CALIFORNIA ENVIRONMENTAL CONTAMINANT BIOMONITORING PROGRAM

(BIOMONITORING CALIFORNIA)

SCIENTIFIC GUIDANCE PANEL MEETING

CONVENED VIA WEBINAR BY: OFFICE OF ENVIRONMENTAL HEALTH

HAZARD ASSESSMENT

CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY

STATE OF CALIFORNIA

TUESDAY, JULY 14, 2020

10:00 A.M.

JAMES F. PETERS, CSR
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Ulrike Luderer, MD, PhD

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James McCord, PhD, Center for Environmental Measurement and Modeling, United State Environmental Protection Agency

Rachel Morello-Frosch, PhD, University of California, Berkeley

Jon Sobus, PhD, Center for Computational Toxicology and Exposure, United State Environmental Protection Agency

Doug Walker, PhD, Department of Environmental Medicine and Public Health, Icahn School of Medicine at Mount Sinai

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1 P R O C E E D I N G S
2 MS. ZALAY: Good morning, everyone. This is
3 Marley Zalay. It's 9:55, so I'd like to run through some
4 logistics before we get started.
5 I would like to welcome you to Biomonitoring
6 California's first virtual meeting of the Scientific
7 Guidance Panel. Today's meeting is being held through the
8 GoToWebinar platform only and is being recorded and
9 transcribed.
10 All attendees are automatically muted when
11 joining the meeting and there will be several options for
12 providing comment during the meeting, which our Chair Meg
13 Schwarzman will be explaining a bit later. If you will be
14 speaking during the meeting, please use a headset, if
15 possible, and remember to speak directly into your
16 microphone and introduce yourself before speaking. This
17 is for the benefit of the transcriber and everyone else on
18 our webinar.
19 Meeting materials are available to download from
20 our website www.biomonitoring.ca.gov on the July SGP
21 meeting page. If you have technical difficulties during
22 this webinar, please send an email to
23 biomonitoring@oehha.ca.gov and we will have someone from
24 our IT department assist you.
25 We will have a break at 12:30 p.m. for one hour

1 for lunch. And we will begin the meeting promptly at
2 10:00 a.m., so until then we'll just have a few -- a few
3 minutes of everyone getting set up.
4 DIRECTOR ZEISE: So shall we start, Sara?
5 MS. HOOVER: Lauren, what we want to do is start
6 promptly at 10:00, so Marley was dong the gathering at
7 9:55.
8 DIRECTOR ZEISE: Okay. I was just checking.
9 Okay.
10 MS. HOOVER: Thank you for checking. And she
11 will introduce you at about one minute to 10:00.
12 DIRECTOR ZEISE: Okay. Very good.
13 MS. HOOVER: Actually, while we have one minute
14 to go, I will remind that everyone who's joining, if
15 you're a speaker, you don't have to show your webcam until
16 you're actually speaking. So the panelists will always be
17 showing. Thank you.
18 The panelists will always be showing their
19 webcam, unless they pause. And you can feel free to pause
20 at any time, panelists, and Lauren. And then your name
21 will just appear in the box.
22 DIRECTOR ZEISE: Okay.
23 MS. HOOVER. Everyone else will share their cam
24 when they're actually speaking.
25 MS. ZALAY: Okay. As we approach 10:00 a.m., I

1 would like to introduce Lauren Zeise, at this time, the
2 Director of the Office of Environmental Health Hazard
3 Assessment.
4 DIRECTOR ZEISE: Okay. Thanks, Marley. Good
5 morning, everybody. I'd like to welcome the Panel and the
6 audience to this virtual meeting of the Scientific
7 Guidance Panel for the California Environmental
8 Contaminant Biomonitoring Program, also known as
9 Biomonitoring California. So thank you all for
10 participating and sharing your expertise.
11 The Panel last met on March 4th, 2020. Just to
12 briefly recap that meeting. After the Program update, the
13 Panel discussed the California Regional Exposure Study, or
14 the CARE study. Unfortunately, due to the COVID-19
15 emergency, the CARE Study has been suspended.
16 The remainder of the meeting focused on the SGP's
17 consideration of the class of quaternary ammonium
18 compounds, or QACs, as potential designated chemicals.
19 The Panel deliberations were informed by presentations
20 from two distinguished guest speakers, a guess discussant,
21 and public commenters. The Panel voted unanimously to
22 recommend that QACs be added to the list of designated
23 chemicals for Biomonitoring California, which means that
24 any QAC could be included in a future Program study.
25 In making this recommendation, the Panel members

1 highlighted the rapidly increasing production and use of
2 QACs, significant data gaps in QAC exposure information,
3 high exposure potential for the public and occupational
4 groups, such as custodians and hospital staff, known human
5 health effects including asthma associated with QAC
6 exposure.
7 So a summary of the input from the March meeting,
8 along with a complete transcript, is posted on the March
9 SGP meeting page on biomonitoring.ca.gov.
10 So since we're meeting virtually today, I'd like
11 to have the SGP members introduce themselves. So starting
12 with our Chair, Meg, you want to introduce yourself and
13 give your affiliation.
14 CHAIRPERSON SCHWARZMAN: I'm Meg Schwarzman from
15 UC Berkeley.
16 DIRECTOR ZEISE: Okay.
17 PANEL MEMBER McKONE: I'm Tom McKone. I'm just
18 going across the picture.
19 DIRECTOR ZEISE: Yeah, that's great. Why don't
20 we just go across the top.
21 PANEL MEMBER McKONE: Kind of like we would at a
22 podium.
23 DIRECTOR ZEISE: Yes.
24 PANE MEMBER McKONE: Tom McKone, retired from
25 Lawrence Berkeley National Laboratory. I'm still an

1 affiliate there and then also Professor of Emeritus at the
2 University of California Berkeley.
3 PANEL MEMBER LUDERER: I'm Ulrike Luderer. I'm
4 the Director of the Center for Occupational and
5 Environmental Health at the University of California,
6 Irvine.
7 PANEL MEMBER FIEHN: Oliver Fiehn.
8 PANEL MEMBER QUINTANA: I'm Jenny Quintana.
9 Sorry.
10 DIRECTOR ZEISE: Go ahead, Jenny.
11 PANEL MEMBER FIEHN: Oliver Fiehn, California --
12 University of California, Davis.
13 PANEL MEMBER QUINTANA: I'm Jenny Quintana,
14 Penelope is my real name, and I'm at the San Diego State
15 University School of Public Health.
16 DIRECTOR ZEISE: Great. So, Eunha, do you want
17 to...
18 PANEL MEMBER HOH: I'm Eunha Hoh, School of
19 Public Health, San Diego State University.
20 DIRECTOR ZEISE: Great. Veena.
21 PANEL MEMBER SINGLA: Good morning. Veena Singla
22 with the Natural Resources Defense Council in San
23 Francisco.
24 DIRECTOR ZEISE: Okay. Carl.
25 PANEL MEMBER CRANOR: Carl Cranor from University

1 of California, Riverside.
2 DIRECTOR ZEISE: Okay. So I think we got
3 everyone, is that right? I think on -- perhaps the orders
4 aren't the same on everyone's screens.
5 So anyway, welcome, Panel. And with that, I'll
6 turn the meeting over to our Chair Meg Schwarzman of UC
7 Berkeley, who will provide more details about today's
8 meeting.
9 Meg, on to you.
10 CHAIRPERSON SCHWARZMAN: Thanks, Lauren. And
11 welcome, everybody, to this new format. Missing seeing
12 you all in person, but it's nice to see your faces here.
13 And I'm just sorry we can't see the other attendees. I
14 want to start by announcing the goals for today's meeting
15 as we usually do. We'll first hear a Program and
16 laboratory update and have a chance to provide input and
17 ask questions about that. We'll review some of the latest
18 developments in non-targeted analysis, and we'll do that
19 through presentations by guest speakers. And then we'll
20 have an open discussion with the guest speakers and the
21 audience to consider next steps for the Department in the
22 area of non-targeted analysis.
23 So because we're in this new format, some notes
24 on how this meeting will work, which is different than we
25 usually do. During the question periods after each talk,

1 we're asking that the speakers who presented that talk
2 remain unmuted with their webcam showing so they can
3 respond to questions from the Panel and the audience.
4 For SGP members, for panelists, if you want to
5 speak or ask a question, please just raise your hand and I
6 will be watching the webcams and call on you. At the
7 appropriate time, you can unmute yourself after I call on
8 you and ask your question or provide your comment.
9 If webinar attendees have questions or comments
10 during the question periods after each talk, you can
11 submit them via the question feature of the web
12 platform -- the GoToWebinar platform or you can email them
13 to biomonitoring@oehha.ca.gov. And a reminder to please
14 keep your comments brief and focused to the items that are
15 being discussed at the time.
16 We'll read relevant comments allowed and
17 paraphrase them, if necessary. We can also receive oral
18 comments from webinar attendees during the public comment
19 periods in both the morning and the afternoon, if you'd
20 rather speak them yourself and during the discussion
21 session that's in the afternoon. So if you want to speak,
22 please use the raise-hand function. Since you don't have
23 your webcam on, we can't see you raise your hand. Use the
24 raise-hand function or the question feature in
25 GoToWebinar, and I'll call on you at the appropriate time.

1 So next I want to introduce Nerissa Wu who will
2 give our first -- who will give our Program update.
3 Nerissa Wu is Chief of the Exposure Assessment
4 Section in the Environmental Health Investigations Branch
5 in the California Department of Public Health. And she's
6 overall lead for Biomonitoring California.
7 Nerissa will be providing our Program update.
8 (Thereupon an overhead presentation was
9 presented as follows.)
10 DR. WU: Hi, everyone. This went so well in
11 practice. Give me a second to get my screen shared here.
12 Okay. Does everybody see my slides?
13 (Thumbs up.)
14 DR. WU: I, of course, can't hear anybody.
15 CHAIRPERSON SCHWARZMAN: Yes.
16 DR. WU: So welcome, everybody. I will be giving
17 the Program updates for today. I first want to start with
18 a kudos to the OEHHA crew for getting this all working.
19 It's amazing to be able to see you all. I'm going --
20 going to be going quite fast through our Program updates
21 and I apologize for that, but I have a lot of material to
22 cover in 16 minutes.
23 --o0o--
24 DR. WU: First, I want to talk about some staff
25 transitions. We have a number of them. First of all,

1 welcome to two new OEHHA staff, who are joining us to work
2 on the AB 617 projects. Both of them may be familiar to
3 many you. Julia Varshavsky who comes to us from the
4 Program on Reproductive Health and the Environment at
5 UCSF, and Susan Hurley who has worked at CDPH, Cancer
6 Prevention Institute, and UCSF. Both are joining us with
7 enormous amounts of expertise and experience, so we're
8 really excited to have the opportunity to work with them.
9 Also, this isn't strictly Biomonitoring
10 California, but EHIB has a new Branch Chief, Dr. Michael
11 Wilson, who sat on the Scientific Guidance Panel for many
12 years, also known as Mr. Meg. And so it's great to have
13 somebody who really knows and supports our Program.
14 Sadly, we also have a few goodbyes from our team.
15 Judy Balmin, who was our outreach coordinator has moved on
16 to the Safe Cosmetics Program and Robin Christensen, who
17 has been such a key part of this program, since she joined
18 in 2009, is moving on to be a Branch Chief of the
19 Substance Addiction and Prevention Branch at CDPH.
20 I also want to just take a minute to remember
21 Reber Brown, who passed away in May. Reber was a
22 long-time staff member at ECL. He did extensive work for
23 this Program, particularly in POPs analysis and he will be
24 missed.
25 And finally, another note on personnel, a lot of

1 our staff here at CDPH have been involved with
2 COVID-related activities. And while they're all working
3 really hard to try to cover biomonitoring work, as well as
4 COVID work, our availability as a crew to cover
5 biomonitoring work has been very much impacted, and that's
6 likely to continue for the foreseeable future.
7 --o0o--
8 DR. WU: So when we last met, we were just
9 gaining momentum with our sample collection in San Diego
10 and Orange counties. And we thought we'd be out in the
11 field until the end of May. And we were starting to pay
12 attention to COVID, of course, wondering if maybe we
13 should go to a urine-only protocol or if there are ways we
14 could change our protocol to limit face-to-face contact.
15 But by the middle March with the State going into
16 shelter-in-place, we knew we had to shut down our study.
17 So we took a very concentrated four days of
18 contacting all of our participants who had been enrolled
19 or had been invited to let them know that we were putting
20 the study on hold. At that point, we had invited 526
21 participants, including a batch of invitations that went
22 out right before shelter-in-place started.
23 About 64 percent of those invited responded,
24 meaning that they at least logged on and activated their
25 account. And we were able to complete sample collection

1 from 90 participants. But 245 people were in the process
2 somewhere and had to be told that we would not be
3 collecting their samples. We got a lot of feedback that
4 people were disappointed and asked to be put on a mailing
5 list. If we were ever able to get back out in the field
6 again, they would like to be part of the study.
7 --o0o--
8 DR. WU: For CARE-2, we had our results go out to
9 individual participants in February. So we're now focused
10 on summarizing statistics and conducting demographic
11 analyses. And we're hoping to have data posted on the web
12 in the next month, and hold a public meeting or webinar at
13 sometime in the near future.
14 So I'm going to show tables comparing the results
15 of CARE-2 to CARE-LA and talk about some of the
16 demographic associations that have been identified for
17 CARE-2.
18 But as we look at the tables, I just want to put
19 the reminder out there that we need to keep the issue of
20 generalizability in mind. This is surveillance. So the
21 goal of sampling is to obtain a participant pool that
22 resembles our overall population as closely as possible.
23 CARE is not based on probabilistic sampling as
24 NHANES is, but we put a lot of effort into matching our
25 region's population the best we can through things like

1 randomized postcard mailings and quota samplings, which
2 is -- which are designed to match census data,
3 --o0o--
4 DR. WU: And our sampling goals are based on race
5 and gender. And we do a pretty good job of meeting the
6 racial breakdown of each region.
7 --o0o--
8 DR. WU: Our participants do skew a little female
9 more so in L.A. than in Region 2. And we don't select
10 participants based on education and income. And you can
11 see our participants have skewed towards a more highly
12 educated group compared to the overall population. And
13 why does this matter?
14 Well, there are demographic trends for many of
15 our analytes, meaning that if levels are -- levels might
16 be higher or lower for a particular group. And, for
17 example, if we see that the levels of mercury are higher
18 in Asians than for other groups, which is seen in the
19 literature, if we under-enroll Asians, we might end up
20 with an underestimate for the mean mercury level for the
21 region.
22 There are lots of ways beyond demographics that
23 study participants might be different from people who do
24 -- who don't decide to enroll in a study and they often
25 can't be measured or quantified the way demographics can.

