turning to the PFAS in CARE. This is a comparison for those 12 PFASs that we do measure. This only shows the ones that were detected in 65 percent or greater of the population in one or other of the regions. So it only shows -- I think there's seven up here that were -- that fall into that category. And there are lots of similarities between CARE-LA and CARE-2, as there were for metals with many of the high detection frequencies being very similar for PFOA, PFHxS, PFOS and PFNA.

We have compared the geometric mean for the ones which -- for which detection is above 65 percent. And you see that Region 2 was lower than Region 1, with the exception of PFOS and PFHxS. So we have not gotten into the point of look at timing of sample collection, the participant attributes, or some of the exposure parameters, which might drive this level of exposure. But that is all to come, and hopefully we'll able to report out to you in the next SGP meeting some more data analyses.

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DR. WU: So this is just an overview of what we do with data as it comes to us from the lab. Our first priority, of course, is our participants. And we turn around the notification of metals results, if there has been an exceedance. We do that as quickly as possible. And we get results back to participants, as a second stage.

We are now going into summary data for CARE-2, where we'll be looking at demographics, looking at comparisons, doing kind of a first run of analyses, so that we can report it -- put it on the website, report it back publicly, report it to the SGP meeting. And then, as with CARE-LA, we'll be digging deeper into those exposure parameters to look at modeling and what predicts exposure.

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DR. WU: And this was just Lauren Baehner about to send out a results return. I mistimed that picture.

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DR. WU: So it has been a little bit of a treadmill getting from one region to the next, in our one region per month -- one region per year scenario. By the time we finish field work in one region, we're turning around and we're doing outreach in the next region to get back into the field in January.

So once we finish Region 3 field work, we are going to take a pause. Rather than follow our typical schedule, we're hoping to launch the next region maybe a year and a half, potentially two years, after the launch of CARE-3. This will get us a little time to reflect on how the -- how the CARE study is going and to think about how we can continue it, given our current funding situation.

So as I mentioned, CARE is currently based on eight regions, conducting sampling in one region per year and three to five hundred participants per region. Eventually, we may come to a scenario where we condense some of those regions into fewer regions.

We may have to slow down the pace of biomonitoring, so that we're covering one region per two

years, one per one and a half years, which would mean a 12- to 16-year cycle to cover the entire state. We could cut down on the number of participants per region. All of these parameters are under discussion and we just need to do some more analysis. We need to take some time to think about what does that save us in terms of costs. We don't really have a budget for field work, for rental of space, for contract staff, for the supplies we need to be out in the field.

So what do these changes mean in terms of savings for our Program? But more importantly, what does it mean in terms of validity of the study, in terms of representation across California? So that's something that we need to take a little time to consider.

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DR. WU: Another reason for us to take a little longer is that we're amassing an enormous amount of data, both within the CARE study, but also from previous studies that predated CARE. And we really need the time for our analysts to get into the data and mine the data and get that information out, so that people can see the benefit of doing biomonitoring.

So one thing we're doing in our epi staff right now is we're doing a lot of cross-training, which is good for a number of reasons. We keep having staff pulled off

for emergency response to things and it's really important for us to have staff be able to continue out the tasks of field work and monitoring what's going on in the Biomonitoring Program, even when we are short-staffed. But also importantly to this discussion, it allows analysts to take a step back from the day-to-day work and really dig deep into the data, which is something that we -- we don't typically have.

So the manuscripts in progress that I have listed here, things like metals in BEST; metals in the Asian/Pacific Islander Community Exposures, or ACE Project, which is -- we had some really interesting findings and it's really important for public health to get this information out; and then PFAS in BEST and the ACE Project, which Kathleen is working on.

These are really important data sources that we really want to have both in the published literature, but also available to researchers to start looking at those numbers in comparison to what else has been published.

And this does not include CARE. There are obviously many -- many questions we want to answer with the CARE data. And so we hope that there will be other manuscripts in progress as well.

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DR. WU: And in addition to the CARE study, our

labs are quite busy doing these lab collaborations. So this is in contrast to what's considered a full biomonitoring collaboration, where Biomonitoring California is working on project design, and field work, and results return. This is where the lab is either directly collaborating with outside researchers, or they are providing a service to outside researchers. And both ECL and EHL have been working with Camp Fire samples, with Commonweal and the San Francisco Firefighter Cancer Prevention Foundation, to analyze samples that were collected immediately following deployment to Camp Fire last year. EHL is working on a couple tobacco-related studies looking at cotinine in almost 3,000 samples.

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DR. WU: And ECL is doing quite a bit of work working with UCSF and University of Illinois on the ECHO study, Environmental Influences on Child Health Outcomes doing 500 PFAS analyses. And they are also doing quite a bit of work with their non-targeted analyses working with D -- with UCSF, and Silent Spring, and Berkeley on a number of maternal infant pairs and women worker studies. So we hope to hear a little bit more about those studies in our next SGP session in July.

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DR. WU: So just in closing, I want to

acknowledge our staff. You don't get to see a lot of them up here, but they are the people who make this work go. They make the Program tick. I particularly want to say thank you to Russ Bartlett, who has played a really key role in field work and data analysis for EBDEP. He's been part of the team that develops fact sheets and gets things up on the web. He is usually here supporting the SGP meeting and he's no longer part of Biomonitoring California.

And I'm looking at Sara, because I feel a little bad about this. He's left Biomonitoring to join my section at CDPH, so I get to continue working with Russ. And I realize this kind of stealing back and forth means that we need more environmental health professionals in general. But he will continue to do the good work he does focusing on heavy metals exposure through skin-lightening cream and other consumer products.

So he's not leaving the world. We hope to be able to still collaborate with him. So with that, I will take any questions.

CHAIRPERSON SCHWARZMAN: Great. Let's start with any clarifying questions from the Panel.

Carl.

PANEL MEMBER CRANOR: A couple of different questions. Early in your slides, you have a penultimate

or final step to do statistics epi results. What does that mean? Are you just compiling averages across people or are you actually looking at health effects?

DR. WU: We do not collect health effect data for this study.

PANEL MEMBER CRANOR: That's what I thought.

DR. WU: So we have -- it's -- we have kind of a tiered approach to doing our statistical analysis. And actually Kathleen who leads our stats team could also respond to this, if you have anything to add. We're -- we do demographic work first and some very simple modeling to look -- to compare across demographic population, and then compared to NHANES, compared between some of our different studies.

But when we start getting into our exposure parameters, then it's a whole different level of model building. And so that's -- that's why there's sort of a division. It just involves a lot more work. And so we try to get that first tier of statistical work out.

PANEL MEMBER CRANOR: Then right toward the end, you're going -- you have manuscripts in progress. Will we be informed when those come out?

DR. WU: Yes, absolutely. They are always posted on our website. And I assume that you're all subscribers to our listserv, and so would get notification of those

manuscripts coming out. But we're also happy to talk about -- I'm sure people will be presenting that data here as they work through it, so -- and we're happy to --

PANEL MEMBER CRANOR: And in those, when you have the exposure information, do you also add in, I don't know, what public health standards are just for comparison?

DR. WU: If there are public health standards, yes. The ACE paper on metals is talking about the LOCs, the limits -- levels of concern. So there is some discussion of where those came from. PFAS, of course, it's a little more of a difficult discussion. But, yeah, there is -- actually, I can't promise what's in the paper. They're not written yet, but --

(Laughter.)

DR. WU: But, yes, I would assume for metals, there will be that discussion.

PANEL MEMBER CRANOR: Thank you.

CHAIRPERSON SCHWARZMAN: We have a clarifying questions from Jenny Quintana on the phone.

PANEL MEMBER QUINTANA: Hi. This is Jenny Quintana. I sent it by email. I'm not sure if you wanted to read it out or have me talk?

CHAIRPERSON SCHWARZMAN: Go ahead. You can talk.

PANEL MEMBER QUINTANA: Okay. Hi. My

question -- thank you, Dr. Wu. This question is regarding CARE-3 for San Diego County and Orange County. Since I'm in San Diego, I feel kind of responsible of making sure you get your participants.

Could you expand a little bit on how participants are recruited? You talked about the postcards, but I believe you have other efforts.

And then just to quickly go through my questions. Can you say what groups are currently underrepresented that might need more efforts? And then the lastly, I was wondering what languages the online application is offered in. And I was looking at that online to -- so I could answer that without bothering you. But I actually couldn't find any link for applicants to apply through the California Biomonitoring webpage itself, and I was wondering if it should on there.

Thank you.

DR. WU: Okay. So how are we recruiting? So we have this postcard that goes out to the households. And as I alluded to, about a third of our participants are coming from there. We post is on Craigslist, which is probably another third of our participants. And then we do do outreach through community venues, both community organizations, but also by posting flyers at nexuses, like libraries, YMCAs, places where people gather. And so

about a third of our participants are coming from those kinds of contacts as well.

Actually, schools are one of our big sources of recruitment. We do hear people -- we ask people where they've heard of us, and they often will say, well, my professor told me about this. So we do have quite a number of people coming from our academic friends in the Program.

What groups are currently underrepresented? It's very similar to what we've seen in other regions, in that we have -- it's -- we have a lot of white popu -- population. It's very highly educated. We have more women than men. And so our efforts to reach out to communities -- difficult-to-recruit communities are underway right now. Kathleen, did you want to add something to that?

PANEL MEMBER QUINTANA: Can you tell me what languages you post your flyers in?

DR. WU: So our flyers and all of our materials are available in English and Spanish. We do say on the pre-screen that if you do want a language other than English or Spanish, you can indicate. And I understand that is written in English, and so you need to at least have the ability to read that or have somebody read that to you in order to respond.

And we do have some other language participants who have indicated an interest in participating. And then we will translate some of the materials and have an interpreter work with you to fill out the survey and the informed consent, and make an appointment, and an interpreter at the appointment where you're having your blood and urine collected. It is --

PANEL MEMBER QUINTANA: Thank you.

DR. WU: Okay. Okay.

PANEL MEMBER QUINTANA: As you might imagine, I'm concerned about missing people that wouldn't respond to postcards necessarily. San Diego is home to a very large immigrant and refugee population. I think we have either the largest or second largest Chaldean Iraqi population, Somali, and many other populations. And so I'm just wondering -- since there's still time, I'm wondering if we could maybe you and I offline could talk about maybe reaching out to groups that serve those populations more specifically just to get a snapshot, and also along the border -- close to the border region trying to increase outreach there.

Thank you for all you're doing.

DR. WU: Yeah. And any groups that you can tell us about that we -- we're happy to flyer -- I mean, we have -- and this is surveillance, and so we're very

careful to not do targeted recruitment in a way that might end up with overclustering from a particular community, but we do want to make sure that we're inclusive. It is a challenge, you know, to get all the interpretation to have access to groups. It is a particular challenge these days to recruit in populations that already feel under threat for various reasons.

This year, we've had a particular issue with recruiting Asian population. And I don't know if that's related to Coronavirus or people not gathering in spots. So we are -- we are -- we have just started. And so we have -- we have our field presence. We have actually people in the field today doing some active flyering in different communities. So we hope -- we hope to see those numbers increase.

Oh, and you asked about the website, Jenny.

So there is a link to the CARE study on the general Biomonitoring webpage. The CARE study has its own webpage as well, which is where you have information and a link to the pre-screen portal.

I'm not -- maybe one of the OEHHA staff can talk about where it is on the OEHHA website, because I can't remember.

PANEL MEMBER QUINTANA: Yeah, I went to the CARE study site, but I -- I mean the -- on your page, but it

wasn't obvious to me, if I were a community person and I heard about it, I couldn't find it with a --

MS. HOOVER: This is -- this is Sara Hoover, Jenny. Actually, we worked with Nerissa's group and Robin Christensen about exactly how they wanted to roll that out. So they have a dedicated website that they send participants to. On our website, we advise people to either email the Program or email the CARE study email. And actually, when we -- on our website, when we set up a new project page, it's generally to release results.

So we created a CARE page. Then when we were ready to release summary results for CARE-LA, we created a CARE-LA page. So, so far, I mean, we actually have had a number of inquiries directed to the Biomonitoring email. And my understanding, too, because of the nature of the CARE recruitment - and Nerissa, you can correct me if I'm wrong - there was some desire to have, you know, a certain structure for advertising that information. And so at one point, we did have a direct link to here's how you can sign up, but that was kept instead on your website.

PANEL MEMBER QUINTANA: Thank you.

CHAIRPERSON SCHWARZMAN: So just to clarify, the flow here. We have until about 11:00 o'clock for discussion and public comment -- or public comment and then Panel discussion. So I just want to invite any more

clarifying questions for Nerissa at this point and then we'll have a quick public comment session and we can have broader ranging discussion at that point.

Any other clarifying questions?

I have one, if no other Panel members do.

This is on slide four, you mentioned the activities under AB 617. And I just wanted to ask if you have more detail, at this point, about those last two -- that last bullet about some targeted biomonitoring studies with AB 617 communities?

DR. WU: I do not, but Sara does.

MS. HOOVER: This is Sara Hoover. I can answer your question, but without a lot more detail. So as you may recall, we had a very extensive discussion, a scoping discussion, in November, and right now, this is where we are. So we're currently working on an internal draft contract, so I can't announce it publicly. But, you know, we're taking into account all the input we received during the last SGP meeting. And this should be done in the next few months and then we'll go live with that.

CHAIRPERSON SCHWARZMAN: Great. So maybe we'll get an update at our next meeting.

MS. HOOVER: You will definitely have an update by July, because we have to finish the contract before the end of June, so...

CHAIRPERSON SCHWARZMAN: And that will contain information about the design of the studies or that's not yet.

MS. HOOVER: No, no, no. The contract is to scope out a design. So it's a big -- it's a big effort as we discussed last time. And we have to be very judicious in how we approach it. It's complicated. The funding was based on EBDEP, which is a small, so that's why these are -- they have to be targeted. And we also have specific goals about trying to address, you know, what the community protection -- the Community Air Protection Program is doing. So we want to add value to that.

So we're talking with many, many different researchers, with CARB, with communities, and really trying to design studies that add value.

CHAIRPERSON SCHWARZMAN: Thank you very much.

José.

PANEL MEMBER SUÁREZ: Hi. I wanted to come back a little bit to the website comments, so -- for the website.

DR. WU: The general Biomonitoring website.

PANEL MEMBER SUÁREZ: So I know there are two different websites. I just did right now a very quick Google search, just imagining as if I were a participant interested in potentially joining CARE. So the top result

was the Biomonitoring California and then the second one was the one for recruitment of participants. When you think about that logic, you know, people usually tend to click on the first, maybe the second option, which takes them to the California Biomonitoring page. But that doesn't really lead them to where they really want to go, which is to the sign-up side of it. So it might be beneficial to include that information in the website.

Right now, I see the website is good. It just needs a little updating. Right now, it says we're starting to collect work on L.A. in 2018. I know there are certain pieces of the recruitment that you don't want so much from the website indeed. But however, I wanted to get your thoughts on that.

MS. HOOVER: Yeah. No. Thank you for that. And I noticed the same thing. So we rolled out the CARE-LA page, but we need to update the main CARE page. But what I think we can do, which will not pose a problem with the DPH concept for the recruitment, is we could add it in our banner, so we could direct people right on the homepage in the banner to go to the CARE page for CDPH. And it's a point well taken. There are also -- there was also an issue for a while where there were multiple CDPH pages that were still available, but had be -- had, you know, been phased out. So, yeah, it's a problem of what -- in

terms of what appears in Google.

So we will definitely address that on our website.

PANEL MEMBER SUÁREZ: Fantastic. And then I had another question more so. I'm looking again at the website from the California Biomonitoring, where it says here that you are collecting information for participants to identify potential exposure sources. So I wanted to know if you could expand just a little bit on that. And then the other question is do you have -- I suppose you're trying to have standard questionnaires throughout all the different regions. But understanding that there may be region-specific exposures, have you been thinking about questions specific to each of the regions?

DR. WU: Let me start with the webpage part of it. Actually, I want to actually address your previous question about the webpage. A lot of our information, the flyers, the postcards, everything have a direct link to the CDPH CARE website. So hopefully people who are saying, oh, I am interested in looking at that, have a direct address to go to and they're not going through the OEHHA -- or the Biomonitoring California page. But we can certainly, as Sara said, address that.

In terms of exposure sources, we do have a standard questionnaire that we are trying to keep fairly

stable through the three -- through all each of our regions. We want to have comparable data, so that people are answering the same question, so that there's something -- there's something standardized about it.

And we're -- we are constantly looking at literature to see if there are things we have missed, if there are other things we should be asking. There's obviously new literature coming out on exposure sources that we want to add. We do have to balance this against the length of the questionnaire, and how a question is asked.

And, I mean, there's literature on questionnaires and we do collect questionnaires from other researchers as well, but we want to be careful to ask questions in a way that have been validated, that we know how people understand it, and how they're going to be -- how they'll be responding to it, so we know what to do with those responses. And so it's quite an effort to change a questionnaire, not to say that we don't do it, but we are -- we do do it cautiously.

PANEL MEMBER SUÁREZ: I think my question is kind of aimed at certain exposures in certain industries that may be really pertinent to certain regions, but not at all to others. Like, if you go to Central Valley, the questionnaires or the information you may want to gather

may be a little bit different than the ones you would get from San Diego, given the differences that we have there from agricultural production versus other industrial processing and whatnot.

So, right now, after San Diego and Orange County, there is going to be a pause. And then after that, then you will be starting with the next regions. And what region would be the next two that you would be thinking about?

DR. WU: Well, we're creeping our way up from the south. So the two that are likely for four and five are Central Valley and the central coast, so --

PANEL MEMBER SUÁREZ: So I think it might be interesting to start thinking about that. I really like the idea of keeping the standard questionnaire everywhere. But perhaps in certain regions, it might be beneficial to start targeting a little bit more to that, especially if you think about Central Valley, maybe adding some additional pieces of agriculture may be beneficial.

DR. WU: Yeah. And certainly if we do have the ability to add on additional chemical panels, for example, pesticides, which would make some sense, we would have to develop a whole other section of the questionnaire. Our questionnaire does not currently address anything about pesticides. So that would be an effort we'd have to

undertake for -- if we were adding that on.

PANEL MEMBER SUÁREZ: Um-hmm. And I mean -- and a lot of people have been doing a lot of questionnaires. And it might be worthwhile just bringing in a few people, and not to have to reinvent the wheel, but actually build on something that's already well-developed.

DR. WU: Yeah. For sure. And we do rely quite a bit on our colleagues, and we ask can them to review the questionnaires. We ask them to give us feedback on how a question worked. And so, Kathleen actually does quite a bit of work with our questionnaire development and -- you want to comment on that?

DR. ATTFIELD: The only other comment I would --

THE COURT REPORTER: Please identify.

DR. ATTFIELD: Sorry?

THE COURT REPORTER: Identify.

DR. ATTFIELD. Kathleen Attfield from Biomonitoring California and CDPH.

The other thing I'd add is for the sake of staff and resource efficiencies, like processing these several questionnaires that we have, we've built a system now that hopefully we can implement -- that we're implementing in each region as we go. So we really want to build on those efficiencies, because it really can slow down the work of the staff, when we're making tweaks year after year.

But, of course, we -- we do want to accommodate questions that are specific to the panels of interest, and as we move from region to region as well.

CHAIRPERSON SCHWARZMAN: Any other clarifying questions for Nerissa?

Okay. Then I want to check for public comment?

MS. KAUFFMAN: (Shakes head.)

CHAIRPERSON SCHWARZMAN: In the room?

In that case, seeing none, we will just continue discussion among Panel members about the Program update and the CARE study update, and any other topics that you want to do before we move on to the main topic of the rest of the day.

PANEL MEMBER LUDERER: Thank you for that overview. And it's really great amazing to hear about all the progress that you've been making with the CARE study. And I have a question about the -- you know, the change in the timeline to -- you know, I completely understand that there's time need to do all these other things that hasn't been able to be done, because of doing the CARE study. But I was wondering if you could give the Panel some idea about, you know, how -- how much would your staff have to grow in order to keep doing the once per year region schedule and also accomplish the other things, like the manuscript writing, et cetera, that you -- that you

obviously want to and need to do. And, you know, maybe how -- what the funding that would be required to do that would be, an estimate of that.

DR. WU: Well, a couple years ago, we were asked to estimate what it would look like to have the Program -- like gold standard Biomonitoring Program doing CARE, doing targeted studies, doing all of these things. And if I'm remembering correctly, it was like a 12 to million -- 12 to 14 million dollar price tag with a staff of maybe 40 to 50 people at CDPH alone. So it's quite an investment above what we have now. But that's really what it would take.

You'll notice that I keep referring to Kathleen for results return, for our statistics, for our participant pool. I mean, Kathleen herself is running like three or four different parts -- facets of the Program, and that's one person. So the fact that we have a staff that is covering so many aspects is just not sustainable. So we would really, I would guess, need to double or triple our staff in order to keep going at this rate.

Some of it is also not in staffing, it's also in the way funding is given to the Program. So we have field staff, and it's remote from where we are, and so it makes sense for us to have contract and temporary staffing in

the field. We don't have people like phlebotomists. We can't move our staff down to a place for three or four months at a time. And so we do need contract dollars. We need to be able to rent facilities in order to have these -- these events for sample collection. And that's funding that we just don't have in the Program right now. So it's staff as well as auxiliary funding.

CHAIRPERSON SCHWARZMAN: Please, Oliver.

PANEL MEMBER FIEHN: Oliver Fiehn.

That leads to the next question. So to say that you have to rely on collaborations, and you elaborated a little bit on collaborations, specifically laboratory collaborations, some of them on PFAS, some of them on PAHs, and PBDEs, but also on non-targeted analyses. And I -- I wonder how these collaborations are monitored, how these are, you know, what they entail, what resources they take, how quality criteria, and other types of criteria that are typical for the Program are being, you know, instilled or delivered, like, you know, delivering data back to the participants, or, you know, other things including quality.

DR. WU: We don't have a lab person here unfortunately, I don't think, to answer some of that. But I think the collaborations really vary. There is typically a memorandum of understanding between the

collaborators, which defines who's playing what role. And the role of Biomonitoring California is different in each up one of those. In some, we are responsible for the results return and are very involved in the crafting of the message, and it looks very much like a Biomonitoring California kind of program.

In others, it's a little more like a service lab, where the lab is just giving back data. But in that case, the lab is still held to its highest quality standard.

PANEL MEMBER FIEHN: Oh, I see.

DR. WU: They're still ISO and CLIA certified. They're still the lab people that they are. They're still providing the really high quality service that we get from them.

And I think you've asked in the past about the resourcing of that. And, you know, it is expensive. And I don't know that that pays for the lab. And there's been talk about like maybe we should take in more of those kinds of samples --

PANEL MEMBER FIEHN: Yeah.

DR. WU: -- in order to support the lab. I don't know that -- I don't know that we could -- I don't know that the financing of that really works out in a State nonprofit lab and how that could work. But I do think that one of the issues with it is that it's -- it is not

sustainable. Like, we have a project and then it ends. You have a project and it ends. And it's very difficult to build a staff, with a guarantee of a job, if you're funded in that kind of sporadic way. And that is one of the challenges that we face.

PANEL MEMBER FIEHN: Thank you.

PANEL MEMBER SUÁREZ: So with the collaborations that I see listed here, the -- I suppose the funding to actually run the assays, that's covered by the collaborators or some of that is covered by the Program here?

DR. WU: So the prices that are -- like a per sample cost that is set by the lab, you know, I don't know how they arrive at that cost. But I think an effort is made to cover things like staff, and supplies, and reagents, and stuff like that. I don't know. I can't really answer to what extent it does that.

PANEL MEMBER SUÁREZ: Okay. But now, it's been opening. I think, in years past, that hasn't really been done too much, right? And we have been talking about perhaps a way to kind of supplement if there's a desire for that from outside institutions, and you have the equipment here, so might as well have the equipment running and to have a little bit of resources coming in as well.

DR. WU: No -- yeah.

PANEL MEMBER SUÁREZ: It seems like this has changed and now may or may not be financial, but at least the collaborations seem to be expanding.

DR. WU: And it's definitely helpful. I mean, don't get me wrong, it is absolutely helpful to have, you know, somebody using -- utilizing our lab and paying for those staffings. My point though is that if you can't tell a staff person that we'll definitely have a collaboration next year, it is harder to maintain that staff. And these are really highly qualified people and very specialized. And when we lose somebody, it's very hard to replace them. So it is at a cost to the Program that we don't have this kind of sustainable funding.

CHAIRPERSON SCHWARZMAN: Other questions, or comments, or discussion points?

Veena.

MS. HOOVER: This is Sara again. I just wanted to respond to Oliver's question about quality standards. So Nerissa explained the lab quality standards. Early on in the Program, we had this split between full project collaborations and laboratory collaborations. But everything that's done under a laboratory collaboration is done with that PI's IRB in place. So it's governed by the same level of standards set by the IRB, including results

return.