1 And this is actually true even if your study does use
2 probabilistic sampling, because if your participation rate
3 is low, probabilistic sampling starts to look a lot more
4 like convenience sampling.
5 So it's just a reminder of that participation
6 rate and how -- how closely you are mirroring your region
7 or your overall population is just something to keep in
8 mind as you compare and interpret results.
9 --o0o--
10 DR. WU: So on to the analytes. Here are blood
11 metal results. Detection frequencies were close to a
12 hundred percent for all of the blood metals. You see that
13 the geometric means are somewhat lower in CARE-2 than they
14 were in CARE-LA. We have seen some associations between
15 race and metals. This may be reflective of the overall
16 demographics of the region.
17 --o0o--
18 DR. WU: For urinary metals, and these are
19 creatinine corrected numbers, these are the urinary metals
20 that were detected in at least 65 percent of participants.
21 So antimony, manganese, and uranium are not on this table.
22 And as with blood metals, the urinary metals are a little
23 bit lower in CARE-2, notably arsenic and mercury. And as
24 in the previous slide, it may be reflective of the
25 region's demographics, specifically the lower proportion

1 of Asians in the region.

2 --o0o--

3 DR. WU: For all the findings I'm presenting,
4 these are results of multi-variable analyses adjusted for
5 other demographic parameters. And for today, I'm only
6 presenting arsenic, mercury, lead, and cadmium. We'll
7 come back another time to talk about the other metals.
8 And there are a few things we can say about demographics
9 and metals. Female participants have higher urinary
10 mercury and cadmium, as well as blood cadmium, but lower
11 levels of lead than male participants.

12 Levels of arsenic, lead, and cadmium increased
13 with participant age. And there were some race
14 associations with black participants having a higher blood
15 cadmium level than white and Hispanic participants, but
16 Asian participants having a higher urinary cadmium level
17 than white and Hispanic participants. We also saw that
18 urinary mercury levels were higher in participants who
19 chose to participate in Spanish as compared to English.
20 And that's something that we did not see in CARE-LA. So
21 we will continue to investigate it.

22 --o0o--

23 DR. WU: For PFASs, we measure 12 of the PFASs.
24 All but one participant had at least one PFAS in their
25 serum. And on average, each participant had seven PFASs

1 detected. Detection frequencies and geometric means were
2 generally lower in Region 2 than L.A., notably, Me-PFOSA's
3 44 percent lower and PFNA was 32 percent lower. The
4 racial breakdown that I just described earlier might
5 explain some of this, but there's also the
6 well-established temporal trend or the decline of PFAS
7 over time that might account for this. The two exceptions
8 PFHxS went up for CARE-2 and PFOS was -- P-F-O-S was also
9 higher.
10 --o0o--
11 DR. WU: As far as demographic trends, men were
12 higher than women for PFOS, PFOA, and PFHxS, which has
13 been seen in the literature. PFAS trends -- PFAS levels
14 increased with age, with an 8 to 20 percent increase per
15 decade. And there were the racial trends that have been
16 seen in literature in CARE-LL previ -- CARE-LA previously,
17 with Asians being generally higher, sometimes quite a bit
18 higher than White and Hispanic participants. And Hispanic
19 participants being generally lower than other race groups.
20 Although, the trends were somewhat less
21 pronounced in CARE-2, and this might be because of some of
22 the -- there were small cells for some of the racial
23 groups, so statistical significance is impacted.
24 --o0o--
25 DR. WU: We also looked at 1-nitropyrene, the

1 biomarker of diesel exposure. And we were able to analyze
2 160 samples for 1-NP, including only samples that were
3 collected in February and March to avoid the seasonality
4 issue that we saw in CARE-LA. So this table presents the
5 two 1-NP metabolites that Chris Simpson's lab reports to
6 us. 8-OHNP was similar for both regions, but 6-OHNP was
7 quite a bit higher in CARE-2.
8 --o0o--
9 DR. WU: Hispanic ethnicity was associated with
10 higher levels, 30 to 35 percent higher, of both
11 metabolites, but the differences were not statistically
12 significant. And again, we did have small cell sizes for
13 some -- for some race groups. And because there are only
14 160 samples, as opposed to the 359 of the whole CARE
15 Study, that was particularly a problem for these subset
16 groups.
17 Age was inversely associated with 8-OHNP. And
18 working with diesel equipment in the three days prior to
19 sample collection was also associated, but with 6-OHNP not
20 8-HO -- 8-OHNP. In CARE-LA, we found an association
21 between smoking and 1-NP metabolites, but this association
22 was not identified in the CARE-2 results.
23 --o0o--
24 DR. WU: And our last panel was phenols. And
25 this panel usually includes three parabens, bisphenol A,

1 and its analogs BPS and BPF, triclosan, triclocarban, and
2 benzophenone-3. For CARE-2, butylparaben and BPF were not
3 reported. So of the seven analytes that were measured,
4 only three hit the 65 percent threshold for calculation of
5 a geometric mean and demographic analyses. And I have not
6 included CARE-LA numbers here, because the CARE-LA subset
7 was -- it was 60 people, it was women only, and we
8 selected those samples equally across racial groups rather
9 than in accordance with the region's demographics.
10 Because there's so much association between race,
11 and gender, and phenols, it really wouldn't be a valid
12 comparison to take the CARE-LA subset and compare it to
13 the CARE-2 subset.
14 --o0o--
15 DR. WU: So levels of methylparaben and BP-3 were
16 significantly higher in female participants, three times
17 higher, than in men. The levels of BPA were also higher
18 in women but to a lesser extent. We did not find
19 significant differences by race and ethnicity for any of
20 the three analytes. And in literature, there has been
21 seen an association. But with 151 samples in the phenols
22 subset, we had some very small cells. And again, that is
23 something that really impacts our ability to identify a
24 significantly -- a statistically significant difference.
25 Age was associated with increased levels of

1 methylparaben and BPA. And in CARE-2, we asked questions
2 about product use in the six hours preceding sample
3 collection. And levels of methylparaben were 91 percent
4 higher among people who reported using lotion in the six
5 hours before sample collection.
6 Methylparaben levels were also associated if you
7 had used body wash in the six hours preceding sample
8 collection, but that association was not significant.
9 --o0o--
10 DR. WU: So in summary for each of these panels,
11 this was just our first pass through the CARE-2 data. As
12 we've outlined in these meeting before, we start off with
13 a look at each analytical panel and the demographic
14 parameters and then we start going into exposure data,
15 geography, residence, and other factors like seasonality.
16 So there will be more to report on each of these panels in
17 future meetings.
18 So what does the future of CARE look like? Well,
19 even before COVID, we had talked about taking a break from
20 field work for the coming year to give us a chance to
21 catch up on analyses and evaluate how CARE was going. At
22 this point, there's even more uncertainty about field work
23 and how we can conduct sample collection in a way that's
24 safe for participants and staff.
25 It's also really likely that our workforce and

1 budget will continue to be impacted for some time. So for
2 now, we are not planning field work in the next year
3 still. And we will take this opportunity to continue work
4 on analyzing our CARE data, as well as data that we've
5 accumulated from ACE, and FREES, and other studies. So I
6 want to take my remaining few minutes to highlight two
7 other biomonitoring activities.
8 --o0o--
9 DR. WU: First, the AB 617 projects, the
10 Community Air Protection Program is continuing to move
11 forward. You've heard about the two new staff who have
12 been brought on to work on this study. And OEHHA has
13 contracts in place to start designing studies and get one
14 of those studies launched in this year. Staff are working
15 on identifying relevant biomarkers to include. And like
16 the East Bay Diesel project, the 617 projects are going to
17 include complementary approaches, like air monitoring and
18 ultrafine particle analysis to help us interpret the
19 biomonitoring data.
20 --o0o--
21 DR. WU: We're also working with Dr. Libin Xu who
22 was here at our March meeting to present his work on QACs.
23 It was a very timely topic. With all the disinfectant use
24 these days, widespread exposure to QACs is really a
25 concern. So we are working with Dr. Xu towards a urinary

1 method to measure QACs exposure. We have urine samples
2 that we've collected through this intra-laboratory pilot
3 project, which is a protocol to collect a convenience
4 sample. We have samples and exposure information from
5 participants in 2018 and we have gone back to those same
6 participants and collected another set of samples and
7 exposure information during the shelter-in-place time
8 period. So we're hoping to use the samples and the
9 exposure information to hopefully get a urinary method
10 working that we'll be able to use in future studies.
11 --o0o--
12 DR. WU: Finally, one recent piece of news, leg
13 report number five, which covers biomonitoring activities
14 from 2016 to '17, it has been approved for distribution.
15 So it's currently on the EHIB website and it will be
16 posted to the Biomonitoring site shortly.
17 And just in closing, I do want to just thank all
18 of our staff. As always, they're very hard working.
19 Everyone is impacted by COVID and shelter-in-place in
20 different ways. And our staff, without missing a beat,
21 took their work home and have continued to move the
22 Program forward despite all the various challenges that we
23 face.
24 And with that, I will close up and take
25 questions.

1 CHAIRPERSON SCHWARZMAN: Thank you, Nerissa.
2 We have -- you actually moved really efficiently.
3 And we have a few minutes for clarifying questions from
4 the Panel. And there will be a discussion session after
5 our two subsequent lab updates. So questions for Nerissa.
6 And a reminder to panelists, just raised your hand and I
7 will call on you.
8 Oliver.
9 PANEL MEMBER FIEHN: Okay. How interesting.
10 Thank you for the -- for the report. It's very good to
11 see that there's a lot of progress made and, of, course
12 sad that some of the field work had to be stopped. I'm
13 also sad for the participants.
14 Now -- now, this -- this situation is going on
15 for many technical studies as well. And many people face
16 the same problem. So have you considered using other
17 types of sampling, for example, in-house sampling, where
18 you could send out, you know, devices from -- I don't want
19 to say dry blood spots, but there are other devices that
20 can also be sampled easily, at least for some contaminants
21 or concerns. Is that something you have discussed or
22 considered?
23 DR. WU: Yes. And, in fact, in the week
24 preceding our shutdown, we talked a lot about whether or
25 not we could use a urine kit, something we did for follow

1 up for participants in the BEST study where we mailed a
2 kit with instructions and participants could freeze it and
3 have it overnighted back to us.
4 We, of course, would miss a number of analytes.
5 We'd be able to do our phenols, and 1-NP, and urinary
6 metals. But PFASs is a huge interest to the State right
7 now and we would unfortunately not be able to look at
8 PFASs.
9 It's something that I think we need to hold open
10 as a possibility, not only in the time of COVID, but also
11 we are facing budgetary limits as we always have. And one
12 of the things that's really expensive for us is going out
13 in the field to remote locations. So it's something that
14 we do continue to explore. I think before we invested
15 fully in something like that, we would want to think a lot
16 about the validity and the instructions. It's very hard
17 to get -- for quality assurance purposes to leave the
18 sampling up to, you know, everybody out in the field to
19 follow. And we have found in a number of studies that we
20 have to keep the instructions very, very simple.
21 And, of course, validity of the sample would be
22 an issue if the instructions aren't followed. But for
23 sure, I take your point, it's something we have to
24 consider.
25 CHAIRPERSON SCHWARZMAN: Yeah, Carl.

1 PANEL MEMBER CRANOR: Nerissa, thank you for your
2 presentation. Would you say a little bit more about what
3 you're looking for vis-à-vis the air pollution. I think
4 that's terribly important. I'm just curious where it's
5 going.
6 DR. WU: This is actually a question for OEHHA.
7 They are leading the 617 study, so maybe Sara or Marley
8 could answer that question.
9 MS. HOOVER: Hello. This is Sara. Carl, I'm
10 sorry, could you repeat that? I was doing some
11 behind-the-scenes logistics when you asked.
12 PANEL MEMBER CRANOR: Just the question of I
13 think air pollution is terribly important. I just
14 wondered what you were -- what you were looking for or
15 where you think that was going.
16 MS. HOOVER: Oh, so that's a work in progress.
17 We did give -- we've given a few updates on AB 617 work
18 and all the research we're doing. So Susan and Julia,
19 which is great, fantastic addition to our team, they're
20 currently delving into all kinds of different options.
21 You know, in the past, we measured 1-NP. We're
22 probably looking for other options, more broadly looking
23 at PAHs. We're looking at diagnostic ratios of PAHs.
24 We're looking at biomarkers of effect. We're -- and as
25 Nerissa mentioned, and which is going to be really

1 critical, we're going to be doing complementary
2 measurements as well in order to help us, you know,
3 actually see if what we're seeing in biomonitoring is
4 linked -- linked to the air.
5 So we -- it's quite -- it's going to be quite a
6 complicated design and we're just embarking on that. We
7 just -- just got the contract approved with UC and we're
8 really in the research phase.
9 CHAIRPERSON SCHWARZMAN: Jenny, go ahead.
10 PANEL MEMBER QUINTANA: Hi. Jenny Quintana.
11 Just to follow up on that, if we wanted to give
12 input or look at that, we would then write to you
13 individually. Would that be the best way to do that?
14 Because I didn't see, for example, black carbon being
15 measured, which would be very critical for 1-nitropyrene.
16 MS. HOOVER: Whoopsie. Sorry. Little logistical
17 problem there. We do have -- we did measure black carbon
18 in East Bay Diesel. And certainly that's on the table.
19 So we're looking at that as well. Feel free to chime in
20 with suggestions now or, yes, you can always email me.
21 One-on-one is never a problem with the SGP, so always feel
22 free to email me or the Biomonitoring California email, if
23 you have input not during an SGP meeting.
24 CHAIRPERSON SCHWARZMAN: Any other questions for
25 Nerissa? And actually, I would invite a little bit more

1 of this conversation about the 617 study, if folks have
2 thoughts, during the short discussion period that follows
3 our next two updates.
4 Any other questions for Nerissa?
5 In that case, we can move on. And I just want to
6 thank Nerissa and really applaud the team for the way that
7 you have so quickly -- everything is moving and changing
8 so fast, and you've really sort of made the most out of
9 the opportunities that still remain, despite the kind of
10 new limitations under -- under the shelter-in-place and
11 COVID-19 situation. So thank you for that update and
12 maybe we'll have time for a little more discussion after
13 the next updates to come.
14 So thank you, Nerissa. And I want to introduce
15 our next speaker. Dr. Jianwen She is Chief of the
16 Biochemistry Section in the Environmental Health
17 Laboratory Branch at CDPH. And he's going to provide an
18 update on the lab activities.
19 (Thereupon an overhead presentation was
20 presented as follows.)
21 DR. SHE: Thank you, Meg for the introduction.
22 Good morning, SGP members and audience. Today I will
23 update SGP what the Environmental Health Laboratory has
24 done since March 2018.
25 --o0o--

1 DR. SHE: My talk today, I will focus on the
2 following activities: completed projects and ongoing
3 projects, publications, semi-targeted analysis, ongoing
4 method development.
5 --o0o--
6 DR. SHE: In 2018, we completed 180 samples from
7 analysis of metals in blood and in urine for Northern
8 California firefighter studies. We also completed 430
9 sample analysis for the metals in blood and urine and also
10 for 60 samples for environmental phenols for CARE-LA
11 studies.
12 --o0o--
13 DR. SHE: Between 2019 and 2020, we completed
14 three projects. We finished 66 samples for Camp Fire
15 firefighters for analysis of metal in blood and urine. We
16 also completed 1,000 samples to analyze cotinine in serum
17 for a study we called MACOTA study.
18 Last project we complete is CARE study Region 2.
19 We finished 359 samples for metals in blood and urine, and
20 also among the 359, we finished 151 samples for
21 environmental phenols in urine.
22 --o0o--
23 DR. SHE: In the middle of the year, we plan to
24 complete three projects. One is 66 samples for PAH
25 metabolite in urine for Camp Fire firefighter studies, 90

1 samples for both metals, phenols. Metals only in blood
2 and urine, but phenols in urine only for CARE-3 study to
3 complete this -- like a submission to stop the project.
4 And we also have a three-year grant to complete
5 1,800 samples for a study, short as, PRECATO. That means
6 each year we finish 600 samples for analysis of cotinine
7 in archived serum samples.
8 --o0o--
9 DR. SHE: At the same time, we published two
10 analytical methods, number one and number three;
11 collaborated with our -- with our collaborators, we
12 published two study findings that listed here as published
13 number two and number four.
14 --o0o--
15 DR. SHE: Now I'd like to talk about a little bit
16 of targeted, semi-targeted and non-targeted analysis.
17 For targeted and semi-targeted analysis, we
18 usually use different data acquisition and data flow
19 approach. So on the top of this slide, I put the targeted
20 and semi-targeted analysis together since they are more
21 similar. So because we have some pre-conception about
22 what we are looking for, we can select the precursor ions.
23 We have -- can compare to an inclusion list to make sure
24 some chemical we are not interested in, like drugs, are
25 not included. We call this approach data-dependent

1 analysis, DDMS or information-dependent because of
2 targeted or semi-targeted we know something.
3 For the full -- fully non-targeted analysis, we
4 use technology data independent or information independent
5 analysis. So we cannot pre-selection pre-cursor ions, but
6 we -- technically, we need to narrow down our search
7 space, so use a small mass-to-charge range. We still can
8 use the exclusion list to make sure we don't find
9 information people are not interested.
10 --o0o--
11 DR. SHE: The examples. I use a group of
12 carbazole chemicals to demonstrate the technique we are
13 using could be used for targeted, or non-targeted, or
14 semi-targeted. Although, I focus on the semi-targeted
15 analysis.
16 Carbazole is a group of chemicals often found in
17 the environmental samples at high levels. Think it would
18 be interested to know if they ever get to human body,
19 their analysis are good examples of targeted,
20 semi-targeted, and non-targeted analysis.
21 Basically, we try to find their fragmentation
22 profile that bear the relationship between the
23 fragmentation profile in our analytical machine to their
24 structure. So they applied to other three different
25 current analysis.

1 --o0o--

2 DR. SHE: In this slide is a spectrum of
3 3-chlorocarbazole. We run the EI-MS. The structured is
4 showed here. And also in accordance with Huckel's rule,
5 these chemicals, the structure we see, is aromatic
6 structure -- aromatic structure. If a compound is
7 aromatic, it means they're very stable. If they're very
8 stable in the machine, you see a very high molecular ion
9 class, which show the most right side of the screen 201,
10 203. Also, 201, 203 shows the chlorine present.
11 Next(inaudible)166 further confirm the chlorine
12 present, molecular ions of chlorine. When....these
13 chemicals -- this group of chemicals will lose group CNH
14 chlorine. And then because our structure very stable,
15 they can form double charged ions. You can see that half
16 mass 100.6 on most of left side of spectrum. But we call
17 this a fragmentation profile we can link to the structure.
18 --o0o--
19 DR. SHE: Another example I use 3-bromocarbazole,
20 other homologue that demonstrates a similar fragmentation
21 profile.
22 --o0o--
23 DR. SHE: If you go further compare this chemical
24 with one the(inaudible)chemical, benzene, chlorine,
25 dibenzofuran, which in the 1980 to 1990s, EPA and CDC put

1 a lot of effort to study it. Even today, we are still
2 looking for.
3 If you compare carbazole and the furan, because
4 they structurally follow the same Huckel's rule. So their
5 fragmentation profile is similar.
6 --o0o--
7 DR. SHE: So with this information, we can
8 definitely say carbazole unfortunately or fortunately is
9 not in human bodies.
10 --o0o--
11 DR. SHE: And targeted, semi-targeted, and
12 non-targeted analysis are complex and curable research
13 topic. I called it forever research topics. In the past,
14 we proposed three separate but still related approaches.
15 In 1980s, we developed a system called automatic
16 structure elucidation systems with mass spectrometry data.
17 In this system, we use library search and we also tried to
18 spectra interpretation. If the -- if the chemical is not
19 in the library, we try to use knowledge-based engineered
20 to us. We call automatic substructure search if the total
21 structure not there. So fragmentation profile is one of
22 the features we are looking for.
23 In 1990s, we developed isotope profile match
24 approach. And then because of, as you know, a lot of the
25 or organic chemicals composed of elements, like oxygen --

1 oxygen, halogens, and sulfurs, they all have very
2 distinguished -- different isotope profile. Specifically,
3 the isotope profile then you can also elucidate the
4 structure of chemicals.
5 Three years ago, we developed another approach,
6 because we(inaudible)technology we can't total accurate
7 mass-based isotope profile recognition program. In these
8 systems, basically now we have accurate mass, so we could
9 build a database. And also, we have spectra, we build a
10 library. We also can use in silica metabolite predictions
11 of this information. Together, we can more accurately
12 predict or identify the structure.
13 So there are related -- separate systems, but
14 related. So they all can be used to guide us to do the
15 targeted, semi-targeted, and non-targeted analysis.
16 --o0o--
17 DR. SHE: This year, we have limited time to work
18 on-site, because we are encouraged to work at home. Here,
19 a few methods we plan to work on in next few months. And
20 then we like develop metabolite in urine of a VOC, which
21 we didn't finish yet.
22 We also tried to improve our phenol panels, which
23 include the metabolite of BP-3 and the phenols. And
24 there's even the metabolite of 13 other chemicals, like
25 triclocarban and parabens.

1 Also, we like investigations of deconjugation
2 step to make sure bisphenol A assay is accurate, cover the
3 total bisphenol A. Some questions there I think triggered
4 us to do this investigation.
5 We also can like to work on the -- I called the
6 semi-targeted analysis and to automate -- automation of
7 data analysis, because like the machine we use is
8 advanced, which cover with -- come with some very advanced
9 program concept, like XTK include, .com included, so which
10 will allow us to do automation.
11 And then we also plan to investigate --
12 investigation of fragmentation profile for other selected
13 chemicals of interest for Biomonitoring California.
14 Thank you. Now, I have time for some
15 clarification questions.
16 CHAIRPERSON SCHWARZMAN: Thanks for that. We
17 have time for clarifying questions from the Panel.
18 Tom.
19 PANEL MEMBER McKONE: I'll make sure I'm unmuted.
20 Thank you. Very interesting set of things going on.
21 I had a question related to exposure potential.
22 So your -- in order to understand how to analyze
23 carbazoles in the environment, you have to do some sort of
24 structure activity analysis, right, I mean, in order to
25 know what fragments and what methods to use. Has there

1 been a thought about using some of that structure activity
2 research that you've done to maybe look at a possibility
3 of estimating exposure potential, so you might know what
4 ranges we're looking for when we do the biomonitoring?
5 DR. SHE: Yeah, that's a very good point. One
6 approach I remember -- if I understand your question
7 practically, one approach we called effect-based
8 analytical approach. Based on the structure and the
9 activity relationship, we group the chemical together.
10 And then with this group within this -- if there are --
11 that have the same response mechanisms and then we can --
12 based on this phase, we can have the biological approach.
13 We call it the effect-based approach.
14 Plus, the instrument analysis can further help
15 with targeted analysis or even improve our sample flow in
16 the laboratory. We haven't done it yet, but metabolite --
17 based on metabolite prediction can be think as one part of
18 this approach.
19 PANEL MEMBER McKONE: Thank you.
20 CHAIRPERSON SCHWARZMAN: Okay. Thank you so much
21 Jianwen.
22 I'm going to introduce our next speaker. This is
23 our third update. June-Soo Park is Chief of the
24 Biomonitoring Branch in the Environmental Chemistry
25 Laboratory at the Department of Toxic Substances Control.

1 And he'll provide an update on the non-targeted analysis
2 work that's conducted by his laboratory.
3 (Thereupon an overhead presentation was
4 presented as follows.)
5 DR. PARK: Hi. Hello, everyone. Can you hear me
6 okay?
7 (Thumbs up.)
8 DR. PARK: Okay. Thank you. So the -- you know,
9 the -- I'm glad to see you all here again. I think that's
10 the number one priority now days. So I'm going to give
11 our DTSC lab update regarding non-targeted analysis,
12 non-targeted study. This going to be overview for the --
13 of the project we've been conducting.
14 So I'm going to call NTA hereafter, in short.
15 You see the -- our NTA team, Miaomiao Wang, team leader.
16 I hope she can chime in for some technical question, if I
17 can't answer. Also our chemist, Ting Jiang, Christopher
18 Ranque, and myself.
19 --o0o--
20 DR. PARK: Our NTA workflow hasn't been changed
21 much since the -- my last presentation here a couple of
22 years ago. So we still maintain similar sample prep and
23 instrumental analysis, and the data acquisition. Still
24 doing the feature extraction and alignment. For your
25 recollection, feature was a potential compound of a not

1 yet identified, but still contained some chemical
2 information like accurate mass, retention time, and the
3 peak intensity.
4 We still trying to get rid of some -- the small
5 noise-looking peaks, also the -- some inconsistently
6 detected peaks, some duplicate or triplicate injections,
7 some laboratory background interference, then send them
8 for the realignment. And I have them ready for the
9 identification. It's called suspect screening analysis,
10 so -- by comparing to the database.
11 So here, we have several database, but here it's
12 human contaminant database. I believe this one has been
13 the most ever gone through most dramatic changes from the
14 last time, because it has grown from 700 chemicals to more
15 than 3,000. Also, they match -- then we resend them to
16 the further confirmatory process by using fragmentation
17 and the reference standard. If they not match, they have
18 to wait for the unknown analysis workflow.
19 --o0o--
20 DR. PARK: This is how the human contaminant
21 database look like. As you can see, consumer product is
22 the major contributor to the growth of this database.
23 Right now, it has close to 1,300. Most of them came from
24 EPA CPDat. CPDat is the chemical in the product database
25 developed in U.S. EPA. Also, it has about 300 PFAS, 200

1 environmental phenols, pesticide, personal care, food
2 additives, and packaging, and 88 flame retardant
3 plasticizers, phthalates, many other industrial chemicals.
4 --o0o--
5 DR. PARK: I'd like to share our challenges and
6 lesson -- lessons we learned so far from one of our major
7 human NTA studies. It's called, Discovery of Novel
8 Chemicals in 300 pairs cord and maternal serum collected
9 Bay Area. This was funded by NIH. We are in
10 collaboration with Tracey Woodruff's group in UC San
11 Francisco.
12 --o0o--
13 DR. PARK: So as I mentioned, we extracted
14 thousand of features, then identified less than 15 percent
15 at best. Even with that -- the identified features, we
16 are not sure if we identified correctly. In other words,
17 we not sure if the compound was the compound that is
18 supposed to be identified.
19 So anyway, the people using confidence levels for
20 identification, Schymanski divided into five groups,
21 starting from the lowest confidence level when each --
22 when only exact mass information available, all the way up
23 to the level one highest confidence level, when you have
24 reference standard to compare available.
25 So if you apply this confidence levels to our

1 compounded list, you can see most of them are falling into
2 the confidence level 3 to 4, of course, sometimes 5. Only
3 some of PFAS we can claim as a confidence level 1, because
4 we have analytical standard available in-house.
5 --o0o--
6 DR. PARK: Having that said, the -- we are
7 sending identifiable -- identified features to our
8 confirmatory processor. But we cannot do that all,
9 because it's just simply too many, wasting too much -- or
10 taking too much resources and time.
11 And that's why we prioritized them, particularly
12 our colleague all-in-one data prioritization, which
13 compounded to go faster in this MS/MS fragmentation
14 experiment. The first thing we -- the compound we
15 collected, the first criteria is the detection frequency,
16 the selected compound showed 100 percent detection
17 frequency throughout the sample, also very abundant,
18 because we don't want to lose signal in the MS/MS
19 fragmentation.
20 We also selected a compound showing any
21 demographic differences, like education, and race, and
22 ethnicity, and household income is, et cetera. And
23 lastly, the -- among compounds showing correlations
24 between two matrices, maternal and cord serums, we
25 selected compound show that -- one matrix showed a much

1 higher intensity than the other.
2 --o0o--
3 DR. PARK: Then we come up with the number of
4 target features, 208 for initial MS/MS test. So Ting
5 Jiang, our chemist, conducted an MS/MS experiment. So 15
6 percent. She come up with a 15 percent as an MS/MS
7 matching rates. That means about 30 compound out of 208
8 been confirmed by MS/MS. It sounds a little lower than
9 expected. I know. But even these matching rates will
10 also match through not only our work, experimental MS/MS
11 fragmentation peaks, but also the -- some matched through
12 the -- some online tools like experimental MS/MS database,
13 and some computational modeling like in silico.
14 Ting presented this work at ASMS last month. Of
15 course, it was all online, order of presentation. With
16 this low matching rate, we may not the only one, because
17 we found other study showed the similar matching -- rating
18 the wastewater. Of course, this is the -- you may say the
19 matrix are quite different between wastewater and human.
20 But this is kind of all we can find -- all Ting can find
21 to compare, because it was very rare, very hard to find
22 any human study that went beyond the suspect screening.
23 That's why the -- we brought this Schymanski's group's
24 paper published 2015.
25 So one thing I'd like to mention, so comparing to

1 their study it's kind of given us some -- the -- you know,
2 the idea that this kind of low matching rates may not be
3 the very far from the reality, I guess.
4 --o0o--
5 DR. PARK: Anyway, these are the example features
6 confirmed by our MS/MS matching. Some used as food
7 additives and preservatives, like paraben. The -- you can
8 count about 13. Plus, we have 17 more I didn't show you
9 here. We already purchased the -- excuse me -- analytical
10 standard. For instance, a standard or designated data
11 available in the market. But a few of them we are still
12 struggling to get access to them -- to the standard in the
13 market. So they are -- they are currently being evaluated
14 for final confirmation.
15 --o0o--
16 DR. PARK: So we are currently applying very
17 similar NTA workflow to our other ongoing human
18 biomonitoring project, NTA project studies that include
19 some EJ communities, like Fresno that we've been working
20 with Lauren Zeise group, and OEHHA. We analyzed the
21 Fresno samples, 70 pairs of cord and maternal serum and
22 currently compare it to the Bay Area data I just presented
23 before.
24 You know, another study, we are working with
25 Rachel Morello-Frosch team at UC Berkeley. We are