And quite often, as Nerissa did mention, they use a lot of our material. So we've worked closely with many of our collaborators to provide fact sheets, to even develop new fact sheets for them, to send -- for example, Duyen supported a study in a community meeting. So we -- we provide that support generally, if asked.

PANEL MEMBER SINGLA: Thank you for that great update. And I want to express my appreciation for how hard the staff's been working on the CARE study and the great progress. My question was about the communication of the results more broadly for CARE-LA and CARE-2, since the results have been returned to participants. I wondered if there have been any write-up in the -- like the Biomonitoring Newsletter or something like that that could inform stakeholders more broadly about some of the findings and results?

DR. WU: Sure. So CARE-LA results were -- they were posted on the web. And I believe there was a little blurb about some preliminary findings on the web that accompanied it. So that was distributed.

MS. HOOVER: It goes on the listserv.

DR. WU: It goes on the listserv. So anybody who has subscribed to Biomonitoring webpage would have gotten that description of that very preliminary exploration.

They were also presented at a public meeting that was done in collaboration with an air quality district. That was an open environmental justice forum. And so that had quite a large attendance. And there was Kathleen, actually, again presented our data there and there was a table. So there was quite a bit of interaction with attendees. We're very open to doing that kind of public meeting for everyone of our CARE, back to the original community, reporting the immediate results. But we -- we would love to be able to do more publication and presentation of findings as we get further into the data.

PANEL MEMBER SINGLA: That's great. Thank you. And I might suggest thinking about doing maybe a write-up for the Biomonitoring Newsletter just telling more of the story of, you know, some of the results that have been found in the interventions especially for the levels of concern for some of the metals in the participants that can kind of demonstrate how this -- the study is identifying issues and bringing in proper interventions.

MS. HOOVER: This is Sara again. Thank you for that suggestion. I will say that in addition to this super brief overview, we are planning and hoping, as we have in the past, to develop one-pagers. So a one-pager on CARE-LA, a one pager on EBDEP, to highlight the major findings. So that's a goal that we've had.

With regard to newsletter three, we have been drafting our table of contents. I can tell you that we do not have dedicated staff for the newsletter. And so it's yet another task of our existing staff in order to write -- you know, write -- our goal in those communications to write things that are still very scientifically accurate yet understandable. So we have many -- a lot of expertise in doing that, but it requires quite a bit of staff time. So, however, it's on our list to produce newsletter three, so we'll think about your suggestion for an article.

PANEL MEMBER SINGLA: That's -- that's great. And the one-pager is -- really that's going to be really helpful.

Thank you.

PANEL MEMBER SUÁREZ: Do you work with interns much, just out of curiosity?

DR. WU: We do. Yes. We have interns. We have fellows. We have people doing their Capstone projects with us. Yes. And if you have candidates, doctoral candidates or M.P.H. students, who are interested in datasets, we are always interested. It takes time. It's also staff time to work with interns. But, yeah, we're -- we use a lot of free labor, if we can.

CHAIRPERSON SCHWARZMAN: Just in the context of

this discussion about what the Program can accomplish and the budget bind, I also just want to recognize the tremendous work that's being done by the Program and the Program staff. And, you know, it's a long time that we've been hearing Program updates that reflect the sort of stress on resources and personal resources of the staff to continue doing the hard work that you're doing.

And I just want to highlight, you know, I feel like this Program is a shining example of what can be done with few resources, and also illustrates what could be done with more resources, because the expertise, and the skill, and the models have been developed, and could be so dramatically expanded.

And so -- and recognize, too, that you're under the double burden of doing the work, and getting it out into the world, and trying to promote it, in hopes that the full potential of things like the CARE study could be realized. And that it's not just the full potential from a scientific or community standpoint, it's also the legislative mandate that the Program has never been able to meet, because it hasn't been given the budget that would permit that.

So speaking just as one Panel member, I would invite other Panel members to, where we have the opportunity, extend the reach of the Program in our own

advocacy with communities and decision makers. I met with staff in Nancy Skinner's office and they were very impressed with the diesel work being done. And so thinking about what -- what work the Program is doing that particularly affects certain decision makers, if that is in something that you want to do.

I've -- I've received some -- that's been well received in some of the conversations that I've had. And so, we -- I would just invite others to not only exhort the Program to promote itself, but where you feel like it's appropriate and in line with your work to do that also.

Any other comments or discussion points for the Program update?

Yeah, José.

PANEL MEMBER SUÁREZ: Yeah. Just following up on your comment. I think it's the same thing that maybe the Program should think about when it comes to a fee-for-service piece of it, how much interest there is in really developing that side. And if there is, it may be valuable to get the word out, when you're thinking about -- say the CDC also, not for profit, they run I don't know how many contracts a year. I think it's over 150 to 200 contracts just to do like some really big stuff with biomonitoring, if not more.

And, of course, they've gotten to the point that they're so big that, you know, scientists are constantly asking them, you know, can you run these assays? And somehow they get their budgets managed and whatnot. With the labs here, which are excellent, it provides another opportunity for these collaborations.

So that's all I wanted to see if there was some thought about that as something -- as a big piece of the budget that should be considered, should be expanded on, or not. But at least to have the thoughts behind that would be great.

DR. WU: Well, we do not have one of the lab managers here today who would be able to talk a little bit more about lab budgeting. But I do think coming up with a fee-for-service cost that will cover things like staff, and the large overhead costs of staff at a State facility, is difficult. It is to our advantage, I think, as a biomonitoring science to have our lab involved with a lot of the biomonitoring that goes on with different researchers, because it means that our results are comparable. We know what the quality is and we can compare across studies knowing that it's coming from the same analysts, the same lab.

But it is hard. I think it's sort of a small business issue, which to get to the CDC level, we would

need to have things like reliable instrumentation that have been serviced, for which we have preventative maintenance. We would need to have staff duplication, so that when one staff is pulled off, you have another staff to do it. And we don't have that right now.

So it -- it is hard to grow from a place of bare bones to a place where we can be a reliable service lab. And it's really a business model to do that, but we're not a business. We're -- you know, we're a public department. And so I think it's a -- it's a little -- it's difficult to get there. But I agree that it is one of the ways we could make our labs more sustainable.

CHAIRPERSON SCHWARZMAN: Okay. Thank you.

Oh, sorry. Go ahead, Oliver.

PANEL MEMBER FIEHN: Oliver Fiehn again, UC Davis.

To our experience we also do both, fee-for-service, and collaborations, and research. And for all our fee-for-service analyses cost is not the issue. People are happy to pay for good quality. So, you know, I'm not -- of course, I understand -- we all understand going from, as you say a small lab, to be able to deliver. But on the other hand, if there are no other public funds, and you know, then the core grant, and people expect, you know, increases in salary over time,

they need promotions, they need prospectives for themselves, the staff, in the laboratories.

I can only encourage what José -- what José said. You know, if the collaborations are one way to go for it, then it's great. Maybe it can be expanded. You know, that would be a way towards more sustainable funding beyond the regular, you know, core grants in a way that seem to be half dried up. And we have discussed it multiple times here. And we need to think about how to sustain this.

If things are too small, they are endangered, and that includes staff and, you know, even the quality, at some point. You need also to be able to replace a person who's becoming sick, or who's becoming pregnant, or who's becoming -- who wants to move away. You know, there is a -- you know, it can't be too small. That's all I wanted to say.

CHAIRPERSON SCHWARZMAN: I just want to check about contributions from our two panelists who are not in the room before we move on.

Oh. Okay. We have -- this is an attempt to answer. "I can try to answer the question from the Panel about the lab". So this is Jed Waldman at CDPH writing:

"Most of the EHL lab collaborations are grant supported. Some were jointly submitted applications, so

the PI came to us after funding. We generally use per sample costs comparable to the CDC and CEH price list. In most cases, the funds are challenged through a fiscal agent..." -- Challenged, maybe channeled? "...channeled through a fiscal agent, such as the Sequoia Foundation. This allows to us hire a contract chemist and purchase supplies. Program staff cannot be supported this way. In smaller projects, some funds may be received for supplies and instrument maintenance. In these projects, State scientists conduct testing as an in-kind contribution".

Okay. Thank you so much, Nerissa.

We're going to move on to the next part of our agenda. I would like to introduce Shoba Iyer. She's a staff toxicologist in the Safer Alternatives Assessment and Biomonitoring Section of OEHHA. She'll present an overview of the topic of our -- the rest of our meeting, which is quaternary ammonium compounds as potential designated chemicals based on the document that we OEHHA prepared.

(Thereupon an overhead presentation was presented as follows.)

DR. IYER: I'll make sure this works. It sounds like it does.

Thanks.

Okay. So as Meg has mentioned, in my

presentation today, I'll provide an overview of quaternary ammonium compounds relevant to the criteria for the SGP to recommend designated chemicals. Also, as Meg mentioned, this the first of multiple agenda items in today's meeting on this class of compounds. Later in the afternoon, the Panel will provide their formal recommendation on this class of chemicals.

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DR. IYER: Here are the past SGP actions on quaternary ammonium compounds, or QACs. In March of last year, the Panel requested a preliminary screening of this class. Last July, the Panel reviewed OEHHA's preliminary screening and recommended that we prepare a potential designated chemical document on QACs. We've provided hard copies of this document today and we posted a PDF of it on the Biomonitoring California website on the page for today's meeting. My talk today will highlight some of the content that is covered in more detail in the potential designated chemical document.

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DR. IYER: Designated chemicals are the entire pool of chemicals that can be considered for biomonitoring by the Program. These chemicals are designated based on inclusion in CDC's national reports on human exposure to environmental chemicals program and recommendations by the

Scientific Guidance Panel for Biomonitoring California.

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DR. IYER: As a reminder, here is a list of the criteria for recommending designated chemicals which also applies for classes of designated chemicals. The criteria are exposure or potential exposure, known or suspected health effects, the need to assess the efficacy of public health actions, availability of biomonitoring analytical method, availability of adequate biospecimen samples, and incremental analytical cost. And note that these criteria are not joined by the term "and".

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DR. IYER: In my presentation today, I'll provide a description of QACs as a class. I'll briefly touch on exposure potential, and I'll talk about possible health concerns, information relevant to the potential to biomonitor, and public health importance.

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DR. IYER: The general chemical structure of QACs includes the cation NR4 plus. These compounds contain a nitrogen atom with four covalent bonds. The R groups are often, but not always, an alkyl chain or a benzyl ring. These are the chemical structures of three QAC subclasses. So there's benzylalkyldimethyl ammonium compounds or BACs; dialkyldimethyl ammonium compounds, or DADMACs; and

alkyltrimethyl ammonium compounds, or ATMACs.

And here are examples of the QACs in each subclass. Benzyhexadecyldimethyl ammonium chloride is an example of a BAC, didecyldimethyl ammonium chloride is an example of a DADMAC, and hexadecyltrimethyl ammonium chloride is an example of an ATMAC. The alkyl chain length for these compounds is typically between eight and 22 carbons long.

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DR. IYER: So here, I'm showing you chemical structures of selected QACs that do not belong to the three subclasses I just reviewed. There are a number of polymers with quaternary ammonium centers, called polyquaternium compounds. Shown here is an example polyquaternium 42. Esterquats are another subclass of QACs, in which the alkyl chains contain ester linkages. Cetylpyridinium chloride is an example of a QAC containing a pyridinium ring. And the herbicides diquat dibromide and paraquat dichloride are other types of QACs.

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DR. IYER: Last July, we shared a preliminary screening document that includes volume of use information for a variety of example QACs. We have hard copies of that screening document available at our meeting today and the PDF is posted as background material on the

Biomonitoring California website on the page for today's meeting. So here on this slide, I'll briefly review some highlights on volume of QAC use.

Of the QACs I reviewed, the national production volume for 20 of them was over 100,000 pounds each in 2015. Of these, 11 had production volume of over one million pounds. Of the QACs we reviewed that have reported pesticide sales in California, about half had sales of more than 100,000 pounds in 2018. Of these, several had sales of over one million pounds.

The QAC pesticides we reviewed that are used agriculturally in the state are generally applied at lower levels. The notable exception is paraquat dichloride, over one million pounds were applied in 2017 and it was ranked number 23 of the top 100 pesticides applied agriculturally.

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DR. IYER: QACs are used in a variety of applications, including as antimicrobials, preservatives, antistatic agents, softening agents, surfactants, and corrosion inhibitors.

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DR. IYER: I'm showing you here a quick picture collage of the variety of products and applications that QACs are used in. I talked about this topic more

extensively in my preliminary screening presentation at our SGP meeting last July.

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DR. IYER: QACs, specifically the subclasses of BACs, DADMACs, and ATMACs have been detected in sediment, sludge, and wastewater treatment plant influent and effluent. Of the studies I located reporting these detections, several described samples collected from the New York/New Jersey area and a very recent publication described samples from Minnesota and the others were international.

BACs, DADMACs, and ATMACs have also been detected in sediment samples collected from the San Francisco Bay. This is preliminary research that's been conducted in Bill Arnold's lab at the University of Minnesota for the San Francisco Estuary Institute.

Other environmental detections reported included indoor house dust samples in Germany, air samples from a hospital where QAC-containing disinfectants were being used, and fish samples from Nordic countries.

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DR. IYER: There are possible health concerns associated with members of this chemical class, such as dermal irritation, respiratory effects, nervous system effects, reproductive and developmental effects,

immunological effects, and altered cellular function and effects on metabolism.

We'll hear about the reproductive and developmental effects and immunological effects of selected QACs in the presentations that our guest speakers, Terry Hrubec and Libin Xu will give later today. I'll share some information here about some of the other possible health concerns.

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DR. IYER: Some QACs are linked with dermal irritation. For example, quaternium 15 is a QAC that is used as a biocide, preservative, and surfactant in cosmetics and personal care products, and in cleaning products. It is a formaldehyde-releasing preservative. And we located some human studies and a case report, in which quaternium 15 exposure was linked with allergic contact dermatitis.

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DR. IYER: Some QACs are linked with respiratory effects. The Association of Occupational and Environmental Clinics has identified some QACs as asthmagens, which they define as a substance known to cause asthma, which is acquired de novo from a workplace exposure. The QACs we found on this list included BACs and one DADMAC.

Studies conducted among hospital staff such as nurses and housekeeping staff have reported that exposure to QAC-containing disinfectants and cleaning products can be linked with work-related asthma.

And Larsen et al. found reduced tidal volume with a concomitant increase in respiratory rate for each QAC they tested in mice. The relative potency they reported for this effect is shown here. So they found that benzalkonium chloride, a BAC, had a greater potency for this effect than hexadecyltrimethyl ammonium bromide, an ATMAC, which was about equal to cetylpyridinium chloride, which was greater than dioctadecyldimethyl ammonium bromide, a DADMAC.

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DR. IYER: We located various in vitro studies of selected QACs. One of the cellular effects reported is inhibition of mitochondrial respiration. This effect has been reported for benzalkonium chloride, cetylpyridinium chloride, and decyltrimethyl ammonium bromide. I'll note that plasma membrane disruption is the general mechanism of action that makes QACs effective as preservatives, disinfectants and biocides, so it makes sense that the mitochondrial membrane is also impacted.

We reviewed ToxCast and Tox21 bioactivity data from U.S. EPA's CompTox Chemistry Dashboard and located 21

QACs that were active in over 100 assays. Three examples are shown here on the slide. Effects that these QACs had at sub-cytotoxic concentrations included altered gene expression and altered cell proliferation.

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DR. IYER: We located some absorption rates reported in summaries of unpublished studies. Dermal absorption rates of selected QACs ranged from less than one percent in vivo up to 8.3 percent, which was from an in vitro study with human skin. Oral absorption rates ranged from 10 to 88 percent. These same summaries reported that the majority of the administered dose in animal studies is excreted in the feces as the parent compound.

We only located limited information on metabolites excreted in the urine. For example, one report identified the major rat urinary metabolites of the esterquat diethyloxyester dimethyl ammonium chloride as dimethyl diethanol ammonium chloride, which is the deesterification metabolite and possibly some further oxidation products.

We'll get to hear more from Libin Xu this afternoon about the research his group is doing on the metabolism of benzalkonium chloride.

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DR. IYER: I'll now move on to some information about chemical properties. The water solubility of selected QACs varies by chain length. For example, the water solubility of an ATMAC with a 12-carbon alkyl chain is nearly 60,000 times more than that of an ATMAC with a 22 carbon alkyl chain. We found limited information on bioaccumulation and bioconcentration.

In the environment, QACs are strongly sorbed by soils and sewage-affected sediments. We located reports describing selected QACs as immobile in soil and sediments. More than 70 percent to 90 percent is reported to be removed in wastewater treatment. We located some publications indicating that QAC removal in wastewater treatment plants is thought to be dominated by sorption to sludge and microbial degradation. And biodegradation appears to be the greatest for shorter chain QACs under aerobic conditions.

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DR. IYER: The only published human biomonitoring studies we located for exposures were for exposures to diquat and paraquat. We found literature reporting the use of hydrophilic interaction liquid chromatography for quantifying polar substances like QACs. So although these aren't biomonitoring studies, we located two methods papers applying hydrophilic interaction liquid

chromatography.

Whitehead et al., which is a CDC publication, used this chromatographic approach for detecting diquat dibromide and paraquat dichlorate -- dichloride spiked into human urine. And this paper by Steuer et al. describes the method for detecting phosphatidyl-derived QACs in human plasma, blood, and urine.

Our guest speakers today, Terry Hrubec and Libin Xu, along with Gino Cortopassi of UC Davis are collaborating on a small biomonitoring study. We'll get to hear more about their analytical method used to measure selected QACs in plasma in Libin's presentation this afternoon.

Biomonitoring California would need to develop methods to measure QACs in future studies.

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DR. IYER: So as we've been doing research and gathering information on QACs over this last year, we've observed that a number of groups have raised the importance of evaluating human exposure and concerns about the potential effects of these compounds. These groups include the California Council on Science and Technology and Lawrence Berkeley National Laboratory in their assessment of oil and gas well stimulation in California.

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DR. IYER: Health Canada, which issued a notice to collect information from manufacturers and importers on QACs to establish a current inventory to support risk assessment and risk management.

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DR. IYER: Authors from UCSF who raised concerns about QAC-containing disinfectants used in child care sites.

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DR. IYER: UC Davis authors in their comprehensive review of uses, regulatory status, and microbial resistance of benzalkonium chlorides.

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DR. IYER: And authors --

(Thereupon the conference call ended.)

DR. IYER: Should I pause?

MS. HOOVER: Yeah, pause.

DR. IYER: Please bear with us, while we address technical difficulties.

(Thereupon a discussion occurred off the record.)

MS. KAUFFMAN: Hello.

PANEL MEMBER QUINTANA: Hi. This is Jenny Quintana.

MS. KAUFFMAN: Hi, Jenny.

DR. IYER: We're waiting for Eunha to rejoin.

PANEL MEMBER QUINTANA: I think you should start. I can text her.

MS. KAUFFMAN: Okay. Thanks. We'll resume.

DR. IYER: Okay. All right. Where we last left off, I was explaining some examples of publications that are calling to the public health importance of understanding more about QACs. The last example I have is in my list here is the screenshot on the slide. Authors from RTI International, which is a nonprofit research institute, and UCSF had a review of the chemicals as possible priorities for biomonitoring, and they noted extensive data gaps in exposure and toxicity information for QACs.

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DR. IYER: Biomonitoring QACs could help address the knowledge gaps related to human exposure to these widely used compounds and inform efforts to reduce chemical exposures of concern.

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DR. IYER: That concludes my presentation and I'm happy to address any questions.

CHAIRPERSON SCHWARZMAN: Thank you so much, Shoba. So we have ten minutes now for questions from both the Panel and the audience before our next presentation.

Tom.

PANEL MEMBER McKONE: Thank you very much. Very interesting. I had just a couple of questions related to, I suppose, environmental fate. When you talk about chemical properties, there's nothing listed with regard to any measurements of lipid solubility such as octanol-water partition or some other oil solubility measure. Is that out there or is that not available or you didn't have an opportunity to...

DR. IYER: We -- we included water solubility information.

PANEL MEMBER McKONE: Yeah.

DR. IYER: So right now, I'm looking at the document in the chemical properties section on page 13. So lipid solubility -- so generally with the -- you know, a longer chain QAC will be more lipid soluble than a shorter-chain QAC. Sort of the inverse of the water solubility information we provided.

And usually, we think of log Kow of at least four as indicating potential for bioaccumulation. I only located a few log Kow's. All but one was below four. The one -- and again, this is just the second paragraph I'm looking at in the chemical properties section of potential to biomonitor in the document.

So the one log Kow we found that was above four, that was 4.26 and another was 4.66 reported by U.S. EPA.

One of the additional pieces of information that report had was that bioconcentration in aquatic organisms is not expected, because the compound is highly soluble in water, and being positively charged is tightly sorbed to soil and sediment, which are --

PANEL MEMBER McKONE: There was my -- yeah. And then to -- just to clarify and make sure, these are dissociating, or ionizing, or at least have enough charge that they're not going to. I mean, they have a kind of charge distribution and they're not going to be very non-polar, which is like -- you know, a lot of the organic chemicals that we really worry about as bioaccumulative tend to not have -- they -- they tend to have a nice -- not a good charge distribution. They tend to be non-polar, so they don't dissolve well in water. Okay.

And then one just quick other question while I'm on is you report about measurements in samples. So it seems like there are very limited environmental samples, some indoors, most of them from Europe. And so I guess the question, is -- and again I'm -- probably this is in the report, but is the profile of use in Europe different like the Nordic countries, where they're seeing this or similar to the U.S.? In other words, you know, is it a -- is it somewhat representative?

DR. IYER: Yeah.

PANEL MEMBER McKONE: Or do they have some, for some reason, very excessive uses.

DR. IYER: I think it's --

PANEL MEMBER McKONE: Unlikely, but I just wanted to...

DR. IYER: Yeah. I think it's difficult to say broadly, because there are so many uses of QACs in a variety of products and applications. One example that comes to my mind as a difference is benzalkonium chloride as the active substance in disinfecting hand wash is something that is here in the U.S., but not in Europe. So that's one example of a difference I can come across.

PANEL MEMBER McKONE: Thank you.

CHAIRPERSON SCHWARZMAN: Other questions?

José.

PANEL MEMBER SUÁREZ: What's the -- or the estimate of the half-lives for these chemicals in the environment versus tissues?

DR. IYER: Versus tissues. I jotted down some notes on half-lives in the environment. One of the -- one of the pieces of information I found is that some QACs are considered immobile in different soil or sediment types. So, to me, I think of that as a sort of an infinite half-life.

But some of the other values I found for under

aerobic conditions in the environment. For example, a ten carbon DADMAC 69 percent of it was degraded after 28 days in a closed bottle test. That's one example I pulled. Under abiotic conditions, the half-life of a test compound was determined to be 227 days with seven percent degradation after 30 days. So I think in the environment it really varies on whether it's an aerobic or anaerobic environment.

And in tissues, I did not locate information on half-life in tissues.

CHAIRPERSON SCHWARZMAN: Ulrike.

PANEL MEMBER LUDERER: Thank you for that wonderful overview. I have a question -- kind of a related question and it's relevant to biomonitoring. When you were talking about that oral absorption range -- rates range from 10 to 88 percent, but then as far as excretion, that you -- I think you said that most of them are excreted as parent QAC in the feces and that there's limited information on metabolites in urine. So I'm wondering if there's information about whether the excretion in the feces is because of lack of absorption or is there excretion -- is there absorption as excreted in the bile? Do we have any knowledge about that?

DR. IYER: Yeah. So some of the reports of unpublished studies are looking at absorption from oral

administration and what's excreted in -- in those cases, I think it's not absorbed. It's passing through the system and excreted in the feces.

The rates I mentioned were the absorption rates quoted from different studies -- from different -- some animal studies and one in vitro study for the dermal rate I reported.

CHAIRPERSON SCHWARZMAN: Other questions. One from the audience.

MS. BRADLEY: Hi. Good morning. My name is Taylor Bradley from the American Cleaning Institute. Thank you for having us. I have a few questions, if you don't mind.

The first one is, is there a particular focus on a certain or certain classes of QACs that you're recommending for biomonitoring? If so, what are they. And if not, how does -- how do you guys plan to monitor amongst the broad -- you know, broad category of QACs? There are many functions, uses, and applications. So, I mean, as you see, you gave us a really comprehensive review. Just curious on how that will kind of go into action regarding methods.

I'm glad you guys noticed there is a kind of a gap in analytical methods for these classes of compounds. And so is there any consideration to maybe narrow the

scope for those that have available analytical methods as of current? What is the timeline on maybe developing methods for the other classes that do not have analytical methods? Just some thoughts around those questions.

DR. IYER: Yeah. Yeah, it is a diverse class of compounds. Today, we're discussing the class as a whole, but folks are free to remark on any particular subclass they want to make comments on or want to share thoughts on.