1 comparing chemical profiles in others, some women
2 firefighters, nurses, and office workers.
3 --o0o--
4 DR. PARK: We currently have NTA-related
5 manuscripts in progress, on number two and three, related
6 what I already presented earlier. And they're are -- they
7 are the human data. Number one is the lead my Miaomiao
8 Wang. And this is regarding the data from EPA NTA
9 studies, NTA.....studies that we have participated in a
10 couple of years ago.
11 So I got five minute warning already.
12 Okay. So and number four is -- this is also the
13 non-targeted PFAS studies investigation in wastewater.
14 Number five is the -- regarding stormwater runoff
15 following 2017 wildfires in Northern California. We are
16 working as two-track redoing(inaudible) and she's took a
17 part -- took a role for some volatile and semi-volatile
18 persistent chemicals. So we are doing some polar compound
19 -- some polar non-target compound.
20 And six, seven, and eight, I think they are much
21 slower progress like the cat and the firefighters exposed
22 to AFFF and even metabolomics, but we'll get there. We'll
23 get there.
24 --o0o--
25 DR. PARK: So we'll continue testing our

1 analytical standard for final confirmation. And then
2 we're going to select 5 to 10 chemicals to quantitate
3 using a calibration curve. Of course, we will continue
4 our effort to improve our identification rate and
5 confidence.
6 Here's two of our biggest challenges. You heard
7 a lot about it. I don't want to say any more, but -- you
8 know, that we cannot control. We are understaffed. So
9 this unknown identification workflow is kind of on hold,
10 even though we have more than 85 percent of extracted
11 features not identifiable by database.
12 Also, some non-targeted volatile and
13 semi-volatile analysis using GC/Q-TOF. We just have
14 installed in branch, but they're not -- they're not much
15 thing I can help. But hopefully we can utilize this
16 instrument soon.
17 --o0o--
18 DR. PARK: I'd like to give many thanks to the
19 funders and the collaborators. I just couldn't display
20 all, because of limited space. There are many others
21 working together, have a lot of fun conducting interesting
22 project.
23 This is it. Thank you very much.
24 CHAIRPERSON SCHWARZMAN: Thank you for that
25 update. I have one quick question and then we'll invite

1 other clarifying questions from the Panel.
2 DR. PARK: Sure.
3 CHAIRPERSON SCHWARZMAN: That's -- you showed the
4 correlation between the maternal and the serum blood, you
5 call it intensity -- sort of intensity of signal. I
6 assume that's in the non-targeted analysis of maternal and
7 cord serum, and that 50 percent went one way and 50
8 percent went the other way, sort of, you know, more
9 intense in the maternal serum compared to cord serum and
10 50 percent were the other way, more intense in the cord
11 serum than maternal.
12 And I was wondering if you -- if it's possible to
13 say anything about the sort of characteristics of the
14 signals or the -- or compounds that you can identify that
15 are consistent among the chemicals that tend to be more
16 intensely apparent in cord blood versus maternal or the
17 opposite.
18 DR. PARK: Well, I think I'm sure that we will
19 get there. Right now, the -- we are under -- are on
20 suspect screening analysis. It's all chemical analysis
21 part. But we are working with Tracey Woodruff's group.
22 Eventually, we will get there scrutinizing individual
23 peaks, you know, that have any significant meaning. So
24 the -- that's -- right now, the two papers is all kind of
25 a prioritization and also chemical analysis by using the

1 MS/MS the fragmentation technique.
2 But the follow-up manuscript, we will be more
3 focusing on the submitting of each individual -- the
4 chemicals we identify than from the -- based on the old
5 demographic information and all the statistical
6 information.
7 CHAIRPERSON SCHWARZMAN: Yeah. Thank you. But
8 one of my -- one question is sort of whether even absent
9 being able to identify individual chemicals if you can --
10 if you can say anything about the characteristics of the
11 chemicals that tend to be more apparent in maternal serum
12 than in cord serum or vice versa.
13 DR. PARK: Yes, probably so, just by looking with
14 bare eyes. You know, the -- if you see some of the
15 parents compound metabolizer tend to be existing higher in
16 test -- in cord blood. And you may be able to tell which
17 one distribute the higher portion each matrix. So I'm
18 sure that you can -- you can the -- evaluate that without,
19 you know, any further deep statistical analysis.
20 CHAIRPERSON SCHWARZMAN: Okay. Great. I would
21 just be curious if you -- if you wind up with a
22 characterization of that?
23 DR. PARK: You're not the only one. Trust me,
24 you're not the only one.
25 (Laughter.)

1 PANEL MEMBER SCHWARZMAN: Oliver, you had a
2 question.
3 DR. PARK: Yeah, I saw a couple of hands raised
4 there. Oliver, did you --
5 PANEL MEMBER FIEHN: Thank you. So I wondered if
6 you have considered also collaborating with external
7 partners in data processing? I mean, chemical
8 laboratories, you know, similar to Dr. She's laboratory
9 who are usually doing target analysis may have not like
10 the necessary experience to look at non-targeted
11 screening, using all the resources, using all the possible
12 tools. It's a little bit overwhelming. So have you
13 considered like contacting others, the various centers in
14 the United States, who actually focus these days on
15 exposome analyses and compound ID.
16 DR. PARK: Yeah, I think -- Oliver I think if you
17 propose your group as a potential collaborator, yeah. Of
18 course, yeah. Also, Jon Sobus used to help us a lot by
19 introducing his teammates who is very expert in this area.
20 Eunha, also the -- you know, the -- also some SFEI folks,
21 and many others. But eventually, the -- a lot of works
22 need to be done. That's our part. So, of course, when we
23 need to reach out for help, you know, you will be the
24 first one we are going to contact.
25 (Laughter.)

1 DR. PARK: I know where you live.
2 CHAIRPERSON SCHWARZMAN: Eunha, I saw that you
3 had a question, but I'm going to put that -- just a
4 minute. I have your name written down. We need to go to
5 public comment for a few minutes and then we'll have a
6 chance to have a discussion based on all three of these
7 presentations. And I have Eunha first to ask a question
8 or start a discussion item.
9 So with that, I want to announce the public
10 comment period starting. We have ten minutes allotted for
11 public comment. And I want to just give you a reminder
12 about how to submit comments. Webinar attendees can
13 submit them in writing via the GoToWebinar question
14 feature or email to biomonitoring@oehha.ca.gov. And you
15 can also speak, if you wish. In that case, please alert
16 us by using the raise hand or the question feature in
17 GoToWebinar platform. And we have staff monitoring that
18 and we will call on you.
19 So I'm going to start by checking in with Marley
20 and Sara, if you know about any public comments.
21 MS. ZALAY: This is Marley. There are no
22 current -- no questions currently.
23 CHAIRPERSON SCHWARZMAN: Sara, you're muted if
24 you're trying to talk.
25 We can't hear you, Sara.

1 No.
2 Okay. We'll have to wait for Sara to communicate
3 in another way. She might message one of us. Inevitable
4 hiccups. And it's okay to leave a moment here anyway, in
5 case people didn't anticipate this moment being public
6 comment and want to still email one or raise hand in the
7 web platform, or anything like that for making a public
8 comment.
9 There is also another public comment period in
10 the afternoon, if you intended to, but sort of don't make
11 this chance.
12 MS. HOOVER: Can you hear me now?
13 CHAIRPERSON SCHWARZMAN: Yes.
14 MS. HOOVER: Okay. I had to leave the webinar.
15 Sorry, now I'm getting an echo. I had to leave. It would
16 not let me unmute.
17 Okay. Apologies for that technical delay. I am
18 going to go ahead and read the public comment. This is a
19 question from Jay Murray. His question is for Nerissa.
20 Were the urine samples spot samples or 24-hour samples?
21 And I can actually answer that. They were spot samples.
22 And then Jay also has a comment to share on Nerissa's
23 talk.
24 He says that molybdenum is an essential element
25 and your geometric mean values for molybdenum in urine are

1 consistent with what is known about dietary intake.
2 And that is the only public comment that we have
3 received.
4 So, Meg, you can go back to Panel questions and
5 comments.
6 CHAIRPERSON SCHWARZMAN: Okay. Thank you for
7 that. Sorry for the wrinkle.
8 We now have until about 11:30 for Panel
9 discussion and any other questions that we didn't cover.
10 So this is meant to be a discussion of all three
11 presentations that we've heard before, the program and the
12 two laboratory updates. A reminder to just raise your
13 hand if you want to speak, and I'll call on you. But I
14 want to start with Eunha who had a question or comment
15 earlier.
16 PANEL MEMBER HOH: This is Eunha Hoh from San
17 Diego State University. I have some questions first,
18 curiosity and clarification, to June-Soo. Great work,
19 June-Soo. It's very impressive that what you've done and
20 presented. I would like to know about the details. A
21 couple questions that you're talking about the
22 uncertainty. Is that -- when you run actually acquired
23 authentic standards is actually ran -- run those authentic
24 standards and then compare them with your data, do you get
25 better matching, you know, compared to your -- comparing

1 with the database?
2 DR. PARK: Eunha, there was the million dollar
3 question. We are working -- we are -- informed you we
4 already purchased and injected most of the standard we
5 were able to acquire from the market. So that's another
6 story. So we have only 15 percent matching rate in the
7 MS/MS fragmentation. Also, the -- in the -- so far, we
8 have successfully acquired data from the standard
9 injection. Also, the some -- some percentage were not
10 matched. So that chance is kind of getting slim and slim.
11 So I think we are getting -- realize, that we are getting
12 into the -- we are now realizing where we are right now.
13 PANEL MEMBER HOH: Um-hmm.
14 DR. PARK: So I think, again, I have to emphasize
15 this takes a lot of time and effort. Our particular
16 outing done in the Bay Area study, in MS/MS, this is all
17 manually -- you know, the -- the -- the -- have to met
18 kind of interpret or the fragmentation patterns by just
19 bare eyes by a synthetic chemist background. So there is
20 no shortcut. Of course, sometimes the software can help
21 you the kind of shortcut, but it's not all the time.
22 PANEL MEMBER HOH: Um-hmm.
23 DR. PARK: You know better than I do.
24 PANEL MEMBER HOH: One more question just for
25 the -- your current human biomonitoring NTA projects, the

1 number two the woman firefighters and nurses, office
2 workers, what type of samples do you use for that?
3 DR. PARK: That's the blood. I'm sure Rachel
4 Morello-Frosch will give more details this afternoon. But
5 that was the human biomonitoring project I've been talking
6 about is all related to the serum samples.
7 PANEL MEMBER HOH: Okay. Okay.
8 DR. PARK: Hi, Jenny.
9 CHAIRPERSON SCHWARZMAN: Anything else, Eunha?
10 That was it?
11 PANEL MEMBER HOH: (Nods head.)
12 CHAIRPERSON SCHWARZMAN: Okay. Jenny, please.
13 PANEL MEMBER QUINTANA: Hi. Thank you for that
14 presentation. I had, I guess, a comment more than a
15 question, as well as a question. But one thing is that
16 you said that you used a hundred percent detection as one
17 of your criteria, which I can imagine you use, because you
18 want to discover environmental chemicals that are very
19 common and might be an important target for intervention.
20 But it also occurred to me you might miss health
21 disparities between populations by requiring a hundred
22 percent detection. So theoretically, if you had a hundred
23 percent detection in a disadvantage population, let's say
24 exposed to a lot of diesel exhaust, you might have very
25 low detection perhaps under your instrument sensitivity

1 for the other people, and so you might miss an important,
2 you know, contaminant that would be important for health
3 disparities. And I guess, I'm wondering if you had
4 thought about that.
5 And my second comment, just to give them all
6 right now, is following up on Meg's comment about the cord
7 blood. It does seem like chemicals that are more present
8 in the cord than the mother would be the first priority
9 for me, ones that are especially, you know, present in the
10 cord. So thank you. Thank you again for that talk.
11 DR. PARK: Should I answer to question?
12 PANEL MEMBER QUINTANA: If you had a comment
13 or --
14 DR. PARK: No. I think -- I just have a brief
15 comment on your first question. I -- again, I already
16 totally agree with your second comment.
17 On the first one, the -- yes, we're going to miss
18 a lot of -- but I'm -- I -- with the presentation slide, I
19 just show you -- it's a very initial study to confirm the
20 compound we -- also, the past compound we identified. Of
21 course, we would -- by doing that, you know, some
22 population disparity, that any compound related to kind of
23 the disparity I think we're going to miss it. But we're
24 not going to ignore those data. We will definitely go
25 back as a follow-up study.

1 Right now, the MS/MS confirmation, that's the
2 main goal of this presentation right now, also the
3 manuscript we tried to see, you know, the -- how many
4 compound we identify can be matched at least as a
5 percentage. And then you -- as you can see, it just
6 dramatically drop the matching rate in the MS/MS. So
7 matching rate is dropped even final confirmation using the
8 standard. So that's what the kind of reality we like to
9 learn from this major project.
10 PANEL MEMBER QUINTANA: Thank you.
11 DR. PARK: So one more thing. Beauty of this
12 non-targeted, data won't go anywhere. So I think it's --
13 it's in the hard drive. Whatever the purpose and goal we
14 are setting, then we will go back to the data and
15 reinvestigate the hypothesis.
16 CHAIRPERSON SCHWARZMAN: Thank you for that.
17 Carl, you had a question or comment.
18 PANEL MEMBER CRANOR: A quick question. It's a
19 technical question, but also maybe a question for Sara.
20 In the air pollution study, is there any way to -- do you
21 detect the particulate matter or do you just detect things
22 that might be carried on particulate matter, if both
23 things happen. I'm curious about that, because if you
24 look at some of the studies out there on particular
25 matter -- particulate matter is particularly worrisome,

1 but it carries other things with us.
2 MS. HOOVER: Yeah.
3 PANEL MEMBER CRANOR: So curiosity question.
4 MS. HOOVER: Sorry?
5 PANEL MEMBER CRANOR: I'm done. That's the
6 question.
7 MS. HOOVER: So as Jenny mentioned, you can
8 measure black carbon. In terms of biomonitoring though,
9 we don't -- and I welcome comments from anyone, but we
10 have not identified a specific biomarker, for example, for
11 PM2.5. So we will tackle it using a variety of tools as I
12 mentioned. You're right, that particulate matter can be
13 associated with certain chemicals. So we'll be looking at
14 that option. We'll be looking at air monitoring. We'll
15 be looking at, you know, this really cool work that a lab
16 in DPH does, which is actually looking at particles and
17 doing source -- exposure source work by looking at the
18 particle itself.
19 The other thing I forget to mention - so thanks
20 for bringing up the study again - we're also hoping to do
21 some non-targeted screening actually on air samples. So
22 as you probably are all aware, there's very specific
23 chemicals that are monitored in air. There's not
24 generally a really broad sweep of what's being found in
25 air. So we don't know if this is going to pan out, but

1 there's certainly the capability of doing an open scan,
2 for example, of VOCs. So we might identify a facility of
3 concern in an AB 617 community and do some non-targeted
4 screening work outside that facility or in a particular
5 location in the community not necessarily tied to a
6 particular facility. So that's another option.
7 So it's very complicated. As you've probably
8 heard in our other talks, it can be really challenging to
9 biomonitor air pollution for a variety of reasons. But,
10 yeah, I'm confident with the team that I have, the very
11 excellent team that I have, and with Asa and all of your
12 advice that we'll figure out something that's going to
13 work.
14 And as I -- I think I mentioned before as well in
15 a past meeting, we're going to try to design something
16 that's specific. We're not going to be doing like broad
17 biomonitoring. We don't have the resources for that, but
18 we will definitely take into account these challenges as
19 we design our targeted biomonitoring study.
20 CHAIRPERSON SCHWARZMAN: Ulrike.
21 PANEL MEMBER LUDERER: Yes. Thank you all for
22 those presentations. They were all really informative and
23 interesting. And I actually had a follow-up to the --
24 regarding the AB 617 study. I think Nerissa mentioned
25 that -- you were planning on looking at some biomarkers of

1 effect. But I was just curious which biomarkers of effect
2 you're thinking of measuring?
3 MS. HOOVER: So same answer. We haven't
4 determined that yet. We're obviously looking at the
5 biomarkers of effect that are associated with air
6 pollution in the literature. So if you have thoughts on
7 that, we are wide open to any suggestions at this point.
8 It's still in the early research and design phase.
9 CHAIRPERSON SCHWARZMAN: Yeah, Veena.
10 PANEL MEMBER SINGLA: Hi. Thanks for those
11 presentations. My question was about the VOC metabolite
12 method development. And if you could give us a reminder
13 of what parent VOC compounds that that would be looking at
14 and the timeline for that potential method development,
15 and I wondered if it might be able to inform the AB 617
16 study at all?
17 DR. SHE: So for the VOC metabolite, we're
18 looking for -- the parents could be smoking-related or
19 organic solvent related ones. Regarding, specifically
20 related to the AB 617, I haven't had a chance to look at a
21 list from which one might be present. In the AB 617
22 is concerned list. And as I am -- but our list is
23 basically 28 metabolites.....from -- four or five from
24 smoking related VOCs and then a group from the solvent.
25 That's how we come up. But....at this moment, the method

1 of focus on the CDC published standard operation
2 procedure. But we always can like expand it to cover 617
3 concerned chemicals.
4 MS. HOOVER: So I'll just chime in. This is Sara
5 again. A couple things. The method that Jianwen just
6 referred to, which he cited, is CDC's method. I can send
7 you the list of the complete set of chemicals covered in
8 that. We actually went through this with Victor De Jesús
9 in a past meeting when we were first talking about air
10 pollution biomonitoring. I'll also add that we've
11 actually looked closely at the VOCs -- the parent VOCs,
12 some of them are strongly traffic-related, like
13 gasoline-related chemicals.
14 So we're actually considering -- I'm not going to
15 say much about it, but we're considering a pilot project
16 potentially to look at some of those stable metabolites of
17 VOCs related to gasoline exposures. And this partially
18 comes out of the big report that we finished on the
19 assessment of gasoline-related exposures throughout
20 California, the 15-year -- 18-year report I think we did.
21 Dan Sultana in my group and I.
22 I can share that with you, if you're interested
23 in it. It does talk about these issues. And so, yeah,
24 we'll definitely be considering, you know, if we can work
25 with Jianwen's lab, we're going to be collaborating with

1 him on some of those issues.
2 I also wanted to chime in on a past comment and
3 question. And Julia Varshavksy, who is listening, said
4 that she could talk a little bit about some of the
5 biomarkers effect -- of effect that she's been researching
6 for 617.
7 So, Julia, do you want to join and give. Go
8 ahead and share your webcam and --
9 CHAIRPERSON SCHWARZMAN: Hey, Sara, I'm just
10 wondering if we could stay on this first topic for a
11 moment and then go back to biomarkers of effect --
12 MS. HOOVER: Oh, sure.
13 CHAIRPERSON SCHWARZMAN: -- because I have a
14 question to this one about VOCs or comment.
15 MS. HOOVER: Go for it. Sorry.
16 CHAIRPERSON SCHWARZMAN: So thank you for that
17 comment, Veena, because I feel like it would be great to
18 make some overlap here. And I do really appreciate that
19 16-year report, and making some of those connections will
20 be great. And I just wanted to mention one more link that
21 Jianwen might look at. This is not published yet, but
22 we're working on -- we've been working with the California
23 Air Resources Board consumer products database really
24 extensively for a while trying to prioritize. So that's
25 about consumer products used very broadly. So that's many

1 products that are mainly used in workplaces, but they're
2 sold in a potentially consumer-facing way.
3 And they're -- that's looking at sales volume,
4 and also VOC, and low vapor pressure VOC content, and out
5 of that analysis have developed some sort of priorities --
6 a short list of priority compounds, because of their --
7 either their volume in commerce or they might be lower
8 sales volume, but higher percent in the products.
9 And I would be curious to kind of put our
10 priority list, and we've prioritized them also about
11 potency kind of against the list of potential analytes
12 that you're looking at methods development around. And
13 there may be great methods already and good overlap, but I
14 would just be curious to make that connection.
15 DR. SHE: Great. We like to have this priority
16 list to work with you to look for further refining and
17 target our analytes.
18 CHAIRPERSON SCHWARZMAN: And we can certainly
19 talk about it now. We're working on writing up methods
20 and publishing it, you know, in the next few months.
21 DR. SHE: (Nods head.)
22 CHAIRPERSON SCHWARZMAN: Great. So thank you for
23 letting me interject that into that discussion.
24 And then I'd love to go back to the biomarkers of
25 effect and invite Julia Varshavsky to answer some of those

1 questions.
2 MS. HOOVER: Great. Thank you, Meg. So, Julia,
3 if you are online, and you can share your webcam, and
4 unmute yourself, can you chime in?
5 She emailed me that she was going to do that.
6 We'll just give her a minute.
7 Okay. Hang on.
8 CHAIRPERSON SCHWARZMAN: If anyone has another
9 question or comment while we're waiting for Julia to get
10 on. Yeah, Tom, please go ahead.
11 PANEL MEMBER McKONE: Sorry. It takes me a
12 minute to unmute. So I actually wanted to know a little
13 more. I'm quite interested in the halogenated carbazoles.
14 And some of this we probably have been briefed on, but
15 I -- it would be helpful to me if there was just a little
16 bit of an update about, you know, sort of what the
17 intent -- what the pathway is where we're going. I mean,
18 the methods development looked really interesting and was,
19 I think, very sophisticated and useful. But I'm trying to
20 remember exactly where those fit in. I mean, they're --
21 they're an air -- certainly an air pollutant, but they
22 come by other pathways too and there's fairly high volumes
23 in some products in some workplaces. But I just wanted
24 some more insight on where we plan to go with that,
25 what specific efforts that's going to be included in that?

1 DR. SHE: Hi, Tom. Thank you for that. Is this
2 question for me or -- sorry.
3 PANEL MEMBER McKONE: Sorry, I muted it.
4 It probably was more a general question for the
5 program. I don't know. I'm not sure if Sara was
6 listening. It might be for Sara to cover about where --
7 you know, where carbazoles fit into the plan, and the
8 halogenated --
9 MS. HOOVER: Yeah, I'm sorry. We're
10 troubleshooting on the side, Tom, so yeah. Basically --
11 PANEL MEMBER McKONE: So I don't know if you
12 heard the question. I was just trying to get more of a
13 sense of, you know, what -- I think I understand the
14 motivations and I know we had some discussions, but I
15 did -- if you could just refresh us a bit on, you know,
16 what are the next steps once we get the methods
17 development, which looks like the methods development is
18 moving ahead very nicely and --
19 MS. HOOVER: Are you specifically talking about
20 halogenated carbazoles or something else?
21 PANEL MEMBER McKONE: Halogenated carbazoles.
22 MS. HOOVER: We have no plans to pursue
23 halogenated carbazoles. That was a pilot that Jianwen
24 did.
25 PANEL MEMBER McKONE: Okay.

1 MS. HOOVER: It was a laboratory study, so it's
2 not on our radar to address those. I'm not actually sure.
3 Maybe one of you, either June-Soo or somebody else, could
4 say what they're used for. If you could repeat that, then
5 I could tell you if it might already be captured in our
6 set of chemicals.
7 Jianwen, do you know what they're used for?
8 DR. SHE: Yes. I can give a try. Carbazoles
9 were found in the Great Lakes in sediment. Professor An
10 Li at Chicago University and others reported carbazole
11 levels in environment is five times higher than PBDEs.
12 Also, from its structure, you can see it's very
13 similar to dibenzofuran. That means they're stable,
14 persistent. But where are they going? They're found in
15 environmental samples and they're found in San Francisco
16 Bay Area in the water samples and the fish.
17 And then we -- we look at it basically because
18 they're so high levels and they're persistent. And then
19 unfortunately we use a sample is archived samples, and
20 then Nerissa can talk about the sample we used. We look
21 for the parents. We didn't find it. And then we talk
22 with Anne and other group that said, oh, you may want to
23 look for some metabolite.
24 So our assumption is because they persist, we
25 should find parent in serum samples. Surprise to us we

1 didn't find them. So --
2 MS. HOOVER: Sorry, Jianwen, let me just chime in
3 for a second. I was asking about the sources, the
4 exposure sources of -- not about your specific project,
5 but where the halogenated carbazoles coming from. I see
6 Jon is sharing his webcam. So maybe, Jon, do you have a
7 comment in response to my question perhaps.
8 Jon Sobus.
9 DR. SOBUS: No, I don't. I was just getting
10 prepped -- just getting prepped for the presentation.
11 That's all.
12 MS. HOOVER: Okay. Great.
13 DR. SHE: Sara, I can answer the question
14 quickly.
15 MS. HOOVER: So, Jianwen, yes, you have a comment
16 on where they're coming from.
17 DR. SHE: They come -- they're coming from a
18 byproduct from refining -- petroleum refinery(inaudible)
19 product, because(inaudible), so the dye industry may be
20 the major one to form the halogenated carbazoles.
21 MS. HOOVER: Okay. So for now, we're -- it
22 doesn't -- it's not captured by our program. Go ahead,
23 Tom.
24 PANEL MEMBER McKONE: They're also used -- I did
25 a look. They are used in dyes in color retention. So

1 they might be in clothing or some consumer products --
2 MS. HOOVER: Okay.
3 PANEL MEMBER McKONE: -- which would make them of
4 interest, I think, to us.
5 MS. HOOVER: Great. So let me --
6 PANEL MEMBER McKONE: They may not show up as a
7 priority, but I just thought that would be because they
8 seem --
9 MS. HOOVER: I -- I'm actually --
10 PANEL MEMBER McKONE: -- a little bit ubiquitous
11 and persistent.
12 MS. HOOVER: Yeah. My question was not to say
13 they're not a priority. My question was at the moment, we
14 haven't flagged them, but if you'd like to flag them as
15 something for us to track and pursue, we can certainly do
16 that, if that's what you're suggesting as some of your
17 input today.
18 Okay. Now, I just -- I'm actually --
19 PANEL MEMBER McKONE: Maybe -- maybe more
20 research on whether they should be a priority as opposed
21 to like moving ahead with that.
22 MS. HOOVER: Okay. I'm actually going to invite
23 Meg to say her comment that she just texted to me, because
24 this is what I was going for actually, if that's true.
25 CHAIRPERSON SCHWARZMAN: I think -- I don't know

1 that much about halogenated car -- carbazoles, but what I
2 understand is they can also come from like the
3 environmental breakdown products essentially of
4 halogenated flame retardants and chlorinated pesticides.
5 I'm sure they're tracked to lots of different sources.
6 MS. HOOVER: So if that's true, then they are
7 included in the -- that's kind of what I was going for,
8 because basically we have -- as you all probably recall,
9 we have the entire class or group of brominated and
10 chlorinated organic compounds used as flame retardants.
11 Anything that could be a marker for those, including an
12 environmental breakdown product would be captured by that
13 listing. We also have a number of chlorinated pesticides
14 listed. So how about if we put on our to-do list, which
15 will show up in the transcript for today, we will follow
16 up and try to figure out whether halogenated carbazoles
17 are already covered by our list, and if not, we'll do a
18 little more research, as Tom has requested, to see if they
19 should potentially be subject to like a preliminary
20 screening. Does that sound okay with everyone?
21 (Nodding heads.)
22 CHAIRPERSON SCHWARZMAN: Good.
23 MS. HOOVER: Okay. So now I'm going to hand it
24 over to Julia. The issue was she's an attendee, so we had
25 to unmute her in order for her to be able to speak. So go

1 for it Julia.
2 CHAIRPERSON SCHWARZMAN: We can't hear you.
3 No. We can see you, but not hear you.
4 MS. HOOVER: Do you see the little red mic?
5 DR. VARSHAVSKY: (Nods head.)
6 MS. HOOVER: Okay. Is it turned green?
7 Marley, can you check if she's unmuted on your
8 screen?
9 I had this problem earlier when I was unmuted
10 entirely and I could not speak in GoToWebinar. So there's
11 some weird glitches happening today too. All right. How
12 about -- well, let's see, we'll do a little more
13 troubleshooting and see if we can get her unmuted. If you
14 want to, in the meantime, invite other comment, Meg. You
15 can do that.
16 DR. VARSHAVSKY: Can you hear me this way?
17 MS. HOOVER: Yes.
18 DR. VARSHAVSKY: Okay. Great. Sorry about that.
19 I wasn't planning to speak, so we had to troubleshoot
20 that. But I just wanted to reiterate what Sara said about
21 how we're really in the information gathering stage for
22 biomarkers of both exposure and effect related to air
23 pollution. But I wanted to share our running list of
24 potential biomarkers of effect, because somebody brought
25 it up and because it would be great to get your expertise

1 or input along the way, so -- so that you know what we're
2 considering. And if you have any input, we would love to
3 hear it.
4 So right now, we're looking at -- we're sort of
5 focused on -- more on urinary measures because of the more
6 ease of sample collection. So in that vein, we're
7 considering oxidative stress biomarkers that have been
8 decently well established in the literature,
9 8-isoprostane, 8-hydroxydeoxyguanosine, potentially paired
10 with prostaglandin to try to get at the different lipid
11 peroxidation versus inflamma-- inflammation pathways that
12 may be more or less relevant for certain outcomes, like
13 for example preterm birth.
14 We're also looking at biomarkers of inflammation,
15 which as we understand it currently is more restricted to
16 serum tissue rather than urine. And those include these
17 panel of cytokines and/or things like plasma CRP, which
18 has been related to air pollution as well in the
19 literature.
20 We're also looking at telomere length in
21 different kinds of human biolog -- biological tissues, so
22 serum, and we're also exploring buccal samples as well.
23 And then one thing we've added to our list recently was
24 nasal IgE antibody, which has been associated with diesel
25 exhaust in the literature as well.