I think, at this point, we're not -- it's premature to think about the analytical method, you know, based on the available analytical method. As I mentioned in the criteria for recommending designated chemicals, those are criteria, but they are not joined by the term "and". So these are -- these are pieces of information that we can have, but we don't have to have all of them for considering a chemical or a class.

MS. BRADLEY: Another question.

MS. HOOVER: This is Sara Hoover of OEHHA. And Shoba did a great job of answering that question. I did also want to note that all this does today is put them on the list of possible chemicals to be biomonitored. That's it. So in terms of decision making for what methods to develop or if we're going to include them in a study, that's further down the road.

MS. BRADLEY: Sure. Thank you.

Just one more question. It's Taylor Bradley with the American Cleaning Institute again. Have you guys considered maybe narrowing this down between the biocidal QACs, which have a lot of available data versus the laundry QACs? Just a question.

DR. IYER: Yeah. As I mentioned, we're sharing information on what we've gathered about the whole class, including both the biocidal QACs and the ones used for the laundry detergent.

But again, if folks have additional thoughts that they want to share during our meeting today during the discussion period, feel free to weigh in at those times.

DR. HOSTETLER: Good morning. I'm Keith Hostetler with Toxicology Regulatory Services. I'm on the list as a guest discussant for later. But I did want to mention the fact that in the published literature, there's not as much available, but we will be covering a fact that both environmental fate and human half-life data is available in a non-published source, which is required for a lot of the regulatory approvals.

So we'll cover that. And it's -- there's -- there's an abundance of data and we'll touch on that this afternoon.

Thank you.

DR. IYER: Thanks.

CHAIRPERSON SCHWARZMAN: We have time for just one more question before moving on.

Yeah, José.

PANEL MEMBER SUÁREZ: What are some of the potential routes that they make it into our bodies? What would be the main sources? I'd like to know how volatile these potentially are versus I would imagine going through the skin primarily, and maybe a little bit less on perhaps intake, oral. What -- what's -- what are your -- what do you know about this?

DR. IYER: Yeah. I was thinking about it on the car ride up actually, because I haven't seen any obvious answers in my research. QACs are not expected to be volatile. So I have come across that in what I've read. I think really with QACs in products that we apply to our skin, things like mouth wash, things like disinfecting wipes that you might wipe down a surface with and then put your snack on. And also some of the cleaning products I came across were scented disinfecting sprays. I might think that there's a combination of exposures from both oral, and some dermal, and some inhalation, but I haven't come across any evaluations of that with data. But in thinking of the wide range of products they're in, that would be my guess.

PANEL MEMBER SUÁREZ: Like, well my question is kind of trying to get at what does a measurement through biomonitoring, what is it telling us ultimately? Especially you mentioned that these were present in stool. However, we don't know if that's really any of that has been absorbed or if -- it seems like maybe less likely, as you mentioned, that it would be excreted from the body via bile, and primarily maybe because it's more water soluble than fat soluble. But then what would be the most ideal substrate in which to measure this in biospecimens?

DR. IYER: I think I might wait for -- ask you to wait for Libin Xu's talk later today when he shares some of his own research with us, and we'll get into some of those considerations.

DR. DATTA: Hi. I'm Sandipan Datta from UC Davis. I have a quick comment on your question. So what Shoba said is correct. Like, it's mostly like a comprehensive exposure. But the most important exposure, as far as I am concerned, is the inhalation exposure, even though they are not volatile components, but they're sprayed around a lot. Like when you use a Clorox spray, you are constantly inhaling that like when you're cleaning your kitchen or your bathroom. So that is the major thing.

And the second is that there are unpublished

studies where like, you know, you can see that there are blood levels of quats. Like Dr. Xu has measured, Dr. Hrubec has measured that like there are blood levels of quats. And they can, depending on which tissue you are in, and my educated guess would be that most of the quats should go and get concentrated in the lipid tissues of our body like, you know, the fat tissues or the adipose tissues and act as a depot. So like I'm not sure like what exactly would be the good way to monitor in humans or the organism level, but it could be, you know, the fat tissue or human -- like the blood plasma or the blood cells would be one to look out for.

CHAIRPERSON SCHWARZMAN: Thank you for that. We'll be continuing to discuss all of these issues as we get more input from speakers, so I want to make sure that we don't run over time.

Thank you, Shoba.

I want to introduce Terry Hrubec. Terry Hrubec is currently a professor of anatomy and embryology at the Edward Via College of Osteopathic Medicine In Virginia. Her research focuses on the effects of environmental influences on early life stage development and maturation. Terry received her DVM and Ph.D. From Virginia Tech.

She'll present a chemical detective story about her laboratory -- how her laboratory transform -- traced

maternal modulation of embryotoxicity to the disinfectant that was used in the mouse room.

(Thereupon an overhead presentation was presented as follows.)

DR. HRUBEC: Thank you for the introduction. This is Terry Hrubec. And as this was introduced, we really had to do a detective study to figure out what was going on with the reproductive and developmental effects we were seeing in our mice.

PANEL MEMBER CRANOR: A little closer to the mic.

DR. HRUBEC: Okay.

Can I remove this? Okay. This way I can walk around too.

So I have no financial or other disclosures to expose at the moment.

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DR. HRUBEC: So due to -- with the detective theme that I'm going through, we're gong to talk about the crime scene first. Okay. And so what happened is very suddenly, we started to notice neural tube defects in our mouse litters. Neural tube defects are birth defects of the brain and spinal cord. In humans this is spina bifida and anencephaly.

Okay. And so his -- historically -- is there a pointer?

Okay. Well, hopefully you can see. On the left slide, historically, we saw no neural tube defects in our mice. And all of a sudden, we started to see about ten percent of the offspring had neural tube defects. We also at the same time noticed a decrease in the litter size of the mice that we were raising.

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DR. HRUBEC: Okay. So we started an investigation. We first checked the animal caretakers. And there was no change to the animal husbandry, diet, source of mice, et cetera.

Okay. The serology, that's levels in the blood, for known mouse pathogens that was negative. We did toxicologic analysis of the food, the bedding, the enrichment material, and all of that was negative. We also reared the mice in a sterile environment, thinking maybe there was a pathogen that's not considered, a known mouse pathogen, that could be affecting development and that had no effect.

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DR. HRUBEC: Okay. So at that point, we were pretty stumped. So I went to talk to the animal care supervisor - okay - who has no actual contact with the animals. And what she said is that they had recently switched disinfectants that they were using in all the

facilities. And that happened, that change happened at about the same time that we started to see the neural tube defects in our mice.

Okay. So disinfectants are used extensively in an animal care facility. The floors, walls, and racks are foamed once a week. The floors are mopped daily. Mouse boxes are sprayed before you open. And then you spray your hands and so they're wet when you actually pick up and handle the mace. This is to prevent disease spread in between the different mouse colonies. It's to prevent you giving a disease to the mice and the mice giving a disease to you.

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DR. HRUBEC: Okay. So here's our prime suspect, a quaternary ammonium disinfectant. And it was composed of a combination of the alkyl dimethyl benzyl ammonium chloride and the didecyl dimethyl ammonium chloride. I'm going to refer to these's ADBAC, A-D-B-A-C, or BAC, and then DDAC.

Okay. So this is the combination that we were concerned with. As you've heard, the ADBAC is composed of different chain lengths in -- when the compound is manufactured, depending on the synthesis technique, you'll get different ratios of those chain lengths. So I've listed the specific ratio that we were looking at. That's

what's in the commercial product that was being used.

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DR. HRUBEC: So for the rest of the talk, I'm going to talk about three types of exposure. So we used dosed exposure in the feed. We used exposure by gavage. And what that is is you insert a stomach tube and distill it -- instill the compound directly into the stomach. And then we also used an ambient exposure. And that's the rate of exposure that the mouse received just from being in the mouse room where the disinfectants are used.

This exposure -- the reason we always include an ambient exposure is to mimic the exposure humans might get from either working in that environment or the exposure in other environments. Okay. So that's our -- our sort of control -- our ambient control.

We know that there's an ambient exposure that has an effect, because that's how we initially saw the defects. That's how they first presented. We weren't dosing them. That was just from use of the cleaner.

Okay. So the first thing we did, once we had our suspect, was to make a mouse room in the facility QAC free. Okay. So we had very extensive requirements for entering the room. All the people had to change clothes. I told my students not to use QAC products at home, in case they were bringing in -- them into -- into the lab.

And we also used disposable mouse cages, because there was a work coming out of Washington State that -- from a researcher, Patricia Hunt, where she found that they -- they were seeing reproductive changes in their mice from the QAC disinfectant and the disinfectant was being transferred to the mice through the animal cages during the cage wash procedure. So we used disposable boxes to prevent that exposure through the mouse boxes.

Okay. So we first put mice and rats into our QAC-free room and also in a room where they were still using QAC disinfectants.

And my pointer still isn't working.

Okay. So what you can see is with the -- both the rats and the mice, the rate of neural tube defects was higher in the QAC room than in the non-QAC -- in the QAC-free room. But they didn't go away, which was a little bit puzzling. And then we also did an exposure study where we were dosing the mice in the feed with 60 and 120 milligram per kilogram per day. And again, we saw an increase in the neural tube defects, but also the controls in our QAC-free room still had neural tube defects.

And we thought, well, maybe they're still getting exposed. So we looked in the residue in the mouse boxes after one week of use. So on the left you'll see a new

box. This is brand new straight out of the package and there's no residue in the box. At the end of a week of use with the mice in there, we measured the residue and our boxes from our QAC-free room had residues. This is a ADBAC that we were measuring.

So somehow these mice were getting exposed, whether it's through the air handler system somehow being carried into the room, we don't know. We didn't pursue this further. We can't continue our research unless our control is actually negative. So what we did is move our mice to a facility that didn't use the QAC disinfectants at all.

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DR. HRUBEC: And so we designed this study. We looked at -- again, I wish I had my pointer. Okay. The FO generation that stayed in the QAC building, these were mice that remained in the facility before they had -- where we used to house the mice. And then the rest of -- the next four bars are going to be mice that we moved to the facility that didn't use the disinfect -- QAC disinfectants at all.

And we monitored them for several generations. So the first one, the FO generation, these are contemporary to the mice that stayed in the QAC-free building. And as you can see, they reduced the level of

neural tube defects, but again, they didn't go away. We raised those mice up and they were the F1 generation. We let them have babies, and the -- their -- those babies still had neural tube defects.

Okay. That's -- F2 generation we raised up and let them breed, have babies, and the offspring of the F2 generation were finally clean and clear of neural tube defects.

We then took the F2 mice, transferred them over to a QAC-use building and they developed neural tube defects again. So in a way, this is a proof through Cox Principle where you have exposure, you see an effect, you reduce the exposure, the effect goes away, and then you reintroduce it again, and you see the defect. Okay. So that's what we have here.

Let me just talk about -- I meant to mention this in the beginning. Mice have litters. They have multiple babies in one litter. And baby mice are called pups. So if I refer to a pup, I'm referring to a baby mouse.

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DR. HRUBEC: Okay. So why do we get three generations of exposure at once? And you can see the effects for three generations. So when you expose a pregnant whom, you're exposing three generations. You have the woman, you have the baby inside her, and then

inside that developing baby, you have the germ cells, the stem cells that are going to form the egg and the sperm of the baby's offspring. Okay.

And those stem cells are actually formed very early on in reproduction. So I have the graph -- the chart in the middle is showing a developing fertilized egg. By day 12 of gestation, before the mother even knows she's pregnant, you have those germ stem cells being formed in that embryo. Okay. So throughout the whole pregnancy, those stem cells are being exposed to whatever the mother is being exposed to.

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DR. HRUBEC: Okay. So now we want to build the case of what's going on, right. And so we have our negative control. It's finally negative. And so we're going to try to show that it's actually exposure to the disinfectant. So in the previous study is when we were dosing in the feed we were using the commercial product. We don't know if it's actual ingredients, the active ingredients in the commercial product, or an emulsifier, or a colorant, or an odorant. You know, we don't know what the active chemical was.

And so we purchased the active ingredients, the DDAC. And then for the ADBAC, we got each of the individual chain lengths of compounds, recombined them in

the same concentration that they were in the commercial product. And you can see here, we saw neural tube defects when the mice were exposed. So we now have sort of shown that it is the active ingredient that's causing the neural tube defects that we saw.

--o0o--

DR. HRUBEC: Okay. So now we need to test our hypothesis. What's actually going on with it and does it cause all the variations in effects, both reproductive and developmental that we've seen?

So we wanted to see is there a difference in facilities that use or don't use a QAC Disinfectants. Is it ambient exposure or oral exposure? If we dose with a cleaning product or the active ingredients at the same proportion, I already showed you that, that we didn't see a difference in that. Oral gavage versus exposure through the feed, versus exposure to the water, versus ambient exposure. Okay. And then male versus female exposure, because they're likely to be different. So I'm going to touch upon all of these in a minute.

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DR. HRUBEC: Okay. So here we're going to talk about the fertility effects. I've been talking about the developmental effects and the neural tube defects. That's because it's a really quick reporter that we can tell

right away the effects of the exposure.

Okay. The reproductive effects are not as definitive as does this baby mouse have a neural tube defects or not. So what we did is exposed litters of mice and also to individual male and female mice. So we looked at -- in the females, we looked at the number of ovulations. And then also, of those eggs that did ovulate, how many implanted? And you can see in the image to the right, that's an ovary of a mouse. And you can see those pink -- large pink circles in it. Those are areas where eggs were and ovulated. Okay. Again, mice have multiple babies in a litter, so you have multiple ovulation sites.

And the image to the left, Image A, that's the actual uterus. The blue bands that you can see here are the implantation sites. So we can see how many eggs are ovulated and how many actually implant. And so we just counted them up and determined that there are fewer implantations.

Okay. We also looked at males and we saw a dramatic decrease in the sperm count in the unexposed to the exposed males.

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DR. HRUBEC: Okay. With reproduction, we also used other parameters. We did a six-month breeding trial

where the mice were exposed continuously for six months. And what we saw is an increase in the days to first litter. So you put the mice together, and they're going to mate, and they're going to have babies that you can quantify. And so we counted the number of days until the pups were born. And that was increased in the exposed mice.

We looked at the number of pregnancies happening over that six months. And you saw a decrease in the number of pregnancies at the 120 milligram per kilogram per day dose. We also saw an increase in late-term pregnancy loss. Now, let me explain a little bit about mouse reproduction. As I said, mice have multiple babies per litter. If a baby dies, it's not advantageous to the mouse to lose the whole litter. And they have a process where they'll wall off that dead baby and reabsorb it, and that's called a resorption. So you can count resorptions in the litter. Because a late-term fetus is large for a mouse, they don't have as great ability to resorp such a large fetus. And they'll tend to lose the whole litter.

Okay. So that's what we're seeing in the late-term pregnancy loss. This is also a problem because a mouse has difficulty expelling a large number of dead babies and they tend to have what's called dystocia, which is delayed or stopped delivery of the mice. And the --

this is lethal to the female mouse.

So the last thing we looked at was a cumulative number of pups born. And as you can see, these are decreased with the different doses.

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DR. HRUBEC: Okay. Additional reproductive monitors that we did was number of estrous cycles. So mice come into heat. When they're in heat, they're -- they'll breed. And then the rest of the time, they don't breed at all. Okay. So we counted the number of times that they actually came in heat and would breed. Okay. And this is decreased in the 120 milligram exposed group.

We looked at sperm count. And again, I showed you the sperm count. That was with a dose at 120 milligrams per liter per day in the feed. Here, we're measuring ambient and a gavaged dose of 7.5. Okay. And there was no difference between whether the mice were ambiently exposed or gavaged with a compound.

If you notice, the 7.5 is a lot lower than the 120. There is a reason for this. When mice eat the feed, they take a couple bites. They run around their cage. They spin on their wheel. And then they come back and take another couple bites. They never get a high blood dose of what you're dosing.

When you instill it directly into their stomach,

they're going to get a spike in the blood dose right away. And so it's going to be more toxic than when it's given in the feed. We found that if there's an ambient dose at the same time as the dose that you're giving by gavage. We have to go down to the 7.5 milligrams per kilogram per day. Otherwise the mice shows signs of toxicity, okay, and they'll die, which isn't good.

So we looked at both sperm count and sperm motility in the study and sperm counts were decreased and the motility was decreased. For sperm to be functional, you have to have a sufficient number, and they have to be modal.

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DR. HRUBEC: Okay. The -- we're going to switch gears a little bit and talk about immune function. Okay. So I'm going to talk about -- this is an in vitro study in cell culture. And we wanted to look at macrophages, since macrophages are involved in that walling off of that pregnancy if the fetus dies.

Okay. So we exposed cells to different concentrations of the disinfectant and they're increasing as they go to the -- to the right of the slide, and we have phagocytosis. That's engulfing of the foreign material. Okay. So that's what macrophages do, they phagocytose.

And so this process was disrupted and almost completely inhibited at the higher dose. Now, if you give a high enough dose, the cells are going to die. Okay. It's a disinfectant. It's killing things, but at the highest dose I list here on the graph. The cells were still viable. They were still quite alive. Again, if you go up to a higher dose, they're going to die. That I showed. But we made sure that we still had good viability for those cells.

The other thing we looked at was cytokine production. Okay. Cytokines are regulatory molecules that affect the inflammatory response. Okay. So they're either going to increase inflammatory response. That's what you get with pro-inflammatory cytokines. And then you can also damp down that inflammatory response with an anti-inflammatory cytokine.

So IL-6 and TNF-alpha are pro-inflammatory cytokines. IL-10 is an anti-inflammatory cytokine. And so what we saw is when you stimulate the cells, you get an increase from the baseline, which was almost zero for that. Okay. And so we get an increase in all three cytokines produced. If you stimulate them in the presence of the disinfectant, you see a massive increase in the pro-inflammatory cytokines, IL-D and TNF-alpha and you see a decrease in the IL-10. Okay. So this gives a double

whammy towards pro-inflammation.

Your inflammatory cytokines have decreased -- increasing and your ability to damp it down is actually decreasing.

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DR. HRUBEC: Okay. Back to development. We've tested the developmental effects further. We wanted to see does it matter if males or females are exposed. If it's only the males, because of the decreased sperm counts, that could be affecting things or it could be the female, because they're actually doing the gestation. And what we found is it didn't matter. If we just exposed the males, we saw neural tube defects in the babies.

And you're going what's going on? How can that be? And it's through epigenetic effects most likely. I mean, it's basically what it has to be. So we're changing the epigenetics of the sperm so that different genes are then regulated and expressed in the offspring.

We saw the same thing if we dosed the females. They had a rate of neural tube defects. When we dosed both, the rate almost doubles to when both are dosed. Okay. And then we also wanted to compare does it matter whether they're -- it's ambiently exposed or gavage exposed. And the rates were similar.

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DR. HRUBEC: Okay. The other thing we looked at are fetal weights and placental weights. Fetal weight is the standard endpoint to monitor in a tox regulatory study. And so we can see decreased fetal weight with the exposed mice. We also saw decreased placental weight in the exposed mice. And this is important, because the placenta is supporting the pregnancy. If you have too small a placenta, you can't support feta growth and the baby is going to die or be born prematurely. And that might be why we were seeing the late term fetal death in the mice is the placentas just weren't able to support the fetal growth. These findings of decreased fetal weight are documented in the literature and documented in the regulatory studies that are presented.

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DR. HRUBEC: Okay. Exposure is ubiquitous. We're moving on to humans. Okay. Over 5,000 household products contain a quat. And these aren't just ADBAC and DDAC. Okay. This is quats in general. So that's a lot of products that we're exposed to regularly.

And we've done two studies, one to look at residues on the hands. Okay. So this was first year medical students. I work at a medical school, so medical students are there. And these are first year, so they spend eight hours a day in the classroom. We don't let

them anywhere near a patient at this point.

And so as they were coming out of the classroom, we took a swab of their hands and we were -- then measured the ADBAC levels on the swabs. And 50 percent of the students had detectable levels on their hands.

We then did a screening trial on 43 participants. And I'll talk about that here.

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DR. HRUBEC: So we recruited participants from a small rural college town, very much like Davis. So if you decrease the size of Davis a little bit and increased the size of the college, you get Blacksburg. Okay. And so just -- we didn't collect personal data on the participants. But just by visual assessment of their age, two-thirds were students and about one-third were non-students. Probably associated with the university just based on the size of the town and the university.

Okay. So 80 percent had detectable levels of ADBAC and DDAC in their blood. We were able to measure all four chain lengths that are used in the disinfectant, plus the DDAC. Okay. And we were able to correlate the amount in the blood with markers of inflammation, decreased mitochondrial function and altered cholesterol synthesis.

So as we heard in the talk previously,

mitochondrial function has been shown to be inhibited with exposure to the disinfectants. This is work by Gino Cortopassi and Sandipan Datta at UC Davis. And then the next speaker after lunch, Libin Xu, did the work on altered cholesterol synthesis. And I think he'll talk about more of that later.

So we know those are active effects of exposure from the compounds in a mouse model, rodent model, and also in cell culture models. And so that's what we were focusing our study on in the human samples. And we saw the same pattern.

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DR. HRUBEC: Okay. So why is this important? It's important because we can measure levels of these compounds in the mouse tissues. Okay. So we heard that they're not absorbed. And that if they are absorbed, they're excreted rapidly through the GI tract. Well, if that was the case, we wouldn't be measuring levels in tissue. Okay. So we were able to level -- measure levels in the liver, in the brain, and in the testes.

And these last two are particularly concerning, because there's a blood-brain barrier. There is a blood-testis barrier that's protecting the brain cells and the developing sperm cells in the testis from exposure to exogenous materials. So because we can measure the

different QACs in those tissue means that they're going past the blood-brain barrier, past the blood-testis barrier.

Okay. We've seen neural tube defects in the mice. Okay. So this exposure to the developing brain may also cause some neurobehavioral effects as well, just due to the presence of the disinfectant in their brain. There was a headline that just came out yesterday about how insecticide pesticide exposure to bees alters their brain development in the offspring. Okay. I thought that was pretty appropriate for what I'm talking about right here.

As far as the reproductive function, there have been numerous patents for use of ADBAC and other quaternary ammonium compounds as contraceptives. And these patents were started as early as 1970. Okay. So in that patent application, they included all mammals, non-human primates and humans, and they included a wide variety of quaternary ammonias not just the ADBAC.

And what they showed in their data was a decrease in ovulation, a decrease in implantation, and also fetal death. So the application was for contraception both pre-fertilization and post-fertilization. So that data is mirroring what we're finding in our reproductive studies.

And based on these patents, they're actually licensed for use in Canada and Europe, as spermicides.

Okay. They're meant as vaginal suppositories to kill the sperm before they can fertilize the egg. But we're wondering, because we can measure levels in the mouse testes, could this becoming systemic and could it actually be affecting sperm production in the testis.

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DR. HRUBEC: Okay. So this is the big -- I am not saying QACs are implemented -- implicated in any disease. I'm going to say it again. I'm not saying they cause any disease. I really want to stress that. But here's the -- here's the big but. Their use has increased dramatically in the last 30 years, partly in response to outbreaks like we're having right now. People have become more conscious. They're using disinfectants a lot more.

This rise in use follows at the same rate of increase as diseases, such as obesity, diabetes, autoimmune disorders, asthma, allergy, and autism. Okay. We also see, over the same time, declines in male and female fertility, increased use of assisted reproductive techniques, and declines in the sperm count. This is not just here in the U.S. This is globally.

And these disorders are characterized by increased inflammation, mitochondrial dysfunction, and altered cholesterol synthesis. The same thing that we've seen from exposure to the quaternary ammonium

disinfectants. Okay. Again, I'm not saying there's a link. If there's not a link, no one is going to be happier than me. I mean, I don't want to know that this exposure is causing these health effects, right?

But it really behooves us to go start monitoring them and try to see what actually is the level of exposure. What is the route of exposure? We don't know. Is it exposure in the workplace? Is it exposure in the home? Is it exposure in the public places? Is it from all those hand sanitizers that are now whisking off the shelf really fast. We just don't know. Okay. So until we start monitoring, we're not going to know.

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DR. HRUBEC: So to summarize, in rodents, they cause birth defects, that alter immune function, they cause reproductive difficulties, and they can accumulate in tissues, particularly the testis and the brain. In humans almost nothing is known, but our study showed that they increase measures of inflammation, decrease mitochondrial function, and altered cholesterol synthesis.

Okay. Again, so our first -- our -- if you're being prudent, the first step we need to start monitoring what's going on, how are we exposed.

I'll take any questions.

CHAIRPERSON SCHWARZMAN: Thank you so much.

We have about 10 or 15 minutes for questions from the Panel and then from the audience before we break for lunch.

Tom, do you want to start?

PANEL MEMBER McKONE: Okay. Thank you. Very interesting. I have a question about the study with the medical students --

DR. HRUBEC: Yes.

PANEL MEMBER MCKONE: -- the first year medical students. I mean, I have a son who's a fourth year medical student, but he spent the first year --

MS. HOOVER: Sorry. Butting in for a technical difficulty. We were just told the webcast has stopped working. So can you contact the AV services?

Okay.

Let's give it a minute and see if we can get the webcast back. So hold that thought.

CHAIRPERSON SCHWARZMAN: Two minutes ahead of schedule, so...

MS. KAUFFMAN: It's likely bad Internet or a browser issue. So they've been monitoring it. The webcast is still happening.

DR. HRUBEC: Okay. Your question.

PANEL MEMBER McKONE: All right. I'll go on.

So the question about the first year medical

students. So having -- as I said, I had a -- I have a son who's now fourth years. But I know the first year he spent a lot of time in anatomy, in labs, cutting up cadavers, and other -- so a lot of exposure to a whole range of chemicals. So, you know, is there a way to account for that -- are they an unrepresented population, because they have so much time in laboratories where their histology, anatomy, cutting up, measuring things, probably wiping things down with some sort of disinfectant?

DR. HRUBEC: Okay. So in anatomy lab -- I teach anatomy. And we are careful not to use quaternary ammonium compounds. Now, they are used in some cadaver labs. Our -- we obtain our cadavers from the State Anatomical Board. And I've questioned them about their preservation techniques. They do not use quaternary ammonium compounds. I can't speak for other states with other procurement situations.

So from anatomy lab, they're not exposed to it. Whether they're using wipes, I don't know. The other labs are all done online. They're virtual. Our histology is a virtual histology lab. They do have a -- it's an osteopathic school. So they do have an OMM lab, where they're learning how to do the manipulations. And they may be using disinfectants there. I don't know. But the labs all tend to be in the afternoon. And we were

measuring as the came out of the classroom right at lunch time.

So, I mean, there could be -- again, we don't know where the exposure is coming from. You know, I just know that they were exposed.

CHAIRPERSON SCHWARZMAN: Ulrike had a question.

PANEL MEMBER LUDERER: Yeah. Ulrike Luderer, UC Irvine. Thank you. That was a very interesting presentation. I have a question about the tissue levels. Just to -- you know, were -- did you also have controls that were not dosed and were the levels -- you know, were there detectable levels in those or not? That's one question.

DR. HRUBEC: Okay. Libin Xu did the analysis for that. And I know he ran controls, but I think he could speak more. I know he's going to talk more about the analysis, and so on, of that later.

CHAIRPERSON SCHWARZMAN: Okay.

PANEL MEMBER LUDERER: We can -- I have another question, which is also related kind of to concentrations and exposures, whether the in vitro concentrations that were used in the vitro results that you presented with the macrophages --

DR. HRUBEC: Um-hmm.

PANEL MEMBER LUDER: -- how did those compare to

blood levels that you measured in humans or is that a comparison you can make?

DR. HRUBEC: It's not a comparison that you can make. Cells in culture are very different than in the body. And there's always caveats. You know, this is in cell culture. This is in an animal model. How does that relate to human exposure? And you just use it as indicators. You can't say there's a direct one-to-one correlation. So I don't know if that answered your question sufficiently.

CHAIRPERSON SCHWARZMAN: Carl.

PANEL MEMBER CRANOR: Thank you.

I found that most interesting. Just your summary slide at the end, you have causation in the animals. You just don't know whether there's causation in people.

DR. HRUBEC: Correct.

PANEL MEMBER CRANOR: But that's a clue. That's an important clue.

DR. HRUBEC: Right.

PANEL MEMBER CRANOR: But I did want to focus on one specific thing, and I've lost which slide it was.

DR. HRUBEC That's fine.

PANEL MEMBER CRANOR: I think you said males exposed, then did that cause adverse effects in the --

DR. HRUBEC: Offspring yes.

PANEL MEMBER CRANOR: -- in the offspring, just the males exposed?

DR. HRUBEC: Correct.

PANEL MEMBER CRANOR: Very interesting.

DR. HRUBEC: Right. And that's we think is due to the epigenetic effect changes to the sperm. Okay. One other thing I should mention is when you do an exposure study like that, you have to expose -- the sperm have a time from when they're first started to be produced from the stem cells until where they're active modal sperm. Okay. And you have to make sure that you're exposing over the full length of that cycle, because if you expose them before the cycle has a chance to go all the way through, you could have sperm that are not affected, if it's affecting it at the stem cell stage.

Okay. So you have to give time. In a human, that's 60 days. In a mouse, it's ten days. So you need to expose at least ten days before you're monitoring for the effect.

PANEL MEMBER CRANOR: Repeat again the difference between the humans and animals what the exposure --

DR. HRUBEC: The sperm cycle, the maturation cycle is 60 days in a human. Okay. So not meaning to be crude or graphic here, but if we have a vasectomy, you have to wait two months, 60 days, to make sure all the

viable sperm are out of the system.

PANEL MEMBER CRANOR: I see.

DR. HRUBEC: Okay. In a mouse, the sperm cycle is ten days. And so from the time the stem cell starts producing a sperm until you have an active sperm is ten days. You need to -- if you dose on day five, unless it's affecting a semi-matured sperm, it's not going to -- you're not going to able to see effects, because it's ahead of other ones in the pipeline. It's ahead of the affected ones in the pipeline.

PANEL MEMBER CRANOR: And you see this how many generations, two?

DR. HRUBEC: We did not do a male-only exposure study for multiple generations.

PANEL MEMBER CRANOR: Okay.

DR. HRUBEC: Okay. I am guessing you would not see it now. Epigenetic effects do carry for multiple generations.

PANEL MEMBER CRANOR: Yes.

DR. HRUBEC: Okay. So when we were looking at the three generational effect, that was in females only due to exposing those multiple generations. If there are epigenetic changes, they can carry for multiple generations, and we might see that same effect. We -- I just don't know.

PANEL MEMBER CRANOR: And the females were how many generations?

DR. HRUBEC: Three.

PANEL MEMBER CRANOR: Three.

DR. HRUBEC: Right. So when you're looking at generations, you have to think of the female -- the mother generation and the offspring generation.

PANEL MEMBER CRANOR: Right. Right.

DR. HRUBEC: So it is the offspring of the second maternal generation, so the F3 baby generation.

PANEL MEMBER CRANOR: Did -- you didn't go to four to see whether it was a whole family line?

DR. HRUBEC: No once we --

PANEL MEMBER CRANOR: Like Mike Skinner's work.

DR. HRUBEC: Right. No, it's not. And we would also -- we -- one of the things we do is regularly refresh our breeding stock. So once a year, I buy new males and new females. We grow them up for three generations and then start using them for our study. I want to make sure that they don't become inbred. And so again, every year, we get fresh stock in and breed them up, so they're not exposed.

PANEL MEMBER CRANOR: Very interesting.

Thank you.

CHAIRPERSON SCHWARZMAN: Thanks.

Yes, please.

DR. XU: So I just a comment on the previous question --

CHAIRPERSON SCHWARZMAN: Introduce yourself.

DR. XU: So Libin Xu from University of Washington. On your previous question on the tissues, we did receive some, I think, control tissues from Terry that we did analyze them. And there were always some background level of these compounds, but they are much lower compared with the exposed one. And like, in fact, there's compound like -- they're so sensitive in a mass spec, you -- it's almost impossible to not to see any trace amount in the mass spec. It's also another indication probably they're ubiquitously present in the environment.

CHAIRPERSON SCHWARZMAN: Yeah, go ahead.

PANEL MEMBER LUDERER: I do have another question, which is about the transgenerational study.

DR. HRUBEC: Um-hmm.

PANEL MEMBER LUDERER: Did you look at any other endpoints besides the neural tube defects in that transgenerational study, the fertility endpoints or any of that?

DR. HRUBEC: No, we didn't. Yeah, it was just the neural -- again, at that point, we were trying to

figure out what's going on, why do we not have a controlled -- you know, why does it go to zero, when we try to limit the exposure?

And so we were just focusing on our endpoint that we can easily monitor, which was the neural tube defects.

CHAIRPERSON SCHWARZMAN: Veena.

PANEL MEMBER SINGLA: Thank you for that very interesting presentation. Could you talk a little bit about how the neural tube defects were assessed?

DR. HRUBEC: Okay. So they're assessed visually. We're looking at day ten of gestation. Okay. So the -- I don't know how much you know about neural tube formation. What happens is you get neural folds that rise up. They bend towards each other and then come together and fuse. If they don't fuse, that's when you get a neural tube defect. Okay. The neural tube -- the only time you can get a neural tube defect is when that neural tube is forming. Once it forms, it's not going to come apart.

Okay. So we look at the stage of development when that neural tube is forming. I should have put a slide up there. But the embryos are really small, at this point. So we look under a dissecting a microscope, but you can see actually spaces where the neural tube is not fusing. And you see it in the head region. You can see it in the spine region, so it's a direct visual

observation.

PANEL MEMBER SINGLA: Thank you. Yeah. That's -- it would -- it would be interesting to look and see if there were other patterning defects beyond the -- just what you could visually observe. And also, I wonder if there's any cognitive deficits even in the -- the pups that didn't show --

DR. HRUBEC: Right.

PANEL MEMBER SINGLA: -- visible neural tube defects. It would be very interesting to explore that.

DR. HRUBEC: Right. I -- well, I think so too. That's a study that I'd love to do. One of the things I sort -- to keep in mind is a number of the therapeutic compounds that are known to cause neural tube defects also have neural developmental defects as well. So valproic acid, carbamazepine, they're known to be associated with neurodevelopmental defects, autism, ADHD. Okay.

They also cause neural tube defects. And my thought is if you're hitting the nervous system with a big enough hammer to cause a neural tube defect, you're going to see some more subtle changes as well.

And then what was the first part of your question?

PANEL MEMBER SINGLA: Looking for neural tube patterning defects. Yeah.

DR. HRUBEC: Okay. Right. So we have looked a little bit into that. And what I know is that PKA staining is different in the brains of exposed mice. PKA is involved in the Sonic Hedgehog's signaling pathway. Okay.

So we do see changes in that, but we haven't actually gone into measuring the other patterning signaling molecules.

CHAIRPERSON SCHWARZMAN: We have time for just the one more question.

MS. KAUFFMAN: Okay. We actually have three requests.

CHAIRPERSON SCHWARZMAN: Then we need to keep them very brief.

MS. BRADLEY: Yes. This is Taylor Bradley from the American Cleaning Institute. Two quick questions. What was your sample size for the rodent studies? And your research shows that you did work with biocidal QACs. Did you have any, you know, thoughts on doing research for softening compounds or anti-static compounds?

DR. HRUBEC: Okay. So, yes, we only worked with ADBAC and DDAC. We haven't looked at other compounds. I would love to do it. Give me money add I'll be happy to look at it.

The second one. Okay. Question about dose,

right?

MS. BRADLEY: Sample size.

DR. HRUBEC: Sample size. Our standard sample size is 15 litters for all the exposure studies. Okay. And then within those litters, they have anywhere from 10 to 20 babies. So we look -- we're evaluating 10 to 20 embryos in 15 litters.

CHAIRPERSON SCHWARZMAN: There are two more questions. I just want to remind everybody we have lots of time for ongoing questions and discussion after lunch too.

DR. RUBIN: Hi. I'm Andy Rubin, Primary State Toxicologist for the Department of Pesticide Regulation.

I have a very utilitarian question for you, but one that's of great interest to regulatory toxicologists. And that is, are there any strain differences, in other words, are you only working with a single strain? Have you looked at rats, rabbits, you know, more expensive experiments undoubtedly, but curious.

DR. HRUBEC: Right. So we did look at rats very briefly and we saw neural tube defects in the rats. I use CD-1 mice. We have -- I have looked for neural tube defects in Black 6 mice and I have seen them. But we haven't gone to the extent of developing a QAC-free strain and testing them as assiduously as we've tested the CD-1.

So I do believe there are species effects and also strain effects in the mice. But again, more work should be done.

CHAIRPERSON SCHWARZMAN: Thank you. We'll have a final question and then we'll break.

DR. HARRISON: Oh, there you go. This is Bob Harrison. I had no idea that the QACs are used in veterinary and research labs for animal disinfection -- for surface infection. Just when I thought I knew everything about every occupational exposure.

(Laughter.)

DR. HARRISON: I am just absolutely amazed. I mean, so I just went on the internet and I see that they're widely used. Like, there's all this commercial stuff that's sold for surface disinfection. So I just queried our epi database to see if we have any asthma cases in workers who work in vet labs or in research facilities, because we submitted comments. And I can't remember of all the asthma cases we had whether there are any veterinary staff who have been reported to us.

But I have a quick question. I know we're about to break for lunch. Why are high-level disinfectants used in animal research labs?

DR. HRUBEC: Again, like I alluded to, in a -- in an animal care facility, you have a wide variety of research projects going on, some are actually infective.

You know, so they're working on a specific disease. You don't want that disease to spread through your whole colony. Okay. You also don't want to make your mice sick with a pathogen that you may have. So, again, it's to protect the mice from you, you from the mice, and the mice from each other in the research facility.

DR. HARRISON: Is that evidence based? Is that based on -- is that lore or is that science, that it's necessary to use high-level disinfectants there?

DR. HRUBEC: There -- animal diseases in animal care facilities are monitored extensively. So when you buy a mouse, it's certified disease free. And we have a monitoring system in place where mice are checked once a month. They have sentinel mice in each room. And they're checked once a month to see if diseases spread.

We recently had an outbreak of a parvovirus in our mouse colony. I wasn't doing any work at the time. So my point is this isn't from a parvovirus infection. But anyway, they stopped all research on campus, until they could get that infection under control.

So the basic -- what they were asking us to do was de-populate, right? And so you get rid of all your mice, which I did, and then everybody has to start anew.

So it's a big -- I mean, that's a lot of money. Okay. It has to get stopped.

CHAIRPERSON SCHWARZMAN: Thank you so much. Really appreciate it.

We are going to break for lunch now. We have an hour and ten minutes. There -- I want to note that panelists have a map in your packet and there's one on the back table for anyone in the audience about some lunch options that are close. We'll reconvene promptly at 1:35.

And at this -- I want to introduce Carl DeNigris, Senior Staff Counsel of OEHHA who is going to provide us a reminder about Bagley-Keene requirements.

SENIOR STAFF COUNSEL DeNIGRIS: Hi. Carl DeNigiris, Staff Counsel, OEHHA.

Just a reminder to the Panel members to comply with Bagley-Keene Open -- Open Meeting Act requirements and refrain from discussing any matters that are before the Panel outside of this meeting.

Thanks. Have a good lunch.

CHAIRPERSON SCHWARZMAN: Okay. We'll reconvene at 1:35.

(Off record: 12:27 p.m.)

(Thereupon a lunch break was taken.)

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

(On record: 1:34 p.m.)

CHAIRPERSON SCHWARZMAN: Okay. I want to welcome everybody back from lunch and introduce our next speaker.

Libin Xu is an Assistant Professor at the University of Washington, where he started his own lab in the Department of Medicinal Chemistry. His research focuses on the role of lipid metabolism and oxidation in human diseases and the development of novel methodologies for the analysis of lipids, metabolites, drugs, and drug metabolites using mass spectrometry techniques. Libin will prevent -- present information on analytical considerations, human metabolism, and effects on cholesterol homeostasis for select QACs.

Thanks.

(Thereupon an overhead presentation was Presented as follows.)

DR. XU: Thank you very introduction. And thanks, Sara and Shoba, for the invitation. Great to be able to contribute to this Panel discussion.

So I'm going to touch base on several aspects that our lab has done research on, including the metabolism, some analytical methods we developed, and also some of their effects on cholesterol and lipid homeostasis.

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DR. XU: So. I guess we have seen plenty of structures of the QAC compounds, quaternary ammonium compounds, and just show --

PANEL MEMBER CRANOR: Can you pull the mic a little closer?

DR. XU: Yeah. Sure.

Yeah so -- and -- so these are some typical structures --

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DR. XU: -- shown here, including the BACs that was mentioned earlier, and also that DDAC, which is on the bottom here, which is our two types of compounds now, mostly focused on in this discussion. And they were obviously widely used.

And to allude to some of the questions on the exposure routes. So it could be on the topically through, you know, your disinfectant use. Also, you could expose them through nose spray or eye drop, et cetera, like -- because eye drop can cause systemic exposure as well. Also, more importantly, like they are used in food production line as a disinfectant. So you could expose to these compounds by ingestion.

However, there's no public data on QAC exposure levels in humans, so we decided to take a look at this.

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DR. XU: And I just want to first touch base on the analytical methods, like this is using liquid chromatography with tandem mass spectrometry. And some of the panelists are very familiar with this. Basically, you monitor the targeted characteristic fragmentation of each compounds, and -- which give you extreme sensitivity.

And in this case, we use reverse face method solvent gradient of -- from -- with water and acetonitrile. And you can adjust the gradient to meet -- to make it faster and slower. But in this case, in this particular round, it's about eight minute.

And we have synthesized deuterated isotope label standards for benzalkonium chlorides and for four compounds with a C10, 12, and 14, 16 carbons. We don't have a deuterated standard for DDAC, but we can get a response factor relative to these deuterated standards.

As you can see, these are the typical -- chromatography peaks that's for these compounds.

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DR. XU: So with the, you know, analytical method in hand, and -- so we decide, because there's currently lack of public data on, you know, exposure level in human plasma, we took -- we purchased a hundred random human plasma samples from BioIVT, which we don't know the -- I

mean, they're supposedly from healthy individuals, but we don't know exactly the source.

And then we look at the levels of QACs in these samples. We find that it's in 40 -- you know, 30 to 45 percent of individual has a detectable level of QAC compounds. And then among them, there are nine individual actually detect a level that's one micromolar or higher. So that's, you know, pretty significant. It's just suggesting even, you know, they are indeed absorbed. But I have to -- I have to clarify on these samples, because we don't know how they are collecting it, so there's a possible exposure of the compound during the collection process as well.

So I think a more well controlled study and possibly through the Biomonitoring Program that could really help to get really well controlled human samples to get true exposure levels on this.

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DR. XU: And so the next question we asked is that can -- so they do get into our blood and can human body actually metabolize them. So in here, we used the benzalkonium chlorides, BACs as examples here.

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DR. XU: So the study we do is -- initially, it's to use human liver microsomes. Human liver microsomes are

a fraction of liver that are enriched with drug metabolizing or xenobiotic metabolizing enzymes, such as cytochrome P450 in this case. And cytochrome P450 are co-factor dependent the co-factor is NADPH. So you see in the black lines are without a co-factor and in the colored line with co-factors. Obviously, the human liver microsome does metabolize these compounds. And the metabolism is dependent on the co-factor, suggesting it's dependent on the cytochrome P450 enzymes in our human liver.

And you can actually monitor the half-life in the human liver microsome, like that range from one to 15 minutes. The longer the chain, the longer half-life they are. And so NADPH dependency suggests cytochrome P450 involvement.

I want to the mention -- you know, emphasize here this is an in vitro system, so it's, you know, isolated human liver microsome enriched with its metabolizing enzymes, so it's not a whole body disposition. So because of hydrophilicity, like the lipid solubility of these compounds, like it's mentioned in earlier talks that they could actually be enriched in certain lipid-rich organs. And so their half-life could be longer in the actual body, and -- which is could be the reason that we actually saw -- observed it in human plasma samples.

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DR. XU: And the next question we asked is what kind of specific isoform of cytochrome P450's revision, the CYP, actually responsible for their metabolism. So in here, we take two examples, a BACs one is short chain with a C10 carbon. The other is a longer chain with C16 carbon. We screen for the metabolism or disappearance of the parent compound basically in the presence of different cytochrome P450 isoforms.

So in the top, you can find the CYP2D6 and 34, and the 4F12 are -- particularly to 2D6 and 4F12 are metabolizing this particular compound with C10 carbon. For the longer chain, we find that 2D6, 4F2, and 4F12 are the major metabolizing enzymes. So that's -- so that's a pretty good step.

I would think there -- another form of 4Fs that's in -- responsible for the metabolism, which we have -- we're in a process to -- trying to confirm that, but identifying the specific isoform metabolizing these compounds is important, because this CYPs genetically they are highly variable. For example 2D6, they're like eight to ten percent of human population that were a actually poor metabolizer, so -- and then the 4Fs, there's some genetic variation associated with it too, so -- which could indicate that certain human population with lower --

you know, decreased metabolizing capability could be of higher risk in -- to exposure to these compounds.

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DR. XU: So then the next question we asked is what kind of metabolites they are formed from the BACs?

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DR. XU: And to do that, we -- basically, we carried out metabolizing reaction and monitored the product formation using mass spectrometry. In here, I show the typical chromatogram biomonitoring. Each compound plus 16 Dalton, which is a mass of oxygen -- single oxygen. So it's the primary hydroxylation, or epoxidation, or other kind of products.

And we typically saw two peaks for each compounds as color coded in here. And so with some synthetic chemistry and also mass spec with fragmentation, we can conform some of this -- the primary products are either omega-hydroxylated, which is adding hydroxy at the terminal alkyl chain or omega minus one hydroxylated, which is adding hydroxy to the omega minus one position toward the end. And the omega minus one tend to elude earlier than omega-hydroxy compounds. So we have conformed them with synthetic standards.

And we further carried out pretty complete metabolism study, like including secondary products. I

mentioned about this primary products. We think some of the CYP4s, particularly some CYP4Fs, two of which we mentioned earlier. I think -- we think there's another form of it that make the omega-hydroxy and the 2 -- CYP2D6 and 4F12 makes omega minus one hydroxy.

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DR. XU: And the omega-hydroxy compounds can be further metabolized to omega-carboxylic acid, and -- oh, and omega minus one hydroxy can be metabolized through ketone compounds. And both of these primary products can be metabolized through this omega minus one dihydroxy compounds in there.

So for the BAC with a C10 carbon, we have synthesized all of these standards. But for the other chain, we haven't synthesized all of them, but we have the primary product standards.

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DR. XU: So, indeed, you can also monitor the metabolites using LC-MS/MS. And this is showing an example for C10 BACs biomonitoring different mass spectrometry transitions. You can monitor different kind of structure, which is shown on here -- on top are di-hy -- hydroxy compound, dihydroxy compounds, and the ketone, and carboxylic acid.

So these are modified from the initial method I

discussed, but you can just change the grid into make it slower or faster. It just depends on what you're monitoring, how much resolution you want to be in terms of retention time.

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DR. XU: And so we then take a look of some of the tissue distribution. So here, I show the kidney tissues in mice fed on a QAC-containing diet. This is the kind of diet that actually follow what Terry has used, using a mixture of BACs and DDACs, and following their protocol using a gel diet. And as you can see on the right side in a controlled diet and there's a minimum amount. And in the QAC-fed kidney tissues, it's significantly elevated compounds. But I do want to point out, there's some trace level of probably QACs in the control tissue. And that could -- could be from, you know, the -- they are actually through some exposure or it could actually be due to the analytical process.

As I mentioned, the QACs are used ubiquitously in everywhere. So sometimes they just got mixed in your liquid sample, they got trace level of those things. So that's one thing to consider, I guess, when we actually monitor this compound to have enough good controls to know what's the based on level that you can see by using different solvent containers that may actually has exposed

to QACs.

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DR. XU: And we then look at whether metabolites are observed in these tissues. Indeed we saw those. Top, it's controlled kidney tissue. In the middle is a QAC-fed kidney tissues. We observed omega minus one, omega hydroxy compounds. And the bottom is the -- just a possible control is human liver microsome metabolites. It has omega minus one, omega hydroxy compounds, which compared with in -- with the in vivo, there's different ratio for these two compounds, but also the bottom is a human liver microsome in the middle it's a mice tissue.

And mice, they tend to express a little bit different profile of cytochrome P450. And also they have a bigger capacity to metabolizing xenobiotics. So we also observed metabolites of BAC C14 and C16.

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DR. XU: And so in -- I guess in last part what I want to touch on is some of the biological activities of the BACs that we're interested in, and specifically their effect on cholesterol and lipid homeostasis.

And I want to give a short background like why do we interested to look at their effect on cholesterol and lipid homeostasis.

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DR. XU: It's originally to our, I guess, research on this genetic disorder in the cholesterol biosynthesis steps.

In the last step of cholesterol biosynthesis, it's capitalized by this enzyme called DHCR7 that reduced 70 hydro-cholesterols or precursor of cholesterol to cholesterol. And genetic defects of these compounds -- of this -- of these gene can lead to a disease called Smith-Lemli-Opitz Syndrome that's characterized by elevated level of 7-dehydrocholesterol precursor and the decreased level of cholesterol.

And then it affects 1 in 10,000 to 60,000 populations. It's characterized by a lot of congenital malformations, mental retardation, and autistic behavior. However, the carrier frequency in caucasian population has been estimated actually pretty high in 1 in 30. So they're suggesting there could some underdiagnosis for that disease.