1 So that's sort of the rundown. We're looking at
2 telomere length, oxidative stress, and inflammatory
3 biomarkers. As a broad categories. So if anyone has
4 insight or wants to talk to us -- our team about potential
5 strategies for doing that, in an effective way, we would
6 be more than happy to hear your input.
7 Thank you.
8 CHAIRPERSON SCHWARZMAN: Great. Thank you so
9 much Julia for navigating what you had to navigate to get
10 in and tell us that. It's helpful.
11 It is time to move to our next talk -- Jenny
12 is -- do you want to raise something about this and then
13 we'll move on?
14 PANEL MEMBER QUINTANA: I'll be very quick. A
15 couple comments. One was to help interpret the data, I do
16 encourage that you measure cotinine or potentially markers
17 of marijuana smoke exposure or vaping. It might help
18 interpret the data, because sometimes disadvantaged
19 communities also have a much higher rate of smoking, but
20 also living in multi-unit apartments with neighbors who
21 smoke. And I think it might help interpret some of the
22 PAH data and things like that.
23 DR. VARSHAVSKY: Absolutely. That's great.
24 PANEL MEMBER QUINTANA: And the second -- second
25 thing is if you are looking at markers of effect, we could

1 talk -- I can email more, but I really encourage,
2 especially for DNA damage or things related to DNA, that
3 you measure folate levels, if it had a huge effect on
4 those kind of biomarkers and they -- I think the
5 recommendation is that you always measure that if you're
6 going to do that kind of monitoring would be the best
7 practice.
8 So thank you. I'm sorry to take the time.
9 DR. VARSHAVSKY: Great. Thank you.
10 CHAIRPERSON SCHWARZMAN: Okay. So, we need to
11 move on to our next presentation. Thank you all for your
12 contributions to that discussion.
13 We're a little bit behind schedule, but I think
14 we will make it up at some point here. I want to
15 introduce our next speaker. We're going to hear about
16 what EPA is doing with non-targeted analysis. So our next
17 speaker is Jon Sobus who's a physical scientist in the
18 U.S. EPA's Office of Research and Development, or ORD,
19 specifically in the Center for Computational Toxicology
20 and Exposure. And he works to develop high resolution
21 mass spectrometry methods for characterizing contaminants
22 of emerging concern in a variety of environmental and
23 biological media.
24 He's team leader of ORD's Non-Targeted Analysis
25 Research Program and co-PI for EPA's Non-Targeted Analysis

1 Collaborative Trial, or ENTACT. And he'll be presenting
2 findings from that trial ENTACT to us now.
3 So welcome, Jon. Thank you.
4 (Thereupon an overhead presentation was
5 presented as follows.)
6 DR. SOBUS: Terrific. Thank you for the
7 introduction. Can everybody hear me okay?
8 That doesn't sound promising.
9 MS. ZALAY: Yep, we can hear you.
10 MS. HOOVER: Yes. Go for it, Jon.
11 DR. SOBUS: Terrific. Can everybody see my
12 screen okay?
13 MS. HOOVER: Not yet. I think -- I think Marley
14 may need to make you the presenter, if she hasn't already
15 done so.
16 Sorry, this is Sara speaking from the...
17 MS. ZALAY: Yeah. You have presenter
18 capabilities Jon. Do you see --
19 DR. SOBUS: I have shared my screen and it says I
20 am sharing.
21 MS. ZALAY: Why don't -- why don't we --
22 DR. SOBUS: I'll try one more time.
23 MS. ZALAY: -- try one more time.
24 Thank you.
25 PANEL MEMBER McKONE: There. Yeah.

1 MS. HOOVER: And Jon, I -- Jon, I also, yes. And
2 Jon, I want to also let you know you have your full 20
3 minutes, so don't worry. You don't have to rush through,
4 because we went over.
5 DR. SOBUS: Terrific. And I do tend to go pretty
6 quickly on these things. So I'll try not to go too
7 quickly. If I can get this panel off the side of the
8 screen, I will go into full presenter mode and we will
9 finally be on our way.
10 Okay. Can you see it?
11 PANEL MEMBER McKONE: Yep.
12 PANEL MEMBER SINGLA: Yeah, it looks great.
13 DR. SOBUS: Terrific. Okay. Okay. So I'm Jon
14 Sobus. I work for the U.S. EPA. I'm going to be talking
15 today about our most recent findings from our Non-Targeted
16 Analysis Collaborative Trial, or ENTACT. So I wanted to
17 first start by presenting kind of a juxtaposition between
18 non-targeted analysis and the classical targeted analysis
19 that we've known and used for so many decades now.
20 With targeted analysis, we typically know the
21 chemicals or chemical classes that we're looking for and
22 we build the methods specific for those chemicals or
23 chemical classes. That's not how we do non-targeted
24 analysis. Here, we don't pick the chemicals. We pick the
25 samples of interest. So these can be environmental

1 samples, biological samples, you name it.
2 We start by doing a basic laboratory preparation
3 of those samples using liquid extraction. We often do
4 some type of cleanup. But generally speaking, we're going
5 to inject those process samples on a high resolution mass
6 spectrometer. And then we are going to generate a lot of
7 information on what we call molecular features.
8 Okay. So this is basically a plot of a number of
9 different molecular features, with each feature being
10 represented as some type of peak. We try and use some
11 type of prioritization scheme, often using statistics, to
12 figure out which molecular features are most interesting
13 or most important. Then we try and propose a chemical
14 formula for each feature. Then we try and propose a
15 structure that corresponds to each formula. And for
16 chemical risk assessment purposes, we might try and want
17 to estimate some type of concentration, which is difficult
18 when we don't have standards. And if there's a potential
19 health issue, we might try and identify the source of that
20 for risk mitigation purposes.
21 So this is just a general workflow and you're
22 going to hear a lot of different approaches to doing NTA
23 in the talks later this afternoon. But I wanted to point
24 out there's at least four really good reasons to do NTA.
25 Number one, we can rapidly screen for known compounds. So

1 I think June-Soo presented a few moments ago that they
2 screen for about 3,000 compounds. We actually screen for
3 about 850,000 compounds right now. And some laboratories
4 screen for in the millions of compounds. So this type of
5 workflow allows us to do that rapid screening of knowns.
6 We can also discover unknown compounds. We're
7 going to hear about this in Dr. McCord's presentation
8 next. These are compounds that don't exist in a database
9 and may not even be known to exist. So this is a good
10 mechanism for identifying those new compounds.
11 Also, as we heard about in one of the last
12 presentations, we archived this data. So while we might
13 not have the best possible methods and workflows right
14 now, we store this data on hard drives. We can always go
15 back in time and reassess the data and uncover historical
16 exposures.
17 And finally, we can look at all this data in
18 aggregate and we can try and identify specific source
19 fingerprints for things like air pollution, or water
20 contamination, or maybe even disease states. So these are
21 four reasons that we really like doing NTA. There's many
22 more and I'm sure you're going to hear many good examples
23 through this afternoon's presentations.
24 --o0o--
25 DR. SOBUS: So NTA has really taken off over the

1 course of the last say five or ten years. And there's
2 been a lot of different commentary and viewpoint articles.
3 I've read most of them and I found a couple quotes in
4 these two articles particularly interesting. One quote
5 came from an ES&T viewpoint article from Ron Hites and
6 Karl Jobst. And they said that, "No single analytical
7 technique is suitable for the analysis of all compounds
8 and that successful non-targeted screening will require
9 the development of multi-platform approaches, facilitated
10 and validated through interlaboratory comparisons". I
11 couldn't agree with this quote more and that's exactly
12 what I'm going to be talking about today.
13 The second article comes from Chris Higgins'
14 group out of the Colorado School of Mines. This was
15 published in Science of the Total Environment. And they
16 commented that, "The novelty of non-targeted analysis,
17 particularly its current lack of implementation by
18 regulatory agencies, has prevented the establishment of
19 streamlined quality assurance and quality control
20 procedures".
21 So I like this quote, but I personally think it's
22 a little bit backwards. I think it's the lack of QA/QC
23 procedures and performance benchmarks that's caused a lack
24 of implementation by regulatory agencies. So that's the
25 real driver for the work that I'll be presenting on today,

1 trying to come up with some type of performance benchmarks
2 in thinking about how we can get a handle on QA/QC
3 procedures.
4 --o0o--
5 DR. SOBUS: So we've been thinking about this now
6 for over five years. And we've had several workshops at
7 EPA. And a lot of the research that we've done and
8 planned has focused on these five key science questions.
9 We know that there's lots of different methods and tools
10 for doing this type of NTA work. So how variable are the
11 tools and how variable are the results from lab to lab.
12 Given that there's so many different ways of
13 doing this, are some methods and workflows better than
14 others? To what extent does sample complexity affect
15 performance? Can you be really good working in one medium
16 and perhaps not so well working in another medium? Can we
17 evaluate and perhaps even predict the chemical space that
18 a given method might cover? And then finally, do we have
19 the adequate sensitivity and specificity with the current
20 instruments and tools to identify with confidence
21 contaminants of emerging concern?
22 So these five questions were the real science
23 drives behind the ENTACT project.
24 --o0o--
25 DR. SOBUS: So ENTACT is a little bit different

1 than many other interlaboratory trials. I think it's
2 actually a bit complex. We've actually developed it in
3 three parts. For part one of ENTACT, shown here on the
4 left-hand side, we started with about 1,200 of our ToxCast
5 chemicals. So these are chemicals that we procured in our
6 toxicity forecaster project. There's about 5,000
7 chemicals in total right now. These are chemicals that
8 are of high interest to the agency for risk purposes,
9 either for humans or ecological species.
10 Here, we took 1,200 of those 5,000 compounds, and
11 these were the highest quality compounds. This means they
12 were very pure and they were very stable. And we put them
13 in ten synthetic mixtures with about a hundred to four
14 hundred chemicals per mixture. We pulled together about
15 36 -- about 30 research organizations and we asked those
16 research organizations to do a blinded analysis, using the
17 non-targeted analysis method or methods of their choosing
18 to try and determine what's in these samples.
19 Once they performed their blinded analysis and
20 sent results back to us in a standardized template, we
21 would unveil the chemical lists only to that group one at
22 a time, and they would perform a final unblinded
23 evaluation and report back to us their final findings. So
24 this is ENTACT part one and this is really what I'm going
25 to be speaking about today. But we realized that we have

1 a bit of a blind spot here, because we're working entirely
2 in synthetic mixtures.
3 So for part two of ENTACT, which I really won't
4 have time to get into today, we're working with actual
5 matrices. So we wanted to work with something that was
6 well characterized using existing targeted methods. So we
7 picked standard reference material house dust from NIST,
8 standard reference material human serum from NIST, and
9 then we had reference silicone wristbands made under
10 contract with a university.
11 So here, we can compare the performance of a
12 non-targeted analysis method with previous performance of
13 targeted methods that have been used for years and
14 reported in the literature. But we also wanted to examine
15 things like extraction efficiency. So to do that, we took
16 one of the synthetic mixtures and actually spiked each of
17 these different media and then we provided laboratories
18 with extracts of these fortified materials.
19 So when all is said and done, all the
20 participating labs were given the option to get the ten
21 mixtures, the three extracts of the reference materials,
22 and the three extracts of the fortified reference
23 materials. So that's ENTACT parts one and two.
24 --o0o--
25 DR. SOBUS: ENTACT part three was basically, at

1 the time we had 4,600 ToxCast substances. We individually
2 plated all of these substances and gave them out to a
3 select grouping of instrument and software vendors, as
4 well as a few select laboratories for the explicit
5 purposes of doing MS/MS analysis or MS to the N analysis,
6 and generating reference spectra to be made available to
7 the public. So this is part three. It is ongoing.
8 --o0o--
9 DR. SOBUS: Again, I'm going to be spending the
10 bulk of my time talking about the mixtures today and I
11 really wanted to spend a few moments talking about the
12 strategy and how we designed these mixtures. So again,
13 there are ten unique mixtures. They're numbered 499
14 through 508. You can see here that we have -- the first
15 four mixtures have 95 compounds, the next two have 185
16 compounds, the next two have 365 compounds, and then we
17 have these last two mixtures that I'll talk about in just
18 a moment.
19 Again, we wanted to understand how the complexity
20 of a sample affects performance. And we also wanted to
21 understand things like reproducibility. So to get at
22 reproducibility, we had to have a substantive compound
23 that were spiked across many mixtures. So you can see in
24 these tiny blue bars, there was actually five compounds
25 that we spiked in all ten mixtures.

1 Then we have, what we called, Grade A replicates.
2 This was a set of 90 compounds that were spiked in one of
3 the mixtures with 95 compounds, one of the mixtures with
4 185 compounds, and one of the mixtures with 365 compounds.
5 So here, we can see if the size of the mixture
6 actually impacts performance on these compounds that were
7 spiked across replicate mixtures. Okay. So this is
8 starting to allow us to get at answering the complexity
9 issue, but we wanted to make even more complex.
10 So we decided to include sample 507 and 508. You
11 can see that 507 is a small mixture. It's 95 compounds,
12 but we included lots of isomeric compounds, so compounds
13 that share the same chemical formula, as well as isobaric
14 compounds. These are compounds that have very, very
15 similar monoisotopic mass. All of the first eight
16 mixtures had very, very few isomers and isobaric
17 compounds, whereas 507 was almost entirely isomeric and
18 isobaric compounds.
19 Then we went crazy with mixture 508. This had
20 365 chemicals, it had tons of isomers and isobars, and it
21 actually had lower purity compounds. So we have a
22 suspicion that there's going to be compounds in this
23 mixture that we did not intentionally add due to the lower
24 purity.
25 --o0o--

1 DR. SOBUS: So in addition to designing the study
2 and managing the study, we also took part in the analysis.
3 So we have now done several different analyses, and the
4 work that I'm showing here is based on our first
5 publication. So this work was entirely derived from an
6 LC-QTOF high resolution mass spectrometer run in both
7 positive and negative electrospray ionization.
8 You can see here on the upper plot, this is
9 what's called a bubble plot. So each little gray bubble
10 represents an observed feature or a peak that I showed on
11 my first slide. So the intensity of the -- the intensity
12 of the feature or the size of the peak is actually
13 displayed as being proportional to the size of the bubble.
14 So the bigger the bubble, the more intense the peak. We
15 then have the retention time of the feature on the X axis
16 and the mass on the Y axis.
17 So you can see that even though we spiked 1,200
18 compounds, when we looked across all ten mixtures, we
19 actually found 26,000 observed features, so 20 times more
20 features observed than were spiked. So clearly, not all
21 of these are real. Some are noise and artifacts and other
22 derivative features.
23 So we implemented a data processing strategy.
24 And we tried to identify things that we believe to be
25 noise or artifacts and things that we believe to be real.

1 When all was said and done, the things in gray in
2 the middle plot are the noise or artifacts, and there was
3 about 14,000, and the things in yellow we believe to be
4 real. We took those 12,000 real features and compared
5 them to the spiked substance lists and ultimately found
6 about a thousand true positives, which leaves 11,000 other
7 things.
8 Now, we don't know if these are actually false
9 positives or perhaps true positives that just weren't
10 deliberately spiked, that is an unresolved question that
11 would require much more additional analysis. But we can
12 take the results of our investigation and we can begin to
13 examine performance using things like a confusion matrix.
14 So here, we have whether the substance was spiked
15 versus whether the substance was identified. And we can
16 see we had a true positive rate across the ten mixtures
17 that maximized at 65 percent and we had a false negative
18 right -- false negative rate that got down as far as 35
19 percent.
20 So we can begin to assess performance with these
21 two metrics, true positives and false negatives. But
22 again, it's very difficult to get a handle on the false
23 positives, because there may be impurities. There may be
24 degradation products. There may be things in here that
25 are real that are being correctly identified. But since,

1 we didn't put them in there deliberately, it's very hard
2 to know whether or not they're actually there.
3 And then true negatives present another tough
4 issue. These are the things that we didn't put in that we
5 didn't see. How do we determine what could be a true
6 negative? Do we use a list of 5,000 compounds, 50,000
7 compounds, five million compounds? The size of the list
8 is going to impact the number of true negatives.
9 So these two things make it very difficult to
10 complete the true full confusion matrix.
11 --o0o--
12 DR. SOBUS: So in addition to the work that we've
13 done, as I said, there's about 30 other participants. We
14 have six contract laboratories. We have six vendor
15 laboratories who are analyzing the full 4,600 chemicals on
16 multiwell plates, and then we have our general
17 participants.
18 So 30 participants, very few of them are using
19 one particular method. Many of them are using two or more
20 methods, like we did positive and negative electrospray
21 ionization. To date, we've gotten blinded submissions
22 from 19 different laboratories and the full unblinded
23 submissions from 15 laboratories.
24 So from the standpoint of mixtures analysis,
25 we're about halfway there on getting the data submitted to

1 us. Given the timeframe and how long it's taken for these
2 analyses to be completed, we've move forward with doing
3 the cross-laboratory evaluation with the data in-hand.
4 --o0o--
5 DR. SOBUS: So this is actually a very difficult
6 thing to do and it takes me quite a while, even though we
7 issued standardized templates, to process the data
8 submitted by each individual laboratory.
9 The first thing that we do is I'm not trying to
10 gauge an individual laboratory's performance. I'm trying
11 to gauge method performance. So if a laboratory submits
12 multiple submissions based on different methods, I'm going
13 to treat them separately. Another thing, some
14 laboratories submit multiple guesses per feature. I'm
15 adamant that we get one guess per feature. So I have to
16 do some data cleaning and ask for the best guess at the
17 mass, formula, and compound level for each method.
18 Also, we've heard about the Schymanski et al.
19 confidence levels. I have found that across many
20 laboratories, a lot of time confidence levels are not
21 necessarily being reported appropriately. And through
22 discussions, we've had to revise those confidence levels
23 on several cases.
24 Once I generate a clean file for each laboratory,
25 I can then match what was submitted and cleaned against

1 the spiked substances at the mass, formula, and structural
2 level. I'm here looking for three metrics. I'm looking
3 for the number of compounds that I believe that method
4 observed. So this is if they correctly identified the
5 structure or correctly identified the formula when the
6 compound was not spiked along an isomer.
7 There is some evidence the compound may have been
8 observed if we get a mass hit. But in my opinion, that's
9 not enough evidence to support an, observation so I'm
10 calling that -- I'm putting that in a separate bin and
11 basically calling that undetermined for the moment. So
12 it's observed if it was a structure match or a formula
13 match not in the presence of a spiked isomer.
14 The compound was identified if it's a structure
15 match. And the compound was reproducibly identified, if
16 it was correctly identified at least 50 percent of the
17 time. So this reproducibility metric is only relevant for
18 things that were spiked more than once and correctly
19 identified at least one time.
20 --o0o--
21 DR. SOBUS: This is kind of the overall view of
22 how the methods stack up against each other. So this is a
23 heat map, where we've got the 1269 compounds on the Y
24 axis, the individual methods on the X axis, and you can
25 see here that I've grouped all the LC ESI positive methods

1 together. I've grouped all the ESI negative methods
2 together. And then we have a hybrid method, which used a
3 very different approach. And then we have a GC EI method.
4 And you can see that the individual cells are colored
5 purple if the compound was not observed, and yellow if the
6 compound was observed.
7 So for the ESI positive LC methods, the percent
8 of observed compounds ranged from 42 to 69 percent. For
9 the ESI negative, the observed compounds ranged from 21 to
10 39 percent. And then we have a 48 percent observation
11 rate for the hybrid method and a 62 percent observation
12 rate for the GI -- the GCEI method. You can see some
13 similarities in performance when you kind of look within
14 method grouping. The ESI positive methods do definitely
15 have some trends. The ESI negative methods do have some
16 trends.
17 But when you look at the totality of this image,
18 you can see drastic differences in what was observed
19 across the different methods. What's fascinating to me is
20 to kind of look at the top purple rows. And this
21 basically shows the number of compounds that were not
22 observed by any method. And basically, we have five
23 percent of the compounds overall that could not be
24 observed by any method. So this is a fairly small number,
25 which is -- is really good to see.

1 When we look across the bottom row, we can see
2 that we have actually fewer than one percent that was
3 observed by all 12 methods. So this is a very, very small
4 number. When all is said and done, it was really only
5 four compounds to date that have been observed by all
6 methods.
7 --o0o--
8 DR. SOBUS: So this is perhaps the most important
9 slide. This is a method comparison looking at total
10 performance across ten methods that I've fully examined to
11 date. So there's three metrics that I want to talk about
12 here. This is a bubble plot. So here, each individual
13 bubble represents one method from one laboratory.
14 The diameter of the bubble represents the total
15 coverage represented as a percent. So, for example, this
16 bubble down here has a coverage of 0.69, which means they
17 were able to observe 69 percent of the compounds. The X
18 axis is the precision metric. This is basically how often
19 they were able to correctly identify a compound. This is
20 the ratio of the percent identified divided by the percent
21 observed.
22 So if a particular method observed a hundred
23 percent of the compounds and correctly identified 90
24 percent, the precision would be 90 percent. Likewise, if
25 a given method observed ten percent of the compounds, and

1 correctly identified nine percent of the compounds, their
2 precision would also be 90 percent. So here, I'm
3 basically allowing precision to be compared across
4 laboratories, irrespective of the coverage.
5 The final piece is the reproducibility. This
6 says, for chemicals that were spiked more than once and
7 that were correctly identified at least once, how many of
8 them were correctly identified more than half the time?
9 So we can look at some specific examples here.
10 We can see, for example, in the green circle, this was
11 laboratory seven that used the GCEI method. They had a 62
12 percent coverage. They had a precision of over 90 percent
13 and they had a reproducibility of over 80 percent. So
14 overall very strong performer.
15 We see similar results for lab four, LCESI
16 positive. They had tremendous reproducibility. Slightly
17 weaker position and slightly weaker coverage. We have two
18 examples here, where we had good reproducibility, good
19 precision, but you can see the coverage was at 22 percent
20 in each case. And these were actually ESI negative
21 methods, which is known to have less coverage.
22 You can also see this one example down here,
23 where we had great coverage at 69 percent, but we had a
24 precision of seven percent and a reproducibility of seven
25 percent. So ultimately, we would like to see groups up

1 here in this upper right quadrant with as big a bubble as
2 possible

3 --o0o--

4 DR. SOBUS: So we need to think about how we give
5 these metrics back to the participating labs and how we
6 communicate these results to the scientific public and to
7 the public in general. So this is something that I am
8 proposing for the first time here today. There's
9 basically a visual report out and then kind of a report
10 card numerically.

11 So this is the same bubble plot I showed a minute
12 ago, where we can report to a given participant their
13 method shown in red relative to the performance of all
14 other methods. We can simply enumerate and say you had a
15 95 percent precision. You had an 85 percent
16 reproducibility and you had 62 percent coverage. But no
17 one laboratory is going to do perfect in probably any
18 given category.

19 So we want to give each lab their results in the
20 context of the best performer in each category. So over
21 here, just like you would get results from a medical
22 examination or results from a GRE test, we're giving them
23 their score relative to the maximum score. So for this
24 particular group, their precision was 95 percent of the
25 maximum precision, their reproducibility was 87 percent of

1 the maximum, and their coverage was 86 percent of the
2 maximum. So they were not the best performer in any one
3 category, but they were a very strong performer across all
4 three categories.
5 --o0o--
6 DR. SOBUS: So I don't have time to get into the
7 experiments with dust today. But if you have questions
8 afterwards or during the Panel discussion, I'm happy to
9 address it.
10 --o0o--
11 DR. SOBUS: I also don't have time to get into
12 some of the applications with *in silico* spectra.
13 --o0o--
14 DR. SOBUS: So I'll just wrap it up with my
15 summary slides real quick. I hope I've shown you that NTA
16 methods are very suitable for many ToxCast chemicals.
17 Only five percent of the compounds to date have not been
18 observed by any method. Multiple methods clearly are
19 going to be required for broad characterization. There is
20 no one-size-fits-all method. There probably never will
21 be. And to date, fewer than one percent of the ENTACT
22 compounds have been observed across all methods.
23 Because I can't complete a full confusion matrix,
24 to date, I've examined performance across three
25 categories. Coverage tells us the ability of that method

1 to observe a compound. To date, we see a range of 21 to
2 69 percent, which is a pretty broad range. Precision
3 tells us the ability of the method to correctly identify
4 compounds that have been observed. We see a massive range
5 of 7 to 99 percent for precision. And finally
6 reproducibility tells us the ability of the method to
7 consistently and correctly identify the compound. And
8 again, here we have a massive range of 7 to 97 percent.
9 Although, I didn't get into it today due to
10 timing issues, our results have shown for the SRN dust and
11 serum that the concentration, media, and extraction
12 techniques are going to affect performance. So while
13 these results in synthetic mixtures are highly useful,
14 they would be subject to change in actual media samples.
15 And then finally, while this cross-laboratory
16 examination is incredibly useful, we do a lot of work with
17 these data in-house to optimize our methods. So these
18 data and these samples are still available for those that
19 would be interested in testing their own methods and
20 optimizing their methods.
21 --o0o--
22 DR. SOBUS: So I'd just quickly like to thank all
23 of the contributing researchers at EPA, all of the
24 participating laboratories, and specifically to call out
25 Elin Ulrich who's my co- -- my co-PI on the study, thank

1 her for all of her help along the way, and I'm happy to
2 take any questions.
3 CHAIRPERSON SCHWARZMAN: Thank you so much, Jon.
4 So questions from the Panel first.
5 Oliver.
6 PANEL MEMBER FIEHN: Thank you very much. It's
7 very interesting. Now, as you say, the people have used
8 different methods. Some methods are more -- have more
9 resulting power dynamics. Like a QTOF has less resolving
10 power than a Q Exactive. You can use ion mobility or you
11 cannot use ion mobility. You can use two-dimensional
12 separation or not.
13 Is there anything you want to say about like
14 resolution versus precision coverage and so on?
15 DR. SOBUS: Yes. And I'd say it's premature to
16 say it right now, because I basically looked at 12
17 methods. When all is said and done, we've got 30
18 laboratories, probably with a mean of two methods per lab,
19 so that's going to be 60 data sets I have to get through.
20 When all is said and done, I'm very comfortable we're
21 going to be able to make recommendations like ion mobility
22 is really helpful or resolution is really helpful.
23 I am starting to see trends. I don't want to
24 necessarily speak definitively at this point, because it
25 is a small sample set, but yes, I do believe what will

1 come from this -- one of many things that will from this
2 is those hard recommendations of this is going to get you
3 in a better place based on the performance metrics that
4 we've laid out.
5 CHAIRPERSON SCHWARZMAN: Other questions from the
6 Panel?
7 Tom.
8 PANEL MEMBER McKONE: Thank you, Jon. That was
9 really interesting. I'm really fascinated by the
10 opportunity of like the non-targeted to really discover
11 things that we weren't looking for. I guess -- the
12 question I have is ultimately it's probably useful to know
13 what you're looking for. And I'm kind of reminded of,
14 there was a paper a number of years ago by Phil Howard and
15 Derek Muir, where they went -- they just basically looked
16 at chemicals in production and looked at chemical
17 properties, and made estimates of chemicals that we've
18 never put on a list that we probably should be looking for
19 because they were persistent, you know, based on chemical
20 property.
21 So it was kind a forward-looking saying this
22 is -- and indeed, once they published the paper, people
23 went out and looked, they did find those chemicals,
24 because they made specific recommendations. But this idea
25 of sort of -- sort of shining a light into saying, well,

1 what should be out there that we're not seeing and then
2 doing these sort of tailoring the non-targeted analysis,
3 the combination of the two might end up being very
4 powerful, you know, for finding the things that we're not
5 dealing with currently.
6 DR. SOBUS: It is. And we really take that into
7 consideration. I certainly didn't have time to get into
8 it today, but we use a ton of molecular modeling, and
9 exposure modeling, and pharmacokinetic modeling to try and
10 determine compounds that are likely to be prevalent, and
11 for which we would see higher exposures. And then we also
12 build models to say which methods would be amenable to
13 observing those particular compounds.
14 So if we screen for them on a large library and
15 we see them as candidates, we can use that information to
16 say this structure is potentially more likely -- based on
17 exposure potential, this structure is probably more
18 likely, based on the fact that its structure is amenable
19 to the method that we're using here.
20 So much of what I've shown today is the tip of
21 the iceberg in terms of what we actually use to do
22 substance identification. But you're exactly right that
23 this stuff for exposomics applications should not be done
24 in a silo, thinking about mass spectrometry, it needs to
25 consider information from the outside world.

1 PANEL MEMBER McKONE: Great. No, that's really
2 good to hear. So you're not just going into the dark.
3 You actually have some -- some little twinkly lights that
4 tell you where you wanted to go.
5 DR. SOBUS: We try and be -- we try and be very
6 intelligent and bring hazard data, exposure data, and use
7 kind of ratios of the two for -- to kind of identify which
8 chemicals are of greatest interest from a risk
9 perspective, and then we try and, to some extent, kind of
10 direct a non-targeted analysis towards that chemical
11 space.
12 PANEL MEMBER McKONE: Really good. Thanks.
13 CHAIRPERSON SCHWARZMAN: Eunha.
14 PANEL MEMBER HOH: Eunha Hoh from San Diego State
15 University. Hi, Jon. I have a couple of questions
16 that -- it's great work. I can't imagine how much you can
17 present from the work. It's variable data that is
18 fascinating.
19 One question was that I was fascinated by that --
20 the graph that you showed us the coverage, the observed
21 and identified. But the five percent of the compounds,
22 did you find them, any common things among those
23 compounds? And if --
24 DR. SOBUS: Yeah, I actually meant to. I meant
25 to say something about that. The truth is I haven't dove

1 into it, because I put this together fairy quickly. But
2 one of the things that, at least in our analyses, that
3 showed up as being missed were the quaternary ammonium
4 compounds that had a permanent positive charge. We
5 typically misassign the mass, when we're using
6 electrospray in positive or negative. And we fell victim
7 to that, and I think several other people did, so that's
8 one good example of a specific chemical class that people
9 are likely to miss using LC-EIS methods.
10 I think there's other similar things and then
11 there's going to be subsets of things that either we
12 thought they were pure and stable and they weren't or when
13 we put them in a mixture with 364 other things, they
14 interacted and turned into something else.
15 So as we -- I don't want to dig too deep right
16 now, because we're going to keep adding results. And that
17 number is going to keep going down. But when we finally
18 get to that baseline number, we are going to dig deep and
19 say why did nobody get these right?
20 PANEL MEMBER HOH: So second question, Jon, is
21 more like comments. Maybe you can think -- you probably
22 thought about that too. But, you know, the lab -- the
23 individual lab like have specialties in certain chemicals
24 groups as targeted analysis. They could have like more
25 knowledge in certain chemicals probably not the other

chemicals, you know. So there might be the variability
possibly to, you know, affecting the results, too.