But regardless, it is the neurodevelopmental defect. And due to our interest in environmental toxicology, we also interested in looking at environmental small molecule that could possibly inhibit this particular enzyme, as some literature is suggesting. Like in drugs, some drugs actually inhibit this particular step. So -- and so -- and that includes breast cancer drug and some

antipsychotic drugs too.

But in our study, we find that its benzalkonium chlorides, and BACs, are actually protein inhibitors of this particular enzyme, which I'm going to talk a little bit more detail now.

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DR. XU: And so the initial study that we find these kind of compounds is because they have high structure similarity to a known inhibitor of this particular enzyme, DHCR7. This is a known inhibitor. It's called AY9944. We did an in silico structure similarity study basically, and we look at similar structure to AY9944. And these are several compounds that were through high similarity.

The benzalkonium chloride, the BACs, showed the highest similarity. You look at it. They both have the benzyl head group, and nitrogen that's charged, and then it's a hydrophobic section group, which is very similar. The hydrophobic part is very different.

The AY9944, the proposed mechanism is that it's actually it's a metabolite after, you know, probably removing one side of the nitrogen to be active. So if you consider that, it's even more structural similarity.

So we did some in vitro study first to look at whether they indeed actually inhibits the cholesterol

biosynthesis. And then -- so the bottom are showing the measurements of cholesterol and the cholesterol precursor, 7-dehydrocholesterol and other precursor, desmosterol.

That's are treatment in dress Neuro2a cells, with a neuro -- which is a mouse neuroblastoma cells that were exposed at 100 nanomolar for two days. As you can see in the first panel, the AY9944 and the C10, and C12 are carbon BACs only inhibits DHCR7 pretty potently. And -- so but a longer chain, the C14, 16 didn't. And then the -- on this shorter chain carbon, BACs seems to reduce the cholesterol level too, but C10 didn't reach statistical significance due to the bigger error.

However, all of the compounds seems to reduce the level of these other precursor, desmosterol, which I didn't talk about. It's -- there are two branch of cholesterol biosynthesis pathway that's on the other branch. Regardless, all these compounds seems to be affecting cholesterol biosynthesis process.

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DR. XU: And then we -- we then look at -- think about it, because you know sterol and the lipid homeostasis are often linked together. They're regulated together by some sort -- pathway, which I'm going to talk a bit later. So we look -- we're asking the question whether they could affects some other lipid homeostasis as

well.

So we did similar experiments treatments in Neuro2a cell. And this time we did a lipidomic analysis, which has -- show -- I'm not discussing that method here, but basically we monitor the whole lipidome, the changes, and we did a statistical analysis on the lipid feature detected in the middle showing the PCA plot, which suggesting the grouping of AY9944 and the C10 BAC grouping together was suggesting they're very similar biological activity. And C16 is group very separately from both control, and AY, and C10 groups suggesting it has probably some other activity on the lipids.

And looking at some of the most significant effective features, including on com -- on three compounds decrease the triglyceride levels. And AY9944 and C10 increased the metabolites possibly to cholesterol precursor, which we think is 7-DHD derived metabolites. And C16 actually increase the level of phosphatidylethanolamine and phosphatidylcholine, and -- but the other AY9944 and C10 didn't lead to significant changes.

So it seems that on the BACs has a biological activity that's dependent on the chain length. And they have effect on both cholesterol and lipid homeostasis overall.

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DR. XU: And so just to look at like trying to sort of invalidate in a way to look at what's the consequence of the gene expression changes related to sterol and lipid homeostasis.

Because you would think if you inhibit the cholesterol biosynthesis, you would see some response to the fact that that would be unregulated. Indeed, that's what we saw. And the top three are the cholesterol synthesis gene. They were upregulated. SREBF2 is cholesterol regulation gene. It's upregulated. We actually -- pretty surprising to see the fatty acids synthesis gene it was also upregulated.

And the last one, ABCA1, is actually a cholesterol efflux gene, which is downregulated. It all makes sense. It's the response to the inhibition of cholesterol synthesis.

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DR. XU: And so the next question is -- we asked is that whether we -- you can actually see this kind of effect in vivo? Can they alter the sterol and lipid profile in development of brain? Because the reason we're interested in the brain, because the brain synthesize all of its cholesterol and most of the lipids locally, which means when you try to do treatments using supplemented,

you know, these compounds will not be effective to other brain development. And also, that's all associated with neurodevelopmental defects as well.

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DR. XU: So what we did is in this study we did in utero exposure to BACs through the mother of the pups that -- so in this study we actually used the isotope labeled BACs just to be sure we're actually getting the -- these compounds in the tissue, instead of the environmentally presence of these compounds. So we, you know, basically customized the mothers to the gel diet, and then -- and then starting to expose to this diet at one week before mating and then keep until the new pups are born.

So we -- and then we collect tissues from postnatal day zero. We analyze BAC distribution, and sterols, and lipids. And also, we did RNA sequencing on the neonatal brains.

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DR. XU: And so first of all -- and just to -- as a confirmation, the BACs indeed cross the blood placenta barrier and also blood-brain barrier in the embryos. The level were pretty low. What's shown on here on the left two panels are the level in the neonatal brain. On the right is in the dam blood. And so we find that both the

C12 and C16 were significantly elevated in the brain and liver of the neonatal pups. But level is like for C -- for the brain, it's sub one nanomolar. And for the liver it will be higher. It's one to two -- one to three nanomolar. In the dam blood however, the level is a bit -- it's much higher from around 15 to 20 nanomolar concentrations.

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DR. XU: And then we look at sterol changes by these compounds. So we monitor cholesterol and also a bunch of cholesterol precursors. And so the first graph is a total sterol level. We see overall decrease by these compounds, 12 and 16. 12 has -- showed a statistical significance, but 16 did not. And cholesterol level also toward the same trends. And what's interesting, what we observed here, is that all of the cholesterol precursor seems to be decreased too, instead of, you know, increasing the particular dehydrocholesterol level like in the third and -- level. We didn't see that.

So suggesting at this kind of level, like subnanomolar concentration, and it's probably not directly inhibiting DHCR7 in this concentration. However, it still has an effect on the total sterol levels, probably through some regulatory pathway that's decreasing the total sterol levels.

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DR. XU: And then we look at the lipids that -- whether they're changed in the neonatal brains. And these are similar approaches. The first is a PCA showing in color different groups. They do color -- they do group by colors roughly. And then we look at features contributing to their separation. We find that again triglycerides which is similar with what we observed in the tissue culture that was decreased triglycerides decreased too. And hexosylceramides decreased by a much smaller extent. While ceramides were -- have opposite effect by the shorter C12 and longer C16 BACs.

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DR. XU: So then, you know, we observed some of, you know, the changes in sterols and lipids as -- you know, even though somewhat different, but there's a lot of similarity to the in vitro study. But what next question is what other pathway or gene expression changes are actually associated with this sterol and lipids homeostasis changes?

So we reserved that to RNA sequencing. So we did RNA sequencing on the neonatal brain for the three groups.

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DR. XU: And so this is to look at the global gene expression changes relative to the control. And

you -- we see that BAC C12 induced a lot more changes compared with BAC C16. BAC C12 roughly overall it's about 500 gene significantly affected, but -- including both upregulated and downregulated ones. And C16 is about 114 genes.

And then what we did is we put on the differentially expressed genes into a pathway analysis.

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DR. XU: We use ingenuity pathway analysis by QIAGEN. And that sort of, you know, give you some idea what kind of pathway were enriched. That's means there are more genes were affecting that particular pathway. And then the cholesterol biosynthesis pathway come out to be a top pathway for both C12 and C16 exposed brains.

And also we find that liver nuclear receptor LXR/RXR were also affected. So on the right, the number indicates the log p-value, the positive number indicates its activated pathway. The negative number indicates it's an inhibited pathway. So in here, cholesterol biosynthesis pathway is activated in LXR and -- sorry RXR is inhibited.

We also see some other interesting signaling like glutamate receptor signaling, which didn't have prediction, but that's certainly very closely related to the neuro -- neuronal function, which we're -- I'm not

going to talk about this today. We haven't pursued that too far.

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DR. XU: So another information we can get from this pathway analysis, you can identify upstream regulators that possibly regulate a bunch of different gene. One of this regulator we find is called SCAP. It's SREBP cleavage-activating protein. SREBP is a cholesterol and lipids homeostasis regulatory protein. So in here, SCAP, on the left is C12 regulated gene that were found to be significant. On the right is C16. And many of these genes can be ascribed to cholesterol synthesis and many of the gene can be attributed to cholesterol regulation.

In fact, there are others I didn't point out. It's more or less related to cholesterol and lipid synthesis. And C16 has a lot less significantly affected genes, but overall trend is the same.

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DR. XU: And the way that SCAP regulated cholesterol and lipid homeostasis is essentially it's a carrier protein. The SREBP is sort of main factor. When you have low cholesterol the SCAP's function is basically carrying the SREBP from the ER lumen to golgi and then cleave off the part of SREBP, which then go to nucleus to activate transcription factors.

When you have high cholesterol level, and SCAP, and -- it will be in coordination with another protein called insig. That will change the confirmation of the complex retainer, whole complex in the ER, which then will now resulting activation on cholesterol synthesis.

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DR. XU: And so we also look patterns on the gene involved in sterol and the lipid homeostasis. And by, you know, looking at upregulated and downregulated genes, what we find in the top on the left is that most of the upregulated gene were again cholesterol biosynthesis related. And like insig was upregulated. Low density lipid protein receptor was upregulated, which is important because LDL receptor is the one that actually circulating your cholesterol back to liver, for example, back to the cell that you want to be. Like, you know, it essentially on the cell can express LDL if they want more cholesterol if there. And also the fatty acids related genes.

And among the downregulated genes, most stand out were apolipoprotein, several from A1, C1, A2. And also, there are other like negative regulator of cholesterol has been found in this -- in this panel as well. Again, the BAC C16 lead to similar pattern of change, but there are less -- there are fewer significantly affected genes in the C16.

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DR. XU: So with that, I'd just like to, you know, give a few summary points that the QACs are indeed observed in a hundred random human plasma samples. And they can be metabolized by human cytochrome P450s. And both BACs and their metabolites can be quantified by using liquid chromatography and mass spectrometry. And both, I think, should be monitored for biomonitoring programs, because that would allow you to gain a full complete assessment of the BAC exposure. And the BAC exposure, and can lead to elevated levels of parent compounds, and then metabolizing the dam and neonatal tissues. We find that both in vitro and in vivo the BACs indeed disrupt cholesterol and lipid homeostasis even though the concentration in the in vivo were very low in the neonatal brain.

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DR. XU: And so with that, I just want to acknowledge I guess the team who has done the work. It's mostly by Josi on the left and Ryan in the back. Josi working on the cholesterol lipids, homeostasis, and Ryan did most of the metabolism studies.

And thank our mass spectrometry center, which has been tremendous to help us get this going. Thank you, I'll be happy to take any questions.

CHAIRPERSON SCHWARZMAN: Great. Thank you.

(Applause.)

CHAIRPERSON SCHWARZMAN: We have time for questions for Libin Xu.

Carl.

PANEL MEMBER CRANOR: I just need some help. Some of the terms I don't understand the consequence of. So if --

DR. XU: Okay.

PANEL MEMBER CRANOR: -- if you decrease sterols or you alter lipidome, what happens to the brain?

DR. XU: So, I guess, there's -- we need to do some background. Like cholesterol is the molecule that brain synthesize all by itself -- you know, and since the -- after blood-brain barrier formation. So that means, you know, cholesterol involves a lot of embryonic signaling pathway, such as hedgehog signaling. The hedgehog protein were modified by cholesterol, and --

PANEL MEMBER CRANOR: And you need the cholesterol for --

DR. XU: For a lot of embryonic developments --

PANEL MEMBER CRANOR: Okay.

DR. XU: -- and neurodevelopment. Yeah. And lipids as well, I guess being -- suggest to play developmental role in the brain as well.

Yeah.

PANEL MEMBER CRANOR: Thank you.

CHAIRPERSON SCHWARZMAN: Yeah. Veena.

PANEL MEMBER SINGLA: Thank you. That was a really interesting presentation.

Could you -- in the random human plasma samples, obtained --

DR. XU: Um-hmm.

PANEL MEMBER SINGLA: -- do you know any information about the population or demographics, and anything about the source of those samples?

DR. XU: I think they're -- when we purchased the samples, there are some demographic like information. But not too much than that. They just claim to be the healthy individuals. So I can choose back on the demographic in terms of ethnic, yeah.

CHAIRPERSON SCHWARZMAN: Ulrike.

PANEL MEMBER LUDERER: Thank you. That was a really interesting presentation. Did -- have you looked at all at any like steroid like adrenal or sex steroid synthesis and whether there are effects of these chemicals on that, since they affect cholesterol?

DR. XU: Yeah, we haven't. That's a very good point. You mentioned if you decrease cholesterol level, more than likely you will decrease some of the subsequent

metabolites, right. That's a very good point. We haven't done that yet.

CHAIRPERSON SCHWARZMAN: Yes, Oliver.

PANEL MEMBER FIEHN: Fatty acids very crucial for, you know, brain development and brain function. So did you, in your lipidomics experiment, see any significant changes there, either for alpha-linolenic acid or for arachidonic acid derived metabolites in your lipidome screens?

DR. XU: So in those studies, I guess we didn't particularly go look for the fatty acids composition for each lipid signals. But if you look at, I think, some of the features that we observed, they are indeed poly unsaturated, and which likely -- like you mentioned -- I don't know whether I have a slide here.

Yes. Sorry. I guess I didn't mark the identity for each of these peaks. But brain is enriched in -- on such lipids, like arachidonic acid and DHA, for example. So we should think likely could be affected, but it's probably in the kind of extent of affecting the whole classes.

Yeah. So we haven't done that much detail in terms of figuring out the specific fatty acid-dependent changes.

CHAIRPERSON SCHWARZMAN: Oh, yeah. Good. We

have two panelists on the phone. Do either of you have questions?

PANEL MEMBER QUINTANA: Not right now. Thank you. Jenny Quintana.

DR. XU: So I think I remembered something like there was a question asked earlier that -- suggesting on a QACs or excreted by -- through feces. But in our preliminary study, which we haven't finished enough replication yet, like we did observe metabolites in the feces, which is indication that they actually go through your body and it got secreted out through the biliary duct like you mentioned earlier, which I think -- some of the study in the literature or has been using radiolabeled compounds to -- like animals to treat how much to come out.

But those obviously doesn't specifically identify each particular component in that radiolabel, because the metabolites, they will have the radiolabel as well.

So I think that we do have some evidence suggesting it does -- even in the feces, they're metabolizing there too.

CHAIRPERSON SCHWARZMAN: Thank you so much for this. Oh, Carl, did you have one more question?

PANEL MEMBER CRANOR: Just one more follow-up question. If -- have there been accidental experiments as

it were, where developing children did not have sufficient cholesterols of various kinds in their brains and something happened?

DR. XU: Um-hmm. So -- yeah, so the particular cholesterol biosynthesis disorder for those children has over -- like 75 percent of the children that were actually diagnosed with one -- at least one type of autism spectrum disorder.

PANEL MEMBER CRANOR: One type of what?

DR. XU: Autism spectrum disorder.

PANEL MEMBER CRANOR: Oh.

DR. XU: So it's a pretty high correlation between lower cholesterol level, just looking at that particular population. I think there's one study that's not very big. It's probably -- it's less than 50 of the enrolled children that look at a correlation between decreased cell level of cholesterol versus the autism occurrence. There seems to be a positive correlation as well. But because autism is so heterogeneous, so it could be only accounted for some subgroup of autism, yeah.

PANEL MEMBER CRANOR: Thank you.

DR. XU: Yep.

Yes.

PANEL MEMBER SUÁREZ: So there seems to be a difference in the amount of fat solubility the different

QACs have.

DR. XU: Um-hmm.

PANEL MEMBER SUÁREZ: Could you tell me a little bit about that, because here you're saying that it is present and in the neonatal brains, which makes me think that there's a fat soluble piece to that.

DR. XU: Right.

PANEL MEMBER SUÁREZ: And some of the other ones, I think, in the first presentation, they were actually highlighting more the water solubility of that. Maybe you can comment on that a little bit.

DR. XU: Yeah. Actually, these compounds like at least for BACs or DDACs, they are more lipid soluble. We have looked at their like Calculated log p-values, basically log p an indication of partition between octanol and water. They have all like larger than one log p-value. That means they are more soluble in lipids in organic solvents compared with water.

So they're very understandable that it could be more enriched in the lipid-rich organs. And actually there was one early study in rats that exposed the BACs by injection or orally. They find that actually the -- it's the kidney and lung accumulate highest level of BACs.

So that could -- relates to some of the lipids, but you could also related to some of the transporters

related to like the kidney and the kidney has the uptake transporter and the efflux transporter, which is important for excretion of the xenobiotics. And so we mean -- just indicating it -- distribution in certain organ could be more serious than the others.

PANEL MEMBER SUÁREZ: So could urine be perhaps a better substrate for measuring metabolites for that matter?

DR. XU: We could do that. I mean, we haven't done the urine measurements and -- but I think both the feces and the urine should be -- should be measured, because feces we'd look at the biliary secretion, where the urine look at actually kidney function. If indeed, that they are accumulating higher level in the kidney, that would indicate the kidney doesn't actually have the full capacity of excreting them.

And so that's some of the thing that we're interested in too like to look at transporter's effect, whether they are substrate or transporters or both uptake and efflux.

PANEL MEMBER SUÁREZ: And you mentioned also concentrations in the lung. Could the --

DR. XU: Um-hmm.

PANEL MEMBER SUÁREZ: Could the potentially biomonitoring be done with breath?

DR. XU: I'm not sure. And I guess we have to see, yeah. But definitely feces and urine are feasible, and plasma as well, yeah.

CHAIRPERSON SCHWARZMAN: In thinking about that, knowing how that they're not particularly volatile makes me wonder about --

DR. XU: Right.

CHAIRPERSON SCHWARZMAN: -- even though they're present in the lung, it doesn't mean that they'll be expired.

DR. XU: Yeah. In, fact they are surfactants, right? So it could actually be sticky on the lung, yeah.

CHAIRPERSON SCHWARZMAN: Terry, you have had a question or comment.

DR. HRUBEC: I had a comment to make about the absorption and excretion. A lot of the studies that are -- and there aren't very many, but the ones that are published in the literature, have their first measurement at about 30 minutes, so they dose -- they start measuring at 30 minutes and then they'll watch out for the next, you know, 24 hours or so. In my experience with the mice, I can start to see signs of toxicity within minutes after dosing them. And they can even die within minutes, if they're given too much. So I think it's quite possible they're definitely getting absorbed in that time. I

can't -- dose in mice have it die if it's not getting absorbed.

So I think those previous studies are looking at a time point way too far out. They are metabolized and excreted well before that time, which is why people are saying, you know, we're only finding it in the feces. That's because it's gone through their metabolic cycle relatively quickly.

I mean, I haven't done the study, so I don't know. But just from my own experience with animals and looking at what the literature says, that's what I think is going on.

PANEL MEMBER SUÁREZ: And in your study -- in your studies, the administration was oral.

DR. HRUBEC: Yes.

PANEL MEMBER SUÁREZ: Just like with other that was presented.

DR. HRUBEC: Yes. Okay. So the -- this is with our orally administered quats that we gave.

PANEL MEMBER SUÁREZ: How much of -- how much is bioavailable from an oral dosage? Have you -- do you have any idea?

DR. HRUBEC: No, no idea. I guess one thing I could add to this -- it's a little bit off topic. But the studies they've done looking at the toxicity are saying

that they -- the structure is similar to acetylcholine. And they work at the muscarinic -- acetylcholine muscarinic receptors and they cause a paralysis. So the main toxicity you see with acute dose, not chronic, but the acute dose is due to paralysis of the respiratory muscles and the mice just can't breathe. So that's what see the clinical signs of, you know, they just are struggling to breathe.

PANEL MEMBER SUÁREZ: And there will be cholinergic overstimulation or --

DR. HRUBEC: Correct.

PANEL MEMBER SUÁREZ: Okay.

DR. HRUBEC: Correct. Yeah.

CHAIRPERSON SCHWARZMAN: Yeah, go ahead.

DR. HOSTETLER: Hi. Keith Hostetler with TRS, a speaker in a few minutes and to get to some of these points. I think it's important in an acute toxicity study to recognize that these in high concentration are corrosive. They can certainly corrode the stomach and cause lethality, which has nothing to do with systemic absorption.

We'll talk more about some of the data that is collected -- proprietary data that's part of registration -- pesticide registration, where we know -- and the absorption is about ten percent or less from an

oral dose. Most of that's excreted directly into the feces in rat studies, where we've done it with radiolabeled studies. But we can come to some of that -- you'll hear some of that just as a little preview.

Thank you.

DR. XU: I probably would say ten percent is pretty significant absorption.

CHAIRPERSON SCHWARZMAN: Any other Panel questions? I want to orient everybody on the Panel in the room and on the webcast to what's going to happen next. We are going to move on to our -- thank you very much for that presentation and discussion.

DR. XU: Thank you.

CHAIRPERSON SCHWARZMAN: We're going to move on to our discussion of QACs as potential designated chemicals. And this is the section for about the next hour before a quick break, after which the Panel will deliberate and then make a recommendation about designating quaternary ammonium compounds as potential designated chemicals.

And there's -- so just to tell you what happens during that later period, there's a significant portion for public comment and also a significant portion for discussion among the panel. So we don't have to do it all in this next chunk before the break.

So to talk about what we're going to do before the break. We have a guest discussant now and then we will have about 45 minutes for Panel and audience discussion, including two scheduled public commenters.

So I would like to start by introducing our guest discussant, Bob Harrison. He is Chief of the Occupational Health Surveillance and Evaluation Program in the Occupational Health Branch of the California Department of Public Health. He's also on the faculty at the University of California, San Francisco in the Division of Occupational and Environmental Medicine.

Bob holds an M.D. from the Albert Einstein College of Medicine and an MPH from UC Berkeley. He'll provide some remarks on occupational exposure concerns associated with QACs.

(Thereupon an overhead presentation was presented as follows.)

DR. HARRISON: Thank you.

As Meg mentioned, I wear two hats. And I'm not officially representing either of your government-funded agencies on the -- organizations, on the one hand, the California Department of Public Health, the other hand the University of California, San Francisco, but I am a bona fide public servant in both capacities.

So I have been, with my team at the Department of

Public Health, collecting data on work-related asthma in California. And we submitted comments about the data pertinent to -- we've always called them the quats. So this is new. I had QACs, or QACs, or QACs. But for the last 25 years, I've called them quaternary ammonium compounds, or quats.

We have many thousands of cases of work-related asthma from physician and hospital reports throughout California. And we categorize these interview and published data on the causes of work-related asthma. And the quaternary ammonium compounds have been on our radar screen for many years, and particularly the BACs. It was mentioned earlier, the BACs are designated as asthmagens or agents capable of causing asthma by the Association of Occupation and Environmental Clinics, or AOEC. So they're one of many hundreds of sensitizing agents to which workers can be exposed.

That is reviewed systematically and was designated as such by a pulmonary researcher at Michigan State, Ken Rosenman and the documentation can be retrieved from the AOEC website.

So I'm going to go on to the next slide.

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DR. HARRISON: And I basically just want to -- oh, I guess I can -- there you go -- remind everybody, I

guess I would say that work-related asthma is really kind of like the worker canary in the mine. It represents an end health effect. It's not an early toxicologic or biomonitoring health effect. And as I was listening today, I raised the question of what is the relationship between sensitization and work-related asthma, and the toxicological findings that I just heard? How does that relate to this case I'm going to show you?

But this is certainly can be a very disabling and significant from a public health impact point of view, significant health effect. There are probably many tens of thousands of workers exposed to the quaternary ammonium compounds in California. I wish I had the number to give you. That turns out to be extremely difficult to estimate. But certainly there are millions of health care workers employed in California. And the quaternary ammonium compounds are widely used as surface disinfectants.

As I mentioned earlier, I wasn't aware that vets could have potential exposure until just now. So I would probably add veterinary clinics and research labs. I would also add emergency responders. We've gotten concerns or called about wiping the inside of emergency response vehicles. Schools are also a big potential user. Surface disinfection and the need to eliminate the germs

at all costs are another area where we see quats being used and the BACs being used. Child care facilities, which are both licensed and unlicensed in California, there's a fair amount of use there.

So there's -- it's probably in the -- probably the hundreds of thousands of potentially exposed, if I had to put a rough kind of is it five figure or six figure. I'd probably say it's six figure worker exposure in California.

The sensitizer asthma is a subset of all work-related asthma. And on this slide in the lower left it's a form -- the BACs cause a form of sensitizer-induced asthma. You can see other forms of asthma include reactive airways disease, which are a immediate, one-time, high-dose ex -- relatively high dose exposure, and then longer irritant-induced exposure causing, on the lower right, irritant-induced asthma.

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DR. HARRISON: It's important to recognize that asthma can be asthma from the sensitizers, including BAC, can occur over the course of months or years of use. And one of the things that characterizes this form of asthma is that there can be a delayed response. So that means the person's at work has exposure and then goes home and develops the classic symptoms, chest tightness, wheezing,

shortness of breath.

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DR. HARRISON: So this was -- is a woman that works at our medical center at UCSF in our custodial department. And she was cleaning a bathroom in one of our research office buildings. So you're seeing the sink there. That's not a patient care room. That is basically a public restroom on the first floor of the old UC hospital, if anybody's ever been to Parnassus. It used to be the hospital, but it's converted to offices right now.

And she developed -- and she had been doing this for a few years. She developed very severe wheezing, cough, shortness of breath. Wound up in our emergency department, was admitted for severe asthma. And I saw her in follow-up in my practice. And she told me what she was working with, when I took a good occupational history, which, you know, I teach, so hopefully I -- I asked her what she did.

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DR. HARRISON: And I followed her to the cleaning closet where she -- where she was getting the chemicals. And she showed me what she was working with. And this is a little hard to make out, but I think this is a BAC, right? If you look at the second ingredient, you see where it says 1.87 percent. That is the structure of what

I think we're talking about today in the animal toxicology studies.

And it's actually at a pretty high percent in this product, because it's used as a concentrate, and it's diluted by her in the cleaning closet. So if you look at other forms of BAC-containing surface disinfectants, the most common that I encounter in the hospital are cloths that are pulled out of plastic containers, the little round containers. They're wipes. And it's sort of like taking a tissue -- piece of tissue. It's impregnated. Those contain about 0.05 percent of BACs, so a much lower concentration. So she's diluting this in the cleaning closet, which is an opportunity for exposure when she's diluting it.

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DR. HARRISON: And this is another cleaner, a disinfectant that she uses to clean the toilets that also has -- you can't make it out the concentration. It's falling off there, but that also has BACs in it.

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DR. HARRISON: And then she's using another product. This has triethanolamine in it, which also is a little bit of concern to me as a potential irritant or sensitizer.

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DR. HARRISON: And I said, well bring me all your products that you're using. Do you know what's in them? Do you know this is a potential risk. So she lined them up on a heater in the hallway outside her cleaning closet. And it wouldn't surprise you that she didn't know what she was exposed to. She didn't have knowledge about the chemicals, which is petty typical in my experience.

So I then, being the good primary prevention doctor that I am, went to her supervisor, who is the head of the custodial department, because I wanted to know who orders a asthma-containing chemical to use in a non-patient care area?

And it turns out our custodial department orders this. And I said, well, you know, she developed -- my patient developed asthma. It would be a good idea if we could identify a substitute. First of all, she doesn't need to use a high-level disinfectant in that bathroom. She could use soap and water or she could get something off of Green Seal or another certifying organization's list. And the answer I got was, well, nobody else has asthma. There's no one else who's affected.

And I said, oh, that's really interesting. Let me explain to you something about sensitization, and health effects, and susceptible populations. And it was like really pretty much of a blank screen there.

And that's a pretty typical response, because her susceptibility, okay, you know, what's the incidence of asthma here? It's probably less than ten percent, maybe even less, among all the janitors who work at UC Medical Center.

And so this idea that we're going to replace and find safer substitutes for a very small number of people who get sick is still pretty alien in concept. It's interesting to me when I heard the toxicology this morning, what if I had a biomonitoring test at my disposal or could have enrolled her in a biomonitoring study? That would be interesting. And we are continuing to use these.

I wasn't successful, by the way, in completely finding safer substitutes for the BACs, because they're very effective disinfectants. And we balance, as you'll find, as you dive into this, a balance between occupational exposure, and patient safety.

They're highly effective in disinfecting surfaces, for instance, with C. difficile, which can be a highly communicable deadly disease.

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DR. HARRISON: So I'll end. We focused primarily in our work on primary prevention thinking about are there safer surface disinfectants that can be used? And identifying those wherever possible to substitute a safer

disinfectant out where BACs are used. Because from our perspective, it's been mostly focused on work-related asthma and respiratory disease. I would also mention that there's a very abundant literature, I think, was summarized in the -- in Sara's OEHHA report on health care workers and respiratory effects. And a fair proportion of that is from the use of BACs.

So -- oh, I also wanted to say that early removal from exposure -- so if a worker gets to this point that I presented to you, she unfortunately now has permanent disability and asthma that's ongoing. If she had been identified early or the substitute was made early, it could prevent. So that's another significant public health impact to consider.

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DR. HARRISON: So green chemistry, I guess, cradle to grave, the whole concept in terms of the value of biomonitoring, if this could help identify risk factors and exposure levels, and then help to move towards the identification of alternatives, that, could be as effective and reduce risk.

I think that would be very important.

Thanks

CHAIRPERSON SCHWARZMAN: Thank you so much.

We have a chance now for some questions and

discussion before we have our next commenter?

Go ahead, Tom.

PANEL MEMBER McKONE: Thank you.

That's very interesting. The comment/question I have is, you know, in response to the -- something like, well, nobody else has this, I think it raises a very interesting point about what level of protection we provide and what level of visibility is associated with that. Like, if you want to protect 90 percent of the population, and, you know, it leaves ten percent vulnerable, and you only have five workers, you know, what are the odds that you actually might see a case.

Well, 90 percent is not a very -- I mean, to me, in a public health context, only protecting 90 percent of the population probably is a pretty low target.

And then, I mean, if you want to protect 95 percent or more, then you know, the point that you need to see frank evidence of effects before you're saying this makes a difference. I guess, it kind of argues to the point about knowing in a population what fraction is susceptible, which we could probably know in advance, I mean, the fraction of susceptibility for a given disease. And then, you know, the question is really could biomonitoring help us determine how many people are actually moving, you know, in a direction where it's going

to affect that fraction of sensitives, if you get my -- my point. I mean, so there's these different numbers.

And again, the incidence visibility is often low, because the numbers are small. And so even -- I mean, if we want to set a reasonable public health target, we need some sort of better tools than just waiting for people to present symptoms. Anyway, I don't know if you want to comment on that. But that's certainly what raises an issue for me.

DR. HARRISON: Great question. I would say from my perspective that if I could have demonstrated or said that all the janitors at UCSF have detectable levels of BAC, or we did a biomonitoring study that demonstrated that, that a fair proportion have it and that's biologically significant, I think that would be a powerful argument that could help drive some better purchasing practices and identification of safer substitutes, because we're not going to get rid of BACs overnight by any means or even ever, because they're -- I mean, I don't think tomorrow it's not going to happen, because there is -- they're very effective licensed disinfectants by the U.S. EPA, and they have -- that's why I was asking my colleague about why are they used in animal care facilities, and if they -- in research labs it sounds like they have to be used or some form of surface disinfectant has to be used.

And if there's a -- if there's a subtle biological effect that can be demonstrated through biomonitoring, I think that that will help push those kinds of conversations around safer substitution, regardless of how many get -- how many people get asthma, because I'm not quite sure the asthma public health impact is -- you know, because I get this response all the time honesty about, well, you know, it's the individual susceptibility. It's not the community biological impact. So I think that's -- that's -- to me, that's the value of biomonitoring.

CHAIRPERSON SCHWARZMAN: There was a comment or question in the back.

DR. RUBIN: Andy Rubin again, toxicologist, DPR. I just thought I would mention in the context of Robert's talk that over the lunch period I read in the New York Times, the Metropolitan Transportation Authority, which oversees subways, buses, and two commuter railroads said late Monday this it has started a major cleaning of all equipment that called for an industrial grade disinfectant to be applied to everything from train cars to metro card machines every 72 hours.

I suppose that's -- those are QACs, but -- yeah. Yeah

DR. DATTA: Hi. So I'm Sandipan Datta from

University of California, Davis. And I think like there is one thing we might be missing over here is that like there is this one person who is getting asthma right away from exposure. But like how many people are moving towards there, and like, you know, they will get asthma after they're retiring, which is from the exposure to these chemicals. But it would be confounded as if like, you know, it's just the old age and therefore they're getting asthma.

So that delayed effect, that chronic effect, is what we will be missing if we don't monitor the levels of these chemicals. And like probably do a long-term association study of the levels of these chemicals and how people are developing chronic disease. So that might be one point that needs to be taken into consideration.

CHAIRPERSON SCHWARZMAN: Thank you.

Carl.

PANEL MEMBER CRANOR: A quick question for Bob. We have a kind of -- in some circumstances, we have a risk, risk health tradeoff for using these disinfectants, because you use them in one circumstance and you prevent other diseases. But I think before all this started even today, you said you thought we were overusing them. If you had recommendations to make, where do we need the powerful disinfectants and where can we skip them, just to

be overly simple about it?

DR. HARRISON: Well, I think in infection control and to prevent disease in patients, absolutely --

PANEL MEMBER CRANOR: Yeah.

DR. HARRISON: -- they're necessary. Now, there are a number of different options that facilities have out there. There's pera -- peroxyacetic acid. There's -- oh, I'm just skipping the other one. You mentioned it to me -- right, hydrogen peroxide. Those are the two other alternatives that I know of. And we -- and we -- and we've looked and done some toxicological analysis and -- you know, in terms of the settings in which they can be used. They also have other impact though on surfaces at hospitals were, for instance, telling me that hydrogen peroxide degrades medical equipment. So they don't like to use it on surfaces of various pumps and equipment in hospital rooms for example or to disinfecting scopes can degrade some of the equipment.

So there's some -- there's some trade-offs, Carl, but I would say that in -- where there's patient or now laboratory impact on animals, and infections, they need to be used. I mean, I -- our infection control colleagues will, you know, have a cow if we were to say otherwise, and they would be correct, in my view, in terms of protecting patients.

But there's lots of examples that I find where, you know, teachers will disinfect school surfaces. Is it necessary? I don't know. Is it necessary to disinfect train cars in New York City with a high level disinfectant? I don't know. Is that necessary for COVID or is it just this idea that we need to get rid of every germ?

There's a lot of -- there's a parallel universe of the need to disinfect surfaces and get rid of germs that is taking place widespread outside of this room in our discussion of quats, that, as we sit here, drives purchasing -- purchases of disinfectant compounds. I don't -- you know, in -- it's a long conversation obviously about what to do, about that.

PANEL MEMBER CRANOR: Yeah.

CHAIRPERSON SCHWARZMAN: If there are no other burning comments or questions, at the moment, I will invite our first scheduled public commenter up Keith Hostetler is currently with Toxicology Regulatory Services, Inc. And prior to joining that consulting firm, he spent more than 20 years in the specialty chemicals area with national expert -- multinational expertise in toxicology and regulatory affairs.

Keith holds a Ph.D. in Pharmacology and Toxicology from the Medical College of Virginia at

Virginia Commonwealth University. And he'll provide comments on behalf of the ADBAC and DDAC Issues Steering Committee.

(Thereupon an overhead presentation was presented as follows.)

DR. HOSTETLER: Thank you very much. And we appreciate the chance to comment and to be commenters. I have a colleague too that trying to split this up about ten minutes apiece and leave time for questions as well.

What I'd like to offer is a perspective first to introduce both the group that I'm representing and that Dr. Osimitz who's following me is representing. The major companies that address the toxicology and regulatory requirements of I'll call them the quats, the QACs, exactly the terminology we're talking about, the two major ones ADBAC and DDAC.

These are companies that have formed a joint program to look at toxicology regulatory in both the U.S. and Europe, and also the member companies that make the formulated products. So these are the folks in the marketplace. These are the folks that are required to register. And what I'll talk about here is a lot of data that isn't in the public domain, because it's proprietary, it's been generated to support registrations, and it's owned by those companies that have done that.

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DR. HOSTETLER: What we'll cover in the next few minutes to give you a sense of this sort of nature of the overall understanding that we have of quats, there are robust studies that really confirm that there are large safety factors from what humans are exposed to and what are known to cause effects or not cause effects in animal studies.

So the uses that are registered, that are on labels, are supported by these consistent datasets across multiple species, more than two decades worth, and they're GLP-compliant studies. So they've followed very strict guidelines for how they're conducted. We do know that they are an irritant. They have irritant potential. They do not cause systemic effects distant from where they're exposed. They are regularly evaluated. This is part of the pesticide registration requirements in both the U.S. and Europe. That's not just a one-time thing. New data has to be generated and they have a long history. I think ADBAC was actually first registered in 1947, DDAC in the 1950s and the real FIFRA antimicrobial registration requirements came about in the late '80s and through the '90s.

Europe had the biocidal products directive, which became the Biocidal Products Regulation that came up

through the early 2000s. And there's regular reviews going ahead.

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DR. HOSTETLER: So this lists the regulatory authorities, including CalEPA, that have looked at and regulate that the existing uses -- I'm really talking about disinfecting and sanitizing uses of these compounds.

So the active ingredients are registered. There's been extensive human safety factor evaluations. There's ecology studies. With ten minutes, we couldn't cover everything on the environmental side. I think what's been touched on, they do bind, they don't enter groundwater. So they're really not particularly mobile. So we're going to focus here more on the human health effects.

Quats are present in low concentrations. A half a percent I think was mentioned earlier. 0.1 percent is typical. Food use, 400 ppm, which is point 0.04 percent is fairly typical.

So they have this long history. And I think it is important that we talk about what are we preventing? Public health. Food safety. There is a benefit risk that really does need to be taken into account.

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DR. HOSTETLER: I won't mention anymore about

environmental fate and effects. I will mention metabolism. In fact, we had a poster at SOT. And I think Dr. Xu which might have spoken in Baltimore at my poster. We're publishing these to get them into the record. There are radiolabeled studies that have looked at oral administration within 72 hours. Ninety-eight percent of quats are gone from animals that are fed in the diet. Most of it's in the feces. A little bit absorbed. It does go to the liver. Hydroxylated polar metabolites are then excreted in the urine.

So that's pretty well established. There's actually in vivo IV studies. So when you inject it into the veins, not a human exposure route. But if you do that in animal studies, it goes to the liver. It gets hydroxylated. Part of that gets into the bile. Part of it gets -- because it's polar then, it will get in the urine, and the kidneys and liver will take care of elimination.

There's a whole battery of oral, dermal, inhalation exposures for acute, and subacute, and chronic, and subchronic exposures. There's a remarkably consistent pattern that we see. Speaking of sensitization or allergic potential, it's negative in classic skin sensitization studies. There have been a case study or two from an asthma standpoint with an immunological

factor. But considering the millions of people that use these, it is extremely low.

In the studies that we really want to focus on here, repeat dose toxicity, multiple routes of exposure, multiple species. We clearly can find no-effect doses. You push the dose high enough, you will get irritation. You'll get gastric irritation. You'll get -- you'll get toxicity from those kind of exposures, but there is a threshold effect.

Importantly, there are carcinogenicity studies, negative in multiple species. Developmental repro studies in particular, a very large dataset exists and I'll expand on that on another slide.

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DR. HOSTETLER: But first, the general picture. They're readily biodegradable. They're strongly absorbed, so you won't find them in groundwater. I just touched on this. They don't produce systemic toxicity. They're poorly absorbed. We have not seen adverse effects in tissues distant from where they're administered. So you don't administer them orally and see toxic effects in the kidney or another distant organ.

So this point-of-contact irritancy has to do with membrane disruption. It's pretty well worked out. Dr. Osimitz is going to mention that. The other thing that's

important is the results are consistently or markedly consistent across species, rats, rabbits, mice, dogs. We see the same effects.

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DR. HOSTETLER: From a developmental repro toxicology perspective, GLP studies are required to do range finding, identify which doses don't cause overt toxicity in the pregnant animals, and then evaluate from there. Those studies have been done in the preferred species, that's rats and rabbits.

You have to have adequate sample sizes. You have to document your exposures. And rigorous experimental design and execution of these kind of guidelines studies resulted in conclusions that these compounds are not reproductive toxicants.

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DR. HOSTETLER: As I mentioned, rats and rabbits are the regulatory species. Oral route of administration is required. We'll talk about exposure shortly. It's a negligible and unlikely exposure route in humans, but possible. There's no evidence in teratogenic effects. Clear no-effect doses were identified. We've also done multi-generation studies to look at effects downstream. At high doses, there are effects on pup weight. These are associated also with effects that affected the parent, in

other words, body weight changes, diet reduction, those kind of things. There are clear no-effect levels identified in doses that aren't toxic to the parents.

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DR. HOSTETLER: So there's been dozens of studies in mice, rats, rabbits, dogs. No reproductive effects seen in these guideline studies. The U.S. EPA has reviewed these and concluded that they're not developmental reproductive toxicants as has ECHA, the European Chemicals Agency in the biocidal products regulation which is under review.

And I just pulled out one particular safety margin, because I think it's important here. What I mentioned here is a no-effect dose in a rat in the developmental study. Human exposures from EPA in pregnant women, or women of childbearing age, are estimated through modeling that has been published and peer reviewed. It's called the IDREAM model.

It points out human exposures are estimated at 0.0159 milligrams per kilogram. So 120 milligrams per kilogram, which has been mentioned in some of the exploratory studies that aren't done for regulatory purposes I appreciate, but that's 7,000 times difference. So we have to take into account some perspective about doses that are causing effects.

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DR. HOSTETLER: So we know humans can be exposed. They're approved for food contact use without rinses. The food contact uses have been approved by California, U.S., Europe. And a point that we've talked about also from an exposure potential, they are not volatile. They are sprayed on surfaces. They don't remain airborne. Inhalation exposures are negligible. There are handling requirements for when they're diluted, when they are -- concentrates are poured. In fact, face protection and gloves are recommended. It's really important to protect workers in that case. There's no question about that.

But the data sets for all these important effects are complete and demonstrate that they're safe when used as directed.

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DR. HOSTETLER: So this restates these same conclusions. The only thing I'll highlight here is that again the consistency across large data sets, the adverse effects and robust guideline studies show you can demonstrate effects in animals, but they're far above what humans are exposed to. So they're approved and widely used, because of their important role in protecting human health, and in the face of existing and emerging pathogens. So I'd be happy to take any questions from the

Panel.

Thank you.

CHAIRPERSON SCHWARZMAN: Thank you.

Questions from the Panel?

Yeah, Carl.

PANEL MEMBER CRANOR: It's probably worth asking that with respect to the developmental and reproductive studies, how recently those have been done and how carefully they've done -- been done, because since about 2007, there's been a -- just a burgeoning of that literature. I've been to most of the international conferences and they're discovering all kinds of things that were previously unanticipated and we had some today. So it depends on how old those databases are and what they were looking for, and how well, and what kind of studies were done.

DR. HOSTETLER: Right. It's a good question. It's -- what we can say is these studies were conducted in the early nineties. The biggest guideline changed in 2000 -- in 1996, which required some additional endpoints, particularly in the reproductive and multi-gen studies.

So they were looking at more subtle effects later on. The principal endpoints of teratogenicity, developmental effects, effects on litters and multi-gen have not changed. So the quality of the science was as

per guidelines then, but there are studies that are two decades old. There's no question about that. It makes them no less valid.

Some of the review that's going on right now for the European Chemical Agency is looking at do we need to look at other endpoints? There's nothing in the structure activity that suggests that they have direct receptor agonist activity or antagonist activity. So there's no other underlying effects that would suggest, outside of academic studies, that in species that aren't particularly normally used for these kind of studies. Not to say that they're perfect and shouldn't be other endpoints evaluated.

CHAIRPERSON SCHWARZMAN: Yes, please.

DR. XU: Libin Xu from University of Washington. So I think, you know, one point on this -- the endpoint thing with the advancement of different technology and the mass spectrometry, and other sequencing, et cetera, like -- or, you know, biological assessment, you know, you can see observed changes, you know, subtle changes that you may not be immediately reflective at the phenotype, like in the changing of the cholesterol level, or, you know, some of the effect on the reproduction that you need to monitor that kind of change over a long time period chronically, and -- but that could be molecular level of

change that you don't have observable phenotype that's obvious to your visual inspection. So that's, I think, in the modern day like should we reassess some of the biological outcome.

And -- yeah, so that's one comment on that.

And another question -- another comment I would say on your claim of the absorption to be less than ten percent, which I believe is using a radiolabeled study and then -- I don't completely buy that, because as we mentioned that we do observe metabolites in the feces, which is suggesting the biliary secretion is one important metabolism pathway. That means the parent compounds could be absorbed and secreted as well. So you're observing in the whole radiolabeled kind of compound secreted by the feces is not complete suggesting absolute parent compounds.

I would say it could well be, you know, certain percentage are already being absorbed and they're secreted by the biliary ducts as well. So I think that -- I need to be more detailed in the molecular study. What kind of species were there -- are they going through your body already going to the feces.

DR. HOSTETLER: Point taken. There certainly is evidence to suggest that what is absorbed from the gut from an oral administration would go to the liver and be

hydroxylated and then would find itself as a metabolite in the feces. That's -- we found that in our rat studies as well.

Approximately, 90 percent was found unchanged in the feces in the rat studies that were done of both ADBAC and DDAC, of unchanged compounds

DR. XU: Yeah. Like I mentioned, even if it's unchanged, it doesn't mean it didn't go through the liver and secreted by the biliary duct.

DR. HOSTETLER: That's -- that's possible. Correct.

The other -- the other point maybe on your first -- on your first point, I agree that subtle sort of longer term effects. And, you know, my recommendation of this panel isn't that we shouldn't be biomonitoring. I think it's a matter of putting resources and prioritizing important ones that could have pub -- could have health effects based on how they're used.

But for some of the biology that's being investigated, I think the importance of the dose response, and the threshold effects, and at what doses these systems are not affected is obviously as important as at what doses and concentrations they are affected.

CHAIRPERSON SCHWARZMAN: I wondered -- I'm going to ask a question and then I'll come to you.

I wondered if Terry might reflect for a moment on -- I'm struck by the difference between the modeled human exposure number that you provided a few slides back that's, I think, four orders -- so that's modeled data on human exposure. And I think it's four orders of magnitude lower, Terry, than what you saw from ambient exposure in your animal husbandry environment.

DR. HRUBEC: Okay. So this is Terry Hrubec. We did not measure the ambient exposure. Okay. We don't have a number to quantify that. It really is going to vary from day to day. If it's a day that they foam the walls, it will be high. Some of the animal care technicians may be more concerned about germ spread and spray the boxes twice as much. But it's not something that we can -- or that we have measured. It would have to take continuous long-term measuring over the course of the study. We just used that as a model to mimic human exposure.

CHAIRPERSON SCHWARZMAN: Can I interject one thing there. One of the slides of yours that I'm looking at is the one where you resi -- you measured the residues in the mouse boxes.

DR. HRUBEC: Correct.

CHAIRPERSON SCHWARZMAN: And I understand it varies. But those residues you converted to a mouse dose.

DR. HRUBEC: Oh, okay. So those were the -- when we did the dosing study and we dosed at 60 and 120 milligrams, we took those boxes from those mice.

CHAIRPERSON SCHWARZMAN: I see. Okay. Okay. I misunderstood. Thank you.

DR. HOSTETLER: And a comment I might add is if mice were dosed, it came out in their feces and the feces in the box.

DR. HRUBEC: It's going to be in the box.

DR. HOSTETLER: Find parts per billion --

DR. HRUBEC: Right.

DR. HOSTETLER: -- concentration is neither surprising nor alarming.

DR. HRUBEC: Right. We expected it in the dosed mice. I mean, if we hadn't seen that, something would be wrong. What we didn't expect, it was in the undosed mice.

CHAIRPERSON SCHWARZMAN: Thank you. That's very helpful clarification.

Yes, please.

DR. DATTA: Hi. This is Sandipan Datta from UC Davis. So I have a couple of comments. The first thing is that like as you mentioned over here that like repeatedly that human exposures are negligible. So how would you reconciliate with that like we are constantly finding detectable amounts. And when I would say

detectable amounts, in terms of nanomolar levels of QACs in the human plasma and human blood. So that's number one.

The second thing is that, like you mentioned in one of your slides, that like, you know, it's very low. It's like half a percent weight by weight solution or mixture that is sprayed over. So most of the concentrations that I've seen are between like, you know, from half to two percent. Some of them have two percent, some of them have one percent, some of them have like half a percent.

So if I convert them into like molar concentrations, the two percent comes to about like 200 to 300 millimolar concentration. And the biological effects that we are seeing at low micromolar concentrations and the plasma level are at like, you know, like nanomolar concentration, but these are random plasma levels. They're not exposed or anything of that sort.

So how do you tie all these three things that like, you know, random avail -- random detection of QACs in the plasma level, like micromolar or biological activity, in vitro, and other academic studies, and the -- like, it's approximately somewhere between 300 to 400 times of concentration that is being regularly used on a daily basis.

DR. HOSTETLER: Yeah, there's a lot -- there's a lot in your question. A few things. I think earlier it was mentioned how do in vitro concentrations compare with what we do have circulating? And that's -- you can't compare them directly, because there are a lot of different systems. Cell cultures have to be exposed sort of continually. We know that we're very adept at metabolizing and clearing things out.

The fact that we can detect these things, I think there is -- Dr. Xu you mentioned the fact that you have to be very careful. They do bind to glassware. They bind to everything. They're very highly charged. If you've used them once in your life, you're going to be able to find -- if you have a good analytical chemist, you'll find nanomolar concentrations. In my view, you shouldn't be worried about that. Can it interpret -- can it complicate your interpretation? Of course, it can, because you have to know where that came from.

So my question would be what evidence is there that nanomolar concentrations are being associated with -- that could result from the kinds of exposures we know humans might get through residues on a surface that's been treated or from the skin from a worker who's using it to spray down.

And steady state concentrations for an

intermittent use product, I'd have to see the model that would predict that we're in concentrations that are alarming. Perhaps monitoring and finding out what those concentrations are would make us all rest better. But I don't see the -- I don't see a huge amount of concern about effects on public health when the products are used as they're -- as directed. And again, detecting it, finding it with a high-powered LC-MS/MS that picks up nanomolar concentrations does not necessarily indicate a problem. They're very still, very low levels.

CHAIRPERSON SCHWARZMAN: Okay. Final question, then we'll move to our second scheduled commenter.

MS. HOOVER: Just real quickly. This is Sara Hoover, OEHHA.

Shoba had mentioned that we did not locate data on half-lives in humans, and you said there was data on that. Could you comment on that?

DR. HOSTETLER: Yeah. I didn't mean to imply we had half-life data in humans. We have it in mammals and rodent studies. And I think -- I didn't see the actual calculation of the half-life value, but I know that 98 percent in a radiolabeled study with orally administered ADBAC and DDAC was eliminated within between 48 and 72 hours. And we know that they don't absorb in the adipose tissue. They get converted into polar substances and

excreted in the urine. But they don't, either in aquatic species or mammalian species, you don't see bioaccumulation. No evidence of that.

DR. XU: Libin Xu from Washington.

Just a quick comment on that. Rodents are much faster metabolizers, which is high capacity compared with human. So their metabolism a lot faster compared with human.

DR. HOSTETLER: Thank you.

CHAIRPERSON SCHWARZMAN: Thank you very much for the comments.

I want to introduce our second scheduled public commenter, Toz Osimitz -- Tom Osimitz is founder and principal of Science Strategies, LLC. Prior to founding that consulting firm, he was Vice President for Global Safety, Assessment, and Regulatory Affairs and Sustainable Product Innovation for SC Johnson and Sons. Tom holds a Ph.D. in toxicology from the University of Michigan. He'll provide comments on behalf of the Quat Residue Group.

Thank you.

(Thereupon an overhead presentation was Presented as follows.)

DR. OSIMITZ: Thank you very much for the opportunity. And I appreciate everybody hanging in there

this afternoon. There's a lot -- a lot to consider. I don't envy your job, because you have to not only recommend things, which you'll be biomonitoring, but coming up with priorities is really a difficult thing. That's probably really what we're talking about.

I think what Dr. Hostetler said earlier makes sense. We know that these molecules are irritating. There's certain conditions, certainly in animal studies, they can be toxic.

But putting it in perspective is something that I'm going to try to do here in the next few minutes.

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DR. OSIMITZ: I'll go a little bit off script, just based on what we talked about so far. But mainly, I wanted to start just by asking the question whether these are really good candidates for biomonitoring. And the criteria you lay out for biomonitoring all make a lot of sense. I'm certainly not going to quibble with that.

But if I think about molecules that are good, or classes of molecules like the organophosphorus compounds, which are good candidates for biomonitoring, we know the exposure routes. There's as many as three -- the main exposures routes are significant, dermal, inhalation, oral. There's well documented systemic human health effects. That's -- that's not a question.

Of course, this is the broad category of chemicals. Some are on Prop 65 list for cancer, some for reproductive. There's good systemic biomarkers for relevant health effects.

--o0o--

DR. OSIMITZ: Even if it's acetylcholinesterase, it's a good surrogate at least for what could be -- considered to be an adverse health effect, and they're excellent candidates. In contrast, I think what you heard from Dr. Hostetler is we're dealing with primarily dermal, point-of-contact effects. Meaning if you get exposed on the skin or in the respiratory tract, that's really where you see the effect.

Now, if you get high-level exposures, you'll have effects subsequent to that. If you're damaging a respiratory tract, that could damage -- you know, it could certainly ultimately have systemic effects. And in animals, that's what could cause death. But the basic proximal effect is that it's a point-of-contact effect. Not cancer or reproductive, there's no question from a Prop 65 standpoint certainly. And is a systemic biomarker really relevant to the health effects that we see? And I would say no.

So contrasting that to a class of molecules like the OPs that are good candidates for biomonitoring, I

would say on the basis of just practicality and the usefulness of the information, the quaternary compounds would not be.

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DR. OSIMITZ: I also want to make a few comments just on the health effects. I live in a wonderful world, because I get to deal with regulatory studies, but also I do a lot of studies with the academic investigators. So I see both -- both worlds. And the challenge in a regulatory context that you're dealing with is how do you reconcile the two of those?

And I've got some presentations at SOT coming up in a couple weeks with academic work and then also with some more guideline work. So I really understand the complex -- complexity and the challenge that this poses.

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DR. OSIMITZ: And to -- for perspective, I just -- a couple thoughts about the difference between the regulatory studies that Keith is talking about and then the kinds of studies you heard this morning. And I think there's value in both of them.

The purpose -- they're different purposes. The regulatory studies really are designed to meet very specific and somewhat rigid regulatory guidelines that have evolved over time. They've gotten better. The old

studies are still valid, but new endpoints have arisen that people look at.

The academic studies I find real interesting, because they're hypothesis generated. They're much more flexible. You can probe specific endpoints. We saw some fantastically interesting biochemical work done on very specific key events and adverse outcome pathway. And that -- and that's very good.

The dose selection criteria -- for regulatory studies are based on maximal tolerated doses and identifying a no observable effect level, you can use for risk assessment. With the academic investigative studies that's really not the point. And it's not a fault of the study. It's done for a different purpose. And one of the things you want to do there is you want to perturb the system and understand what that perturbation means. You can use these chemicals as tools to understand biochemical and physiological processes.

Study plans and protocols. Very different. Dr. Hostetler mentioned the reg -- relatively rigorous and well-documented aspects of regulatory studies. Less so in academic studies. Nothing wrong with that, except sometimes it's hard to put that in the context of safety assessment.

And then with regard to other factors, there's

very careful control efforts to look at compounding factors. Everything you can think of that could possibly confound a factor is thought of with regard to regulatory studies. In university environments, that's just hard to do sometimes, because you're renting space, you're sharing labs with other people. But the attention there is paid to carefully conducting the assays and refining the assays. So the purposes are somewhat different. How you put those together is a challenge. I'll make a couple comments on that in a minute.

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DR. OSIMITZ: One thing I do want to spend a few seconds on though is the kind of work you saw with the steroid metabolism and the whole issue of these pathways, which is fascinating and really, really super elegant work.

I like to look at this in the context of adverse outcome pathway. And I think some of the people close to toxicology have heard this term evolve in the last decade or so. And it really is a framework that allows you to take these individual events and link them to an adverse effect.

And the purpose of that is to use that adverse outcome pathway to define data you can use for risk assessment. And again, this -- much of this comes from

the National Academy of Sciences Program and their foundational report the *Toxicity Testing in the 21st Century*. And we're already almost a quarter into the century and it's just starting to get applied a little bit more.

Now, those molecular level work, the kind of level work you heard, is very useful. It's especially useful if you want to design screening assays for which you don't have a apical endpoints. So if you have some unknown chemicals and you know that one of the things that can happen is perturbing steroid homeostasis, understanding the relative effects of those chemicals can be very useful to predict adverse effects.

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DR. OSIMITZ: But the endpoint of that adverse outcome pathway - I'm going to move ahead here - really is the altered development. It's an apical endpoint, because from a risk assessment standpoint, I don't think you can regulate on steroidogenesis or those types of things. And I happen to be fortunate enough to be on the Endocrine Screening Testing Advisory Committee about a decade or two -- two decades ago now, that worked on the whole endocrine screening program. And we struggled a lot with the idea of screening assays versus apical endpoints.

The screening assays have an awful lot of value.

But ultimately, they have to be tested against their ability to predict or to mimic what you see in the altered development or the apical endpoint, especially for the purpose of risk assessment and public health protection.

From a standpoint of looking at biochemical effects and understanding modes of action, it's tremendously valuable. This is the adverse outcome pathway for altered development from adverse anti-androgenicity. And one of the ways you can -- one of the many ways you can affect -- get estrogenic or anti-androgenic effects is affecting the steroidogenesis way over here in the left. I don't have a pointer working.

But the left end of this shows the altered steroidogenesis. That pathway causes a decrease in estrogen, decrease in estrogen receptor activation. You then start seeing effects at the organism level, decreased uterine weights, gonadal weights, some histopathology changes. You see difference in estrous cycling as a result of that, change of age and time of vaginal opening, and altered development.

So this is the kind of way that I think about looking at all the assays and some of the -- some of what we heard today. So putting this together and saying what do you do when you have the kinds of studies that Dr.

Hostetler presented, but yet you have some very provocative data along the pathway of the steroidogenesis and homeostasis and some of the work that Dr. Hrubec presented as well. To me, that gets to the whole weight of evidence discussion.

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DR. OSIMITZ: And that's a difficult thing sometimes to do. But really just quoting ECHA here, it's really useful when you have either deficiencies in the studies or you have individual studies that provide difficult -- difficult -- different or conflicting conclusions. And that's really, I think, what is in front of a number of you today. You have to look at data quality, consistency of results, severity effects, and the relevance of the information, especially for risk assessment.

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DR. OSIMITZ: And when I've gone through this exercise here for example, I'm just going to move up to cellular function and metabolism, there's a number of studies, including some of what you heard today that clearly show that at certain levels the quats can affect mitochondrial respiration. And the work that Steve Levine did at Monsanto back in 2007 in the early days of endocrine disruption and steroidogenesis, he clearly

showed that that can have an effect on Leydig cells.

On the other hand, when it comes to regulatory and again protection of public health, which ultimately is the goal of the Biomonitoring Program, there's really no evidence from the regulatory guideline studies that would suggest there's any issue that's resulting from changing that cellular function metabolism back of the outcome adverse pathway.

There are a couple of the other slides in here I can let you look at. I think it's more important I went through a couple of these other things in more detail.

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DR. OSIMITZ: But if we look to conclusions based on in the way that I've looked at these data over the last few weeks in particular in getting ready for this, you heard about the benefits of the quats. They've been valued -- they've been evaluated globally. There's a lot of studies available.

The significant human health effects I think they're really lacking, with the exception of point-of-contact effects. And that means to me at least and to us that the biomonitoring and looking at systemic exposure is less important than it might be for other classes of molecules. Again, I understand that you have many criteria to look at when it comes to deciding what

goes on the list. But from a priority standpoint, we would say that the existing data and considerate -- consideration of the various types of studies we're looking at and the relative value, I would say that this should not warrant a high priority at least for biomonitoring.

So thanks very much for the opportunity to talk. And again, I really enjoyed hearing the presentation today. It was very enlightening.

So thank you.

CHAIRPERSON SCHWARZMAN: Thank you very much for the comment. First, I want to ask if our Panelists on the phone have any questions or comments at this point just to give them a moment to chime in. I know there's a little bit of a delay.

PANEL MEMBER QUINTANA: No, thank you. Jenny Quintana.

CHAIRPERSON SCHWARZMAN: Panelist questions?

Carl.

PANEL MEMBER CRANOR: I do want to ask about your emphasis on the regulatory scientific standards, because those have been the outcome of a political process that are influenced by a variety of factors, and they may not be up-to-date. And so I don't -- I'm not inclined to take them as the gold standard for adverse effects on people,

certainly given the recent research in a variety of areas. So I would be cautious about those, I suppose.

And another point, you didn't make it, but your -- the previous speaker did. Just because substances have thresholds on individuals doesn't mean that there are thresholds or the same threshold for an entire population. It can approach a linear effect if you have enough heterogene -- genetic heterogeneity. And so you've got to be kind of careful about that. So two cautionary notes and implicit questions.

DR. OSIMITZ: Yeah, fair points in both regards. With regard to the sensitive subpopulations, clearly there's some genetic subpopulations where you have a biphasic response, like this, as opposed to a log normal distribution. Those are tough to predict certainly. And there's some that have been documented. But when it comes to the log normal distribution or something more of just what's the variation of a thousand people with regard to a acetylation, or hydroxylation, or those types of things, I think when you -- when you look at the work that the CalEPA does, and U.S. EPA, and ECHA NET, they build that into their safety factors that there is going to be a difference between individuals, in that regard.

And I think that's where it comes out. So from a qualitative standpoint -- from a quantitative standpoint,

I think that is dealt with ultimately. With regard to the comment -- I'm a scientist not a politician, but I do realize there is a policy aspect of how the guidelines were set up. And --

PANEL MEMBER CRANOR: Especially with the agency.

DR. OSIMITZ: Absolutely. There is -- and I realize that. And sometimes that policy change lags develop in science and I'll agree with that.

So I know we're open to advances in science. I use it just as a framework to say ultimately we want to get to a apical effects. And what was an appropriate apical effect now, or in 1996, or 2007 may change over time. I agree with that. Fair point.

PANEL MEMBER CRANOR: Thank you.

DR. OSIMITZ: Thank you.

CHAIRPERSON SCHWARZMAN: Other questions or comments?

Yes, please.

DR. XU: Libin Xu from University of Washington. So in your conclusion slides - could you go there - you mentioned that there's lack of significant human health effect. I'm wondering like where did you get that conclusion from? Because, obviously, there's's not enough data for QAC exposure in human. And how do you do that? How do you draw to that conclusion even now what -- what's

needed to be done?

DR. OSIMITZ: Well, it is difficult to prove a negative. But I think if -- I'm comparing this to -- I should have put this in the broader context of how I started out. If I compare it with something like organophosphorus compounds -- I'm just using that, because that's an easy poster child. Some of the other ones are a little more complicated, phthalates and other things like that.

But, to me, if you look at it and you say are there obvious human health effects that aren't related to point-of-contact exposure, I'd say the evidence is very weak for that.

DR. XU: Because there's no such monitoring program. That's why we need to do that.

DR. OSIMITZ: Well, monitoring and what's --

DR. XU: There's -- I mean --

DR. OSIMITZ: When you say monitoring what do you mean by that?

DR. XU: To have the level of the exposure established and it has -- do epidemiologic study with health effect. In fact, your conclusions says lack of significant human health effect is because we don't have that data.

DR. OSIMITZ: Well, yeah, I think we're going to

go in circles on this. But as -- I agree with that, but it's a difficult thing to tease out. In fact, one of the difficult things with regard to the respiratory studies, of course, is teasing out the ADBAC, DDAC from surfactants and certainly the volatile things such as fragrances. So that's even difficult enough to sort of out. I think what you're saying would be a wonderful thing to have. I don't know how we ever get that.

DR. XU: So what I mean is this -- that conclusion is not evidence based.

DR. OSIMITZ: It is --

DR. XU: There's no data.

DR. OSIMITZ: Well, it's -- there's an apparent lack of significant health effects. But again, you can't prove there's no significant heath effects. You're not going to be able to do that. But again, if you take a look at something like OPs, there's clearly data. It kind of hits you in the face that there's toxicity associated. There -- that is lacking with regard to these molecules.

DR. HRUBEC: Hi. This is Terry Hrubec. I think it's all a matter of time. So back in the -- well, when I was in vet school, OPs were touted as a safer alternative then to the insecticides that were used previously. And then the research came out, the data showed that, yes, they are not -- or no, they're not safe. Yes, they do

cause problems.

And you could even go back to in the 1940s and '50s with cigarette smoking, everybody even thought that those were beneficial. And then the data started to come out that they're not. And again, I don't -- I can't look into a crystal ball and tell the future, but are we at the point where we're identifying maybe some adverse health effects from the QAC exposure, and that with time, we'll have a different picture of it. We'll look back in history and say why did we ever think this?

DR. OSIMITZ: Good example that you gave, I think. Well, one reason is because if we had done studies like apical studies on cigarette smoke and organophosphorus compounds, we wouldn't be thinking that they were safer. So that's one thing that's different, because now we have apical studies that integrate all these endpoints, and you can see. Are you seeing changes in -- I mean, if you did an apical study on organophosphorus compounds, you'd see all kinds of things and you wouldn't be wondering and thinking they're safe. So that's one big difference. We have much more of a database on these molecules.

That's not to say we still won't find things out or develop new endpoints. I agree with that. But I think it's we've come an awfully long ways, certainly even since

the 1960s as far as screening. Not just screening, but actually doing definitive studies, looking at robust endpoints in whole animals and multi-generation. I think that's pretty valuable. We didn't have that before.

We can still make a mistake and can still miss something, but I think that is much less than it once was.

CHAIRPERSON SCHWARZMAN: Veena

DR. HRUBEC: This is Terry Hrubec again.

CHAIRPERSON SCHWARZMAN: Oh, sorry. You finish and then I have another comment.

DR. HRUBEC: Okay. If you look at the documentation for the regulatory studies that are given in a package to the regulatory bodies to make decisions on it, there often are a number of studies that were done following the regulatory guidelines that have different outcomes than those that are actually presented to the regulatory committees.

So you can go look through the literature and find these preliminary studies that were done through regulatory agencies. And they'll go and determine, is this one we should include? Is this one we should not? And some of the ones that they even include, showed different results than what's actually presented.

And so in a number of those studies, you see some of the effects that we're seeing, but they're not included

in the package that gets submitted for review.

DR. OSIMITZ: Well, I --

DR. HRUBEC: And there's a lot of documentation on those types of studies. In fact, California did one, I don't know, about 20 years ago. And there's a whole summary of studies that were conducted looking at ADBAC -- potential ADBAC toxicity and the possible regulation.

DR. OSIMITZ: Well, I can't speak specifically to ADBAC or DDAC in that regard, but I have seen studies that were rejected from regulatory agencies. A good example of all our studies, which are done at so high a dose level so you'd have toxicity in the parent, especially in reproductive studies.

If you're having significant toxicity - and that doesn't even just mean lethality - some of the studies that I've seen were viewed as invalid, so the agency didn't accept it. The registrant went out and repeated at a lower dose at great time and expense, and then they were accepted. So there are some examples like that. I don't know the specifics, but --

CHAIRPERSON SCHWARZMAN: Thank you. I think we need to move on.

DR. OSIMITZ: Okay. Sure.

CHAIRPERSON SCHWARZMAN: Thank you.

DR. OSIMITZ: Thank you.

CHAIRPERSON SCHWARZMAN: Veena, what was your comment?

PANEL MEMBER SINGLA: Yes. Thank you for your comments. I had a couple questions about the developmental toxicity studies, either for yourself or the previous commenter.

I wondered did the developmental toxicity studies assess for neural tube defects?

Keith, are you able to answer where that would show up?

DR. HOSTETLER: Yes. Speaking.

Those studies weren't designed to do end -- to do the endpoint or to actually sacrifice and look at the time point. There were certainly the development of studies that followed the guidelines looking at resorptions, fetal effects, no lost -- lost pups, the entire spectrum, but they weren't designed to look specifically for neural tube defects, but there weren't any reported.

You know, part of what neural tube defects do, there's a delay. Looking at one particular time point, if it is a stressed animal, you can actually delay the normal closing. So stressing a pregnant mouse, looking for neural tube closure at one particular time point, what you may be seeing is a delay in a process that's going to eventually close and not be a neural tube defect. So

that's one potential interpretation of that -- of that particular effect.

DR. OSIMITZ: But, Keith, also if there -- if that effect persisted, even though you weren't sacrificing at time, you would have seen that at sacrifice at --

DR. HOSTETLER: That's right. There were no reported neural tube defects at birth.

DR. OSIMITZ: Or cesarean, yeah.

PANEL MEMBER SINGLA: Thank you. And I had, sorry, just two more questions of -- no.

MS. HOOVER: Save it for after.

PANEL MEMBER SINGLA: Okay.

CHAIRPERSON SCHWARZMAN: We're scheduled to take a break. So let's pick this up after the break.

DR. OSIMITZ: Excellent.

CHAIRPERSON SCHWARZMAN: And I know who was going to request. Yeah, so we're going to resume -- do you want to take a 15-minute break.

MS. HOOVER: Yes.

CHAIRPERSON SCHWARZMAN: Okay. We will be taking a 15-minute break and we'll resume at 3:40.

Thank you.

(Off record: 3:23 p.m.)

(Thereupon a recess was taken.)

(On record: 3:38 p.m.)

CHAIRPERSON SCHWARZMAN: We are going to restart the meeting. And for the questions and comments that didn't make it out earlier, we'll do that after Sara does her brief presentation here.

So I want to introduce Sara Hoover, Chief of the Safer Alternatives Assessment and Biomonitoring Section in OEHHA. Sara is going to briefly outline for us the options for the Panel in our consideration of quaternary ammonium compounds as potential designated chemicals for Biomonitoring California, and then we'll have our discussion and there's more public comment opportunity also.

(Thereupon an overhead presentation was presented as follows.)

MS. HOOVER: Thank you, Meg.

I think I can be even briefer than five minutes, so we'll make up some of the time. I realized I thought it would be helpful just to remind everyone before we talk about options for the Panel what the criteria are. The way that the law was set up is to encourage exploration of emerging concerns and emerging chemicals.

So the criteria are exposure or potential exposure; known or suspected health effects; and, as we've been discussing, the need to assess the efficacy of public health actions to reduce exposure to a chemical; the

availability of a biomonitoring analytical method; the availability of adequate biospecimen samples; and the incremental analytical cost. The -- whatever you consider, it does not have to meet all of these criteria.

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MS. HOOVER: So the options for the Panel are pretty simple. You can recommend adding the class of quaternary ammonium compounds to the list of designated chemicals for Biomonitoring California. You can choose to defer, pending more information. You can recommend against adding the class to the list. And you could also propose other options.

I invited Taylor earlier, if she had a specific alternative proposal for narrowing the class. Shoba and I actually did research on this and we looked at possible ways to look at the class. But in the end, it seemed just -- most simple and easy to define to stick to quaternary ammonium compounds. So that's what we presented, but you can certainly entertain other options.

CHAIRPERSON SCHWARZMAN: Sara, can you remind us about the consequences of listing QACs as designated chemicals and biomonitoring?

MS. HOOVER: Sure. So really, in a way, you can think of the list of designated chemicals as a laboratory list. It's essentially the pool of chemicals from which

we can choose to biomonitor in future studies, and that's it. So there -- there are certainly items on the -- chemicals on the designated list that have not been biomonitored in California. So it's really creating the pool of chemicals that we might want to consider for future studies.

CHAIRPERSON SCHWARZMAN: Great. Thank you.

So we have 20 minutes for -- if needed, for public comment. At this point, I want to return -- let Veena finish her questioning line, and then we have something from Kathleen, and then I'll call for further public comment before our deliberation.

PANEL MEMBER SINGLA: Great. Thank you. My other question was the -- I saw toxicology studies mentioned. Did any of them test mixtures of the compounds or were they testing single chemicals?

DR. HOSTETLER: Hi. It's Keith Hostetler, TRS, Inc. The studies all reported were on single compounds. The question behind might they be acting synergistically has been addressed though by the regulatory authorities. Both ECHA and U.S. EPA have determined that compounds that act through a similar mechanism can be treated similarly.

In fact, the food use -- food uses, the tolerance exemptions for ADBAC and DDAC for food contact talk about a total quat of the 400 ppm, whether it's ADBAC or DDAC.

And that's in recognition of the fact that it's accepted that one plus one equals two, simply put, from a toxicity standpoint. They do not act synergistically. They act through a common mechanism. And therefore, combining the two isn't expected to have any, for example, synergistic effects.

Anything to add, Tom?

CHAIRPERSON SCHWARZMAN: Is that it, Veena?

PANEL MEMBER SINGLA: Yes.

CHAIRPERSON SCHWARZMAN: Thank you.

And Kathleen.

DR. ATTFIELD: My question was I was wondering if you -- one or both of you could expound a little bit on what the mode of action is for the uses in spermicides that was mentioned?

DR. HOSTETLER: I haven't looked through that. It's Keith Hostetler from TRS. I haven't -- I'm not familiar with that patent literature. A lot of things, when you look at patents, there's all kinds of unique effects and evaluations. It's certainly not unexpected that a general membrane disruptor would have an effect on germ cells. So that's from sort of a general perspective, but I'm not specifically familiar with that literature myself.

DR. OSIMITZ: And, Keith, how is it used on that?

Not systemically?

DR. HOSTETLER: No, I think it's local effects. I mean, the spermicide or the contraceptive effects vaginal -- or vaginal suppositories, those kind of things, I think are for local effects. Is that --

DR. HRUBEC: Terry Hrubec. In humans, I'm not sure if they've looked at any systemic effects. In pigs, you can see systemic changes in cytokines with a vaginal administration of the QAC product.

DR. HOSTETLER: And just to comment on that. Cytokines, in general, inflammatory markers are not unexpected in response to irritation membrane disruption.

CHAIRPERSON SCHWARZMAN: Other public comment?

DR. DATTA: Hi. This is Sandipan Datta from UC Davis.

So the question I'm kind of following up on Dr. Singla's question is, you know, a single compound or a multiple compound. So the ADBACs, by their own nature, are not a single compound. They are a mixture of compounds. So, you know, when you're using the ADBACs, there can be variable mixture of like, you know, from C8, C12, C16, C14. There can be a variable mixture. So when the regular -- regulary -- regulatory studies are done, then like it -- are they then characterized -- do they characterize the mixture of what is the ratio between each

of them? And in each regulatory study they do, do they keep it consistent throughout the study or is there variability?

DR. HOSTETLER: Do I have it on now?

Keith Hostetler, TRS, responding. That's a good question. Every regulatory study has to be complete verification of the composition of what's applied. And there is a difference, depending on -- the way these are manufactured are actually the alkyl chains come from plant-derived sources. So these are actually vegetable oils that are then reacted with -- with the chemical nucleus to create this. So depending on which source you use, you're going to have different C12, C14, C16, C18.

So actually, a tip of the cap to U.S. EPA when they first were dealing with the registration of these. In the early 1990s, they recognized that if they were to try to register every single potential different quaternary ammonium compound on its own and have testing, that it would be impossible.

But what they were able to do is looking at the consistency of effects, independent of what the distribution is. And it really doesn't change a lot, but they do have different clusters. So an ADBAC cluster will have to be within certain bounds, and certain ranges, and have to be -- and are known to behave similarly. And they

do occasionally read across from one cluster to another for particular endpoints, because they're known to behave through a similar mechanism that is membrane disruption. So because it's not a receptor -- a receptor-mediated effect for the point-of-contact, irritancy, and in the AOP that the Dr. Osimitz mentioned, specific chain length doesn't have significant differences when they're tested.

DR. DATTA: Sandipan Datta from UC Davis.

Has there been any study from -- for absorption of the quaternary ammonium compounds when they're exposed to mucosal membrane like, you know, buccal membrane during your oral rinse mouth wash, the vagina mucosal membrane when you're applying for the spermicide, or any kind of other like, you know, mucosal membrane that they're exposed to on a repeated periodic basis?

DR. HOSTETLER: Keith Hostetler, TRS. I would say from the antimicrobial pesticide registration standpoint, since those aren't required studies, they aren't part of the datasets owned by the manufacturers. Companies that are in that may have developed that proprietarily, but I'm not aware of published literature. Although, we haven't looked for it. My guess would be there may be some literature out there on that, but absorption across different mucosa can be important. And my guess would be for as many years as these have been

out, there may be some literature out there, but I'm not familiar with it.

CHAIRPERSON SCHWARZMAN: Sara, do we have any online comments?

MS. HOOVER: Yes, we do. Thank you for asking.

This came in from Emily Bryson, who's a Senior Environmental Scientist in the Worker Heath and Safety Branch of the Department of Pesticide Regulation.

And she says, "In response to some of the questions that have been raised about how and where QACs are used, I highly encourage anyone interested to query quaternary ammonia in the California Department of Pesticide Regulation's CalPIQ database. Though this database only provides information on acute injuries associated with quaternary ammonia exposure, and it will certainly not provide a comprehensive overview of usage, it should provide some insight into how broadly these products are used and the various industries and organizations that use them".

And I will just tack on my own little comment just to remind people that we did do an extensive survey of uses in the previous preliminary screening document. And I wanted to add one more small clarification of time, which is we'll still plan to finish up this entire item by 4:30, but then we'll leave time for open public comment,

so we may go ten minutes over, depending on how this discussion goes.

CHAIRPERSON SCHWARZMAN: Thank you.

Comment there.

MS. BRADLEY: Hi again. It's Taylor Bradley from the American Cleaning Institute. And I don't know if I explained earlier, we represent the cleaning products industry, where a lot of these products are used.

So I just have a few comments that I'd like to say for the Panel, maybe some things to consider. One is maybe -- you know, we had a lot of presentations today. And I think there was a lot of information given for biocidal QACs, but there's another side for laundry, anti-static agents, and softening agents that we kind of didn't explore today. So my first suggestion would be to kind of narrow the scope down for biocidal QACs that we've gotten a lot of information on today.

The next would be to maybe collect more information on the non-biocidal QACs, so maybe defer your decision. And let's see if we can gather a little bit more information on what's happening on the laundry side of things.

And then also, there was -- early in OEHHA's presentation, the first presentation they gave, they mentioned analytical methods. And I think we're kind of

limited here, in that there are very few analytical methods for these QACs. And so there was two that was given in their document. And maybe that another suggestion would be to kind of narrow the scope down for the QACs that we do have analytical methods on, because as they said, we would have to develop some for monitoring the whole class. It's pretty broad. And I think if we can kind of focus it, it might be more feasible.

CHAIRPERSON SCHWARZMAN: Can I follow up with a question about that. Can you say more about the chemical compounds that fall in one category or another, if you're talking about narrowing the scope and creating a class of biocidal QACs versus those that are used in other applications.

MS. BRADLEY: Yeah, sure. So the ones that were mentioned today, BACs obviously, ADBACs -- I don't -- DADMACs, and I think the anti-static agents and the softening ones are going to be your esterquats, your polyquats, those. I believe that those ones would be the ones that are used in laundry. And we had a lot of focus today on the biocidal ones. And I think there's an opportunity for us to collect a little bit more information on the other side before we, you know, make a decision.

Thank you.

CHAIRPERSON SCHWARZMAN: Other -- is there anything else online?

MS. HOOVER: No.

CHAIRPERSON SCHWARZMAN: Okay. Shoba is going to add to that. I know there's some on this early on in the designating -- in the document.

DR. IYER: Yeah. Yeah. So Shoba Iyer, OEHHA. I'll just add a little more information to what Taylor provided. So, last July, when we did the preliminary screening, in that document, in that presentation, I included various QACs and spent some more time on the longer chain ones used in fabric softeners and dryer sheets. So, yeah, my understanding is that it's esterquats used in those products. There are also longer chain QACs that are ATMACs and possibly some DADMACs used in hair conditioners or anti-frizz products, these kinds of softening -- for those kinds of softening properties.

So some of those do also fall in the three main subclasses that I shared with you, the BACs, DADMACs, or ATMACs. I think more -- not so much the BACs, but the other two subclasses.

CHAIRPERSON SCHWARZMAN: Thank you, Shoba. That's what I was wanting to get at is, is there a very clear delineation or is there some cross-over, and it sounds like you're saying there's cross-over.

DR. IYER: From my research, I think there is cross-over. I couldn't see clear lines.

CHAIRPERSON SCHWARZMAN: Thank you.

DR. COOPER DOHERTY: And this is Anne Cooper Doherty from DTSC. And just to add to that, what Shoba said about the longer chain ATMACs with the alkyl trimethyls, at least from environmental monitoring that we did, in New York at least and sediment cores, you can see really sharp increases in the last 10, 15, 20 years in those chemicals in the environment.

CHAIRPERSON SCHWARZMAN: Any other public comments?

Anything we need to tend to online?

MS. HOOVER: (Shakes head.)

CHAIRPERSON SCHWARZMAN: Okay. In that case, we are going to move on to the Panel deliberation. And Sara has outlined our options. And we've seen a couples times today the non-inclusive criteria for designating a chemical as a designated chemical in the Biomonitoring Program. So I just want to invite panelists now to start and contribute to the discussion on the possibility of any of these actions that are before us today.

Tom.

PANEL MEMBER McKONE: I guess I'm going to speak -- I'll get to the point. I'm going to speak in

favor of the first option. And the reason -- so I've before on the Panel -- actually, I've been on this panel since the beginning, so I've seen a number of these deliberations. And this reminds me a bit of cyclic siloxanes, which I don't know how many years ago we did those. And -- but in the sense of consistency, we've tended to have a process of, you know, giving priority to things that we see a rising production in the marketplace and I mean large numbers.

We see some small evidence of possible human harm, but insufficient human data, some animal data in that case, a little bit more in this case. And so in that -- and for the cyclic siloxanes, in spite of a strong push from some not to go forward, in the end, it really came down to the fact that here's an opportunity to look at something where there's an exponential rise in the production, and, of course, correspondingly the level of exposure, where we could not wait until after the fact and look backwards and say why didn't we look at it, that we could get on that curve and start looking.

And again, we're not declaring these substances - we're not giving them a label - as toxic. We're saying that they meet our criteria, which is -- you know, is there a large potential for exposure, where the numbers are really big. You know, these are large production

chemicals. The uses tend to be quite intimate. I mean, even more so than the cyclic siloxanes, which were in electronics and consumer products.

But these are things that actually cross that threshold. They're used in the indoor environment, you occupational environment, indoor environment, or some personal care products. So the opportunity for exposure is very large. And I think the real thing that I think is a real mistake to interpret a lack of data as a lack of evidence for human harm. I mean, you can't say, well, I don't have any evidence, because I didn't collect any evidence, therefore I don't know of any harm.

And I think we won't -- you know, it's a cycle where you get caught up and say, well, there's no harm, so we're not going to learn anything about it until we see overwhelming evidence of harm, or something else.

Human -- you know, the gold standard in any agency that's looking at health effects, you always want to start with human -- what you know about humans, because we know animals aren't humans. There's many differences. For example, IARC the International Agency for Research on Cancer always gives priority and is looking for human studies, anything in humans.

And I think here, it would be the same thing. We really don't want to take a subset -- a set of compounds

that is very large, existing uses, has probably some maybe sufficient human data, but no -- or animal data, but no human data. I think we have to move this forward. And the way you do that is get data, right? This is science and we want to get that data.

So anyway, I would favor probably at least recommending that we put these compounds on a list -- a list of designated compounds and perhaps with some designation of priority.

CHAIRPERSON SCHWARZMAN: Thank you.

Other panelists?

Ulrike.

PANEL MEMBER LUDERER: Yeah. I wanted to agree with what Tom said, and also just really emphasize that there's clear potential for human exposure. And we also heard evidence today that for absorption and metabolism of these compounds and some human biomonitoring data that were presented. And we also -- I think there's quite strong support, as we also heard about today, that these chemicals are human asthmagens. So they are associated with that human disease, whether it's by -- you know, there seem to be two mechanisms, irritant and, you know, less common sensitization, but that's also been documented.

And then there are -- at least in the publicly

peer-reviewed literature, there are studies suggesting that there may be developmental or reproductive effects and effects on cholesterol biosynthesis. And so I think we meet a number of the criteria for listing these chemicals, as designated. I would support that.

CHAIRPERSON SCHWARZMAN: Carl.

PANEL MEMBER CRANOR: I concur with the two previous comments. It seems to me that the -- we have -- we've had a presentation today about concerns regarding the exposure of mammals to these substances. And that's not nothing. And with any steps we take are merely preliminary. And then it's up to other State agencies to decide whether there are risks or harm sufficient to act under the State law. But this just puts them on the list. And it seems to me that's a desirable thing to do.

CHAIRPERSON SCHWARZMAN: Thank you.

Great. Oliver.

PANEL MEMBER FIEHN: So I find these quaternary ammonium compounds to be the most impressive list of chemicals that we should put on the list of many other chemicals we have discussed. It's very clear that they have biological activity. That's what they're made for. It's very clear that there are numerous exposure routes. It's very clear that there is 5,000 products. And, you know, therefore a clear risk for all sorts of exposures.

The -- including inhalation, obviously.

In fact, I was concerned after our initial, you know, discussions we had. So we met with Gino Cortopassi's group and developed an assay just to look at, for example, the incorporation into membrane lipids and into mitochondrial membrane lipids. And we indeed, together with Sandipan, we found those incorporations. They go through different membranes into the mitochondrial membrane, where they can act on mitochondrial respiration.

You know, so in terms of analytical chemistry, these are clearly compounds that are relatively easy to be analyzed and to -- we developed assays, so there's absolutely no reason why it shouldn't be done.

In fact, as part of our studies, in the future, we will make validated studies, put them into the clinical use or -- clinical and pre-clinical use in our service laboratory at UC Davis, so that people can order the assay, you know, at cost, because we are concerned, and I am concerned, and that's why I will do it.

CHAIRPERSON SCHWARZMAN: One of the things that, just to jump in on my own, is, that I'm sort of intrigued by with this class of compounds, is exactly this -- sort of just to echo some of the other things that I'm hearing, is the mix of what we know and what we don't know, that I find it a very compelling reason to add them to the list

of designated chemicals.

As Tom said, that's often the space that this Panel tries to inhabit is -- is creating the opportunity for OEHHA to move into a space that needs action. That's sort of an emerging need. And I see that very much in this case with some suggestions of health impacts, some established health impacts and known widespread use in these dispersive uses, and yet, this -- this big absence of data on exposure.

And when I -- you know, when we think today over the presentations and some of the early evidence of possible health effects are neurodevelopmental health effects in both -- after -- following exposure to both men and women, or male and female animals anyway, and then we think about who is working in janitorial services, and who is in schools, the idea that we might be using compounds in a very widespread way, that is -- could be contributing to multi-generational neural development effects is something that I want to know more about.

So I don't want to make assumptions about it, but there's a bunch of dots that I think are bare, seeing whether they are connected. And, to me, that's the role of designating a chemical is it enables the State, if they are able, to collect data that would then inform other decision making about this.

One other thing I want to raise, just in my role as Chair, is I've heard from two panelists a suggestion that they might even want to prioritize these compounds. And what that enables -- I mean, what that entails would be an ask to the Program to prepare materials that would start a deliberative process to prioritize QACs as a class.

First, we would vote as a Panel to designate them, if that's the inclination, which is today's task. And -- but I wanted to raise that, because I'm hearing it, and find out whether we should add that to our list or deal with it after we answer the designation question.

MS. HOOVER: Yeah, I would suggest you complete this --

CHAIRPERSON SCHWARZMAN: One at a time.

MS. HOOVER: -- do your vote, and then check in about whether you want to take the next step.

CHAIRPERSON SCHWARZMAN: Great.

MS. HOOVER: -- and then you can advise us on that.

CHAIRPERSON SCHWARZMAN: Okay. Thank you. I want to make sure that we've given the panelists on the phone a chance to comment at this stage.

CHAIRPERSON SCHWARZMAN: Is that Eunha?

PANEL MEMBER HOH: Yes.

CHAIRPERSON SCHWARZMAN: Okay. Please go ahead.

PANEL MEMBER HOH: Okay. So I pretty much agree with that -- the first option listing the QAC in the list of the biomonitoring. We have -- I think I'm pretty much compelled by the scientific evidence today that were presented. And then the amount of the quat used currently, and more and more, I think it's -- it's a very right time to include it for biomonitoring. Yes.

CHAIRPERSON SCHWARZMAN: Thank you for that. Jenny, do you want to chime in?

PANEL MEMBER QUINTANA: I have nothing much to add to the excellent comments from my colleagues. But I do want to say I find the occupational exposures and the potential for very high exposures in the occupational setting by multiple routes of exposure very compelling as well.

CHAIRPERSON SCHWARZMAN: I don't want to prematurely cut off conversation and hear other comments from panelists, if need be, but I also want to invite a motion, because I'm getting a sense of a critical mass. Would anyone like to make a motion?

Tom.

PANEL MEMBER McKONE: Tom McKone.

So just a questions before I make it. We're not going to add anything about prioritization in the motion

at this point?

CHAIRPERSON SCHWARZMAN: I heard from Sara that that would be a second step, if we wish to.

PANEL MEMBER McKONE: That would be a second step. Okay. So I would like to move that we recommend adding quaternary ammonium compounds, QACs, as a class to the list of designated chemicals under the Biomonitoring Program.

CHAIRPERSON SCHWARZMAN: Do we have a second?

PANEL MEMBER CRANOR: I second it.

CHAIRPERSON SCHWARZMAN: Okay. We'll just hear from each of the Panel members about a vote in favor or against. So let's just go down the line.

PANEL MEMBER CRANOR: What was the question?

CHAIRPERSON SCHWARZMAN: To vote in favor or against the motion that Tom has made.

PANEL MEMBER CRANOR: Second. In favor.

PANEL MEMBER McKONE: I vote aye or in favor.

PANEL MEMBER SINGLA: In favor.

CHAIRPERSON SCHWARZMAN: I vote in favor.

PANEL MEMBER LUDERER: In favor.

PANEL MEMBER FIEHN: In favor.

PANEL MEMBER SUÁREZ: In favor.

CHAIRPERSON SCHWARZMAN: And for our two panelists on the telephone?

PANEL MEMBER QUINTANA: Jenny Quintana in favor.

PANEL MEMBER HOH: Eunha Hoh in favor.

CHAIRPERSON SCHWARZMAN: So the Panel unanimously votes in favor of adding quaternary ammonium compounds as a class to the list of designated chemicals. And that's our recommendation to the Program.

So to bring up the second issue, I guess I would want to know from the Panel whether there is interest in making a request that the Program start the process of preparing materials to allow us to recommend prioritizing QACs as a class. And do you need to hear anything more about that? Would you like to hear from Sara a little bit abut what that means, what that entails? Maybe it would helpful. Because it's been a while since we've designated new chemicals, maybe it would be helpful to hear that.

MS. HOOVER: Sure. It's a second list, the list of priority chemicals. And again, that is just under the purview of the SGP. They're different criteria for the list of priority chemicals. And you can choose to ask OEHHA could you please prepare a document on QACs as a class as potential priority chemicals and schedule that on a future SGP meeting agenda.

PANEL MEMBER McKONE: Comment. So I think rather than, you know, just voting immediately to put it on the priority list, I mean, it makes sense to request that

OEHHA prepare the document, so then we could vote at the next meeting. I mean, to me, that would --

CHAIRPERSON SCHWARZMAN: That would be the process.

MS. HOOVER: Yeah, we've got to clarify. You cannot vote on that today. So it's not a formal recommendation.

PANEL MEMBER McKONE: Oh, sorry.

HS. HOOVER: You just have to ask us to bring that to you.

PANEL MEMBER McKONE: Oh, okay. Well, it's not a motion.

MS. HOOVER: You have to --

CHAIRPERSON SCHWARZMAN: It's really to the Panel.

MS. HOOVER: There's no motion.

PANEL MEMBER McKONE: All right.

MS. HOOVER: It's just informal input, where the Chair would then summarize and say OEHHA could you please do this.

CHAIRPERSON SCHWARZMAN: Okay. So thank you for clarifying. My question to the Panel is --

PANEL MEMBER McKONE: I'll speak in favor of making -- you know, asking OEHHA to prepare --

CHAIRPERSON SCHWARZMAN: So I've heard some

interest in asking OEHHA to take on the process of posing the issue to us, whether we think it's -- and starting the process of considering these as priority chemicals under the Program.

Are there other -- are there other panelists who want to weigh in on that, either in favor of or not seeing the value of it?

PANEL MEMBER SUÁREZ: Yeah, This is José Suárez. Yes, I would be very much in favor of obtaining more information specifically about the state of the science in that regard. We have heard some very compelling presentations from Dr. Xu and Hrubec. We have heard as well some of the studies presented by Drs. Hostetler and Osimitz.

And I think it would be very good to get a little bit -- a very -- in the document that you provide for us what's the latest information on the state of the science in this regard with regards to the health effects.

MS. HOOVER: So just to clarify, what I will do is I will send the Panel links to past examples of the priority chemical documents which are very brief documents. But if you have a specific request like could you follow up on X, we could prepare, you know, some additional materials to cover a particular question. I mean, what we just did was a pretty in-depth review of

known or suspected health effects. So if you have a specific piece that you want us to follow up on further, we can certainly, you know, do an updated literature review and add that in.

PANEL MEMBER SUÁREZ: Yeah. Okay. So I'll follow up specifically with what I am thinking in that regard, yes. Thank you.

CHAIRPERSON SCHWARZMAN: Any other thoughts?

Carl.

PANEL MEMBER CRANOR: Let me add just one point. I didn't know about these substances before I came today. But two or three weeks ago, my wife was cleaning something in a closed space, and she had a bad breathing reaction to it. So I'm going to go home and check those --

(Laughter.)

PANEL MEMBER CRANOR: -- because I'm a little concerned about them now. And a person without asthmatic condition or anything like that, it was, in that closed space where she had to clean up something, that was worrisome.

CHAIRPERSON SCHWARZMAN: Oliver.

PANEL MEMBER FIEHN: Yeah. I would like to second the motion to ask OEHHA to give us documents that would allow us to put a vote and to prioritize these types of chemicals maybe including analytical methods. So, of

course, when we want to, you know, prioritize chemicals, are there any that are -- that don't have analytical methods, for example, or also, you know, a little bit about, you know, production values. I mean, I haven't -- are there -- among those, there are six, eight, ten or so chemical classes that -- within the QACs, right? So there might be very different values in terms of productions, and therefore, you know, maybe some of them are higher priorities than others. Very simple.

MS. HOOVER: So just to remind you that we covered that in the preliminary screening document in July. Now, we use -- we did use example QACs, so if there's particular ones you're interested in. Also, this document does talk about what we know about the analytical methods. But given your expertise, because there's not much known, and it also was covered before - there's not much known - if you and, you know, with Libin's work, we can certainly update that.

But if you have -- you know, Oliver, if you have specific input to that, again, we welcome any input on that that we can incorporate.

CHAIRPERSON SCHWARZMAN: So just to reiterate, this is not a formal motion or a vote, but that there's interest in the Panel on -- in having OEHHA bring material to us about the process, and the consequences, and the

content around potentially designating QACs as priority compounds in the -- under Biomonitoring.

Yes, if Jenny or Eunha have any comments on that, it would be great to hear them.

Sounds like there's no further comments from the Panel. So I want to take one last look at the Panel members and make sure I'm not leaving anything unsaid. And if that's the case, then we would move on to our final open public comment period.

We have ten minutes for public comment on any topic related to Biomonitoring California. And that's available to people in the room and also to people online by emailing comments to the email address, which is biomonitoring@oehha.ca.gov.

MS. BRADLEY: Hi. It's Taylor Bradley again from American Cleaning Institute. I just have a clarification question. When you say priority, do you mean it will be a priority in the pool of chemicals that you can pick to biomonitor or what does priority actually mean?

PANEL MEMBER FIEHN: Actually develop an assay and...

MS. HOOVER: Excellent question. Basically, what priority means is that the Scientific Guidance Panel is advising the Program that they think these are priorities for biomonitoring in California.

So I mentioned that the designated chemicals is the pool from which we can choose. The list of priority chemicals are chemicals that the SGP has flagged as we want you to pursue these for measurement. That's essentially the distinction between the two.

Ultimately, it's still a question -- you know, what actually gets biomonitored is a question of the Program retains that final decision, in part because of resource considerations and so forth. Yeah. So it's advice from the Panel to the Program.

MS. BRADLEY: Sure. Thank you for that clarification. So next question is will there be like a public release of the specific QACs that will be biomonitored, since the class is so broad? Will you -- yeah. Will you guys develop something that you can publicly release?

MS. HOOVER: We always -- everything we do is public. So our entire ethic is full transparency to the public. So the answer is if, at some future date, we choose particular QACs to biomonitor, that will become public definitely. This is all theoretical at this point.

MS. BRADLEY: Thank you very much.

CHAIRPERSON SCHWARZMAN: Any other public comments?

Nothing on the email, is that right?

MS. HOOVER: Um-hmm.

CHAIRPERSON SCHWARZMAN: Okay. In that case, I want to wrap-up the meeting and we can adjourn. A transcript of the meeting will be posted on the Biomonitoring California website when it's available. Our next SGP meeting will be on July 14th. And that's going to be in Oakland. I want to thank the Panel and the audience, our guest presenters, and our commenters for contributing to today's meeting. And I now adjourn the meeting.

(Thereupon the California Environmental Contaminant Biomonitoring Program, Scientific Guidance Panel meeting adjourned at 4:19 p.m.)

C E R T I F I C A T E O F R E P O R T E R

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

That I am a disinterested person herein; that the foregoing California Environmental Contamination Biomonitoring Program Scientific Guidance Panel meeting was reported in shorthand by me, James F. Peters, a Certified Shorthand Reporter of the State of California, and thereafter transcribed under my direction, by computer-assisted transcription.

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

IN WITNESS WHEREOF, I have hereunto set my hand this 21st day of March, 2020.

JAMES F. PETERS, CSR
Certified Shorthand Reporter
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