DR. SOBUS: Right. Right. And it's -- it's
really -- there's so many layers to this that it's
really -- you know, it kind of fries your brain, but your
point is well taken that I've had many level one
classifications submitted that were not spiked substances.
So I haven't even really treated all of these other highly
confident identifications that were not spiked right. But
clearly, in seeing those types of results, that makes your
point that different groups have different specialties.

As I go through this, I'm trying to be as fair
and unbiased as possible to try and, you know, implement a
universal approach. And if I get too far down and see
that something that I implemented can't be universal, I
have to go back and figure out something that is universal
and reimplement, which I've now down four times. So it is
very, very difficult to do.

PANEL MEMBER HOH: Um-hmm.

CHAIRPERSON SCHWARZMAN: John I had just one
question and then we're -- we'll need to move on, which is
I was really -- my ears kind of perked up at the -- your
first slide, one of the four points about what is so
useful about non-targeted analysis is the ability to look
at historical exposures or make comparisons within

1 historical exposures.
2 And I was just really struck by the potential for
3 doing that and -- and whether doing this kind of analysis
4 and storing the data might ultimately -- maybe not now,
5 but ultimately make it possible not to even have to store
6 the matrices.
7 DR. SOBUS: That's an interesting thought.
8 That's an interesting thought. So I would say a couple
9 things on that. One is we have research centers that run
10 thousands of samples, if not per month, per year, and they
11 can only go so deep in the analysis, and that data gets
12 stored.
13 Two, we do analyses very quickly. To the extent
14 that those methods are solid and the data are collected
15 with care and stored with care, that's a great point, that
16 if -- if we were to come out of something like ENTACT and
17 say this number of methods gives you appropriate coverage
18 to get 95 percent of the chemical universe of interest for
19 these types of applications, conceivably you could run
20 that number of methods, run it well, have QHX store the
21 data, and then not have to store the samples. That is
22 conceivable.
23 CHAIRPERSON SCHWARZMAN: Thank you for
24 entertaining the idea. Thank you so much for your
25 presentation. We really appreciate it and we're going to

1 move on to our next presenter.
2 So I want to introduce James McCord, who's a
3 chemist in the Multimedia Methods Branch of the Center for
4 Environmental Measurement and Modeling at U.S. EPA. His
5 research uses non-targeted analysis and high resolution
6 mass spectrometry to identify and characterize novel and
7 emerging contaminants. He will be presenting on
8 "Multimedia Exploration of Emerging PFAS and Their
9 Sources".
10 (Thereupon an overhead presentation was
11 presented as follows.)
12 DR. McCORD: Thank you. Thank you. Can everyone
13 see?
14 CHAIRPERSON SCHWARZMAN: Yep.
15 DR. McCORD: All right. Excellent. So thanks
16 for the introduction. As explained, I'll be presenting on
17 the multimedia exploration of emerging PFAS and sources.
18 So I am applying non-targeted analysis as part of
19 our broader PFAS efforts. So non-targeted analysis is, in
20 many cases, sort of the beginning or one small part of
21 large biomonitoring and exposure assessment activities
22 that we're doing in association with states and regions.
23 --o0o--
24 DR. McCORD: So historically, PFAS usage has been
25 investigated by targeted LC-MS techniques. And there has

1 been a historical effort to ban and replace certain PFAS
2 chemicals species with new replacement compounds with a
3 variety of different chemistries. And non-targeted
4 analysis allows us to expand beyond the simple targeted
5 historical list to identify a lot of these replacement
6 compounds as Jon just described.
7 --o0o--
8 DR. McCORD: So what I mean by this, if you're
9 looking at things like PFOS and PFOA, whose structures are
10 shown here, these are some of the most historically
11 prominent PFOS -- or PFAS and they've been banned in their
12 primary application. In fluoropolymer manufacturing, PFOA
13 has been replaced by a series of compounds. In metal
14 plating, where PFOS was widely described, it's also been
15 replaced.
16 Many of these are still perfluorinated compounds,
17 but they introduce novel chemical moieties. In some
18 places, fluorines are removed or replaced by hydrogens.
19 In others, they're introducing ether linkages that are
20 designed to make the compounds less persistent, and then
21 they're also adding other halogen species for a variety of
22 reasons that are discussable.
23 --o0o--
24 DR. McCORD: So this, within the context of our
25 beginning discussion, gives us a driving research question

1 for a lot of states and other regions, which is, in places
2 where there's historical PFAS usage, are we seeing
3 replacement compounds present the same sort of
4 distribution profiles and how can we identify and monitor
5 these compounds to help with source attribution and to
6 sort of set the stage for follow biomonitoring and
7 toxicity assessment.
8 --o0o--
9 DR. McCORD: So to somewhat rehash what Jon went
10 through, we see this as being a tiered approach to
11 chemical measurement. So the classic tried and true
12 methods are the use of targeted approaches for selected
13 chemicals with available reference data and chemical
14 standards. This is a straightforward method, if not
15 always simple, but you can get good quantitative
16 information on a list of analytes. Normally, this is
17 using some sort of targeted LC-MS triple quad type
18 approach.
19 There's also screening approaches, which have
20 been discussed by a number of people today, when you have
21 a very large or smaller chemical library and you apply
22 general non-targeted type approaches and then you screen
23 against a reference library. In this case, you're still
24 somewhat limited by the reference library that you have
25 and how much data is available in those reference

1 libraries, whether it's structural, or just a chemical
2 formula, or sometimes MS/MS data, but you're not going to
3 be making assumptions about exactly what you're looking
4 for before you process the sample.
5 The majority of my work is done in the sort of
6 discovery space. So we're looking for the things that, in
7 one of the presentations, discussed earlier the large
8 unidentified screening space, where sizable fraction of
9 the chemical features that are identified have no known
10 structure or no confirmed structure. So in many cases,
11 we're working with things that are not described at all,
12 don't exist in reference libraries and there may be one or
13 two references in patent literature or no references at
14 all in order to identify that chemical feature.
15 So our workflow is very similar to what screening
16 does and what Jon just described.
17 --o0o--
18 DR. McCORD: So we begin with the data
19 generation, collecting non-targeted data on normally a
20 high res instrument. We do molecular feature extraction
21 to identify individual molecular features. Here's a whole
22 bunch of chromatograms stacked up on top of each other.
23 You can pick one. You can, using high res
24 instrumentation, do formula assignment. And from a
25 particular formula, you can begin to either draw chemical

1 structures from databases or your own estimation. For
2 example, here, we have a bunch of different compounds that
3 all share the came chemical formula.
4 And then using a list of tentative structures,
5 you can do structural confirmation using MS/MS, MS to the
6 third, interesting gas phase experiments, depending on
7 your instrumentation. Then once you have a structure, you
8 can start to think about quantitation.
9 Typically, for non-targeted analysis quantitation
10 is relative. Sometimes we will do estimated absolute
11 quantification using non-matched standards, which is
12 always a little bit sketchy in terms of analytical
13 reproducibility.
14 --o0o--
15 DR. McCORD: So I'll talk about a few case
16 studies. So historically, the Cape Fear River of North
17 Carolina, which is very close to where I live and work, is
18 a place where PFAS has been known to be a major
19 contaminant. So this watershed affects roughly five
20 million residents, including the City of Wilmington, North
21 Carolina, down here at the end of the Cape Fear.
22 There's a couple of rivers that make it up. And
23 this study going back to 2007 did, as I said, targeted
24 analysis of the underlying watershed. So they're looking
25 for a series of legacy compounds, both carboxylic acid and

1 the sulfonates, sampling all of the major watersheds, and
2 identifying hot spots for PFAS levels.
3 So in the Haw River in the northern part of the
4 watershed, there is high levels of C10, 9, and 8. Towards
5 the middle of the Cape Fear, there's a spike of C7, a
6 little bit of C6. And then on the Little River, there's
7 an elevated level of PFAS. And if you start to
8 investigate the sources for all of these, they could be
9 assigned to historical manufacturing in the Haw River and
10 biosolids application. This location at five in the Cape
11 Fear is associated with fluoropolymer manufacturing. And
12 then the Little River is down water stream of both an
13 airport and a military base. So there's historical AFFF
14 usage in an airport.
15 So this is sort of how you map out historical
16 contamination using targeted approaches. So the follow-up
17 to that is to do non-targeted analysis and try to identify
18 what replacement compounds or other things there might be.
19 So this paper in 2015 was using a TOF instrument,
20 so a somewhat older high res instrument by just doing
21 sampling down the river and then comparing the appearance
22 of chemical features between different samples to assign
23 them to a source that occurs in the middle.
24 --o0o--
25 DR. McCORD: So if you sample upstream and

1 downstream of a factory, and you identify pronounced peaks
2 in the downstream sample that are in the upstream sample,
3 you can start to assign them to a source.
4 So you collect a bunch of surface water, do your
5 sample preparation, do your feature extraction as
6 described, and in this particular instance, we were able
7 to identify one compound with a reference standard, which
8 is somewhat unique. This is GenX, which was a chemical
9 that's sold by the Chemours company. And there were a
10 number of other chemicals that didn't have any reference
11 data or any compounds that could be used to quantify them.
12 Most of them, mono and polyethers, as well as
13 some sulfonates with structures that kind of look like
14 this. So they're perfluorinated compounds with the
15 variations that I described in an earlier slide.
16 --o0o--
17 DR. McCORD: So to follow up on that, we look at
18 not just the service water, but also the drinking water.
19 So here, we have three drinking water facilities along the
20 Cape Fear River, where they're drawing their intake from
21 the Cape Fear, and if you do targeted analysis on legacy
22 compounds and then also the single individual compound
23 that we were able to obtain a reference standard for, you
24 can see upstream of the Cape Fear where you have
25 historical contamination of legacy PFAS they're somewhat

1 high. But then as you move downstream, the legacy
2 contaminants drop off and the emerging contaminants
3 drastically outpace them.
4 So this is the only compound that we could do
5 targeted analysis for at the time. And if you do
6 non-targeted analysis on the same sample and you compare
7 raw spectral abundance, which is a very loose
8 approximation of chemical concentration, you can see that
9 very abundant targeted compound is the minority of the
10 chemical abundance compared to other emerging PFAS in
11 these drinking water facilities at places that are
12 affected by fluorochemical manufacturing.
13 --o0o--
14 DR. McCORD: So the State of North Carolina
15 started an extremely intense investigation of this
16 compound, which sort of became the face for it. It was
17 involving both the Department of Environmental Quality and
18 the Department of Human Health. We were brought in as
19 sort of the technical support to do a lot of the sampling
20 and analytical work associated with that investigation.
21 This is both targeted and non-targeted experiments as part
22 of an ongoing study.
23 So the very first thing that they did was to shut
24 off the outfall from the specific GenX manufacturing line
25 and then we started doing repeated continuous sampling

1 over the course of the next several months, developed some
2 methods, and so on. And it's still undergoing litigation.
3 --o0o--
4 DR. McCORD: So what we were able to do was,
5 using MS/MS, we could assign structures to a number of
6 unique chemicals that were being emitted. And it turns
7 out that the company was aware of these chemicals and even
8 had names for a lot of them. So some of the major
9 versions are shown here. These are just the most abundant
10 ones from each of the different chemical classes. And
11 then our sampling over time, even though we can't quantify
12 any of these species originally, we can just track their
13 abundance in non-targeted analysis. And we could show
14 that when you shut off one particular manufacturing line,
15 certain chemicals would drop off, but others would either
16 stay constant or even spike as they're changing over
17 manufacturing lines.
18 And ultimately, the State decided that they
19 needed to start sending all of their outfall to another
20 location, because every single manufacturing process that
21 they were performing was emitting PFAS into the river. So
22 to reference something that Meg had asked earlier, we
23 actually did have historical sampling from data that was
24 collected as far as back 2010 that had been done with
25 non-targeted analysis, and we were able to see some of

1 these compounds going back well before this sample, just
2 from looking at the raw data. No stored samples.
3 --o0o--
4 DR. McCORD: So following the analysis of those
5 samples and the identification of a lot of those
6 compounds, NC State led a collection for a bunch of serum
7 asking if these emerging PFAS were in the exposed
8 population in Wilmington. They were able to get 344
9 participants total, about 44 of whom were able to provide
10 multiple samples. And eventually, the State was able to
11 pressure the company in order to provide analytes so that
12 we could do targeted analysis.
13 --o0o--
14 DR. McCORD: So just doing screening on the human
15 serum, we were able to identify three of the emerging
16 contaminants. They were in the river water. And because
17 we were able to obtain standards, we could quantify for
18 them and show decreasing serum levels after the emissions
19 were shut off.
20 The half-lives for many of these compounds are
21 shorter than things like PFOA and PFOS, but still quite
22 long, months to years.
23 --o0o--
24 DR. McCORD: So in total, Chemours eventually
25 provided the 12 novel compound standards that they had

1 names for to us, NC State, DEQ. And they were able to
2 identify a drinking water target for GenX specifically
3 based on some reference data, both in Europe and in
4 America. NCDHHS performed that analysis. And there's a
5 reference if anyone is interested. And there's a current
6 consent order in Chemours where they monitor the list of
7 compounds that were identified in Mark Strynar and my
8 follow-up non-targeted list showing the major compounds
9 are reduced in their permission -- in their emissions.
10 And then they've installed air emissions controls
11 as well, because we only examined water, but there is the
12 belief that the air is providing a widespread
13 contamination of the immediate surrounds. So that's
14 ongoing, but it involves non-targeted analysis.
15 --o0o--
16 DR. McCORD: In New Jersey, we have a similar
17 sort of case study. So New Jersey has historical
18 contamination of PFOA and PFNA, which are drastically
19 higher than other places in the nation, based on UCMR data
20 and their own studies. And it's believed to be one of the
21 most PFNA contaminated locations in the world, because of
22 historical manufacturing and West Deptford. So there's
23 both air and water contamination that they performed
24 studies on. And because they've identified legacy PFAS,
25 we follow up with non-targeted analysis.

1 --o0o--
2 DR. McCORD: So we did a non-targeted analysis
3 multimedia sampling campaign. So in this region of
4 south -- southwestern New Jersey, we collected soil,
5 surface water, and well water. DEP was interested in
6 knowing whether there was replacement PFAS, and if we
7 could identify legacy and emerging PFAS with their
8 fingerprints that could be used to assign a specific
9 source.
10 --o0o--
11 DR. McCORD: So we were able to identify a bunch
12 of legacy compounds, which I won't talk about, but we did
13 find a novel emerging contaminant, which is shown here.
14 Structurally, we were able to identify it based on MS/MS.
15 This is an MS/MS spectrum. Each of the compounds is a
16 fragment of that parent molecule in the upper right, shown
17 here with their accurate mass and the nice chlorination
18 pattern, which indicates that they're halogenated.
19 And we are actually able to identify a whole
20 family of these compounds, because it's produced by a
21 polymer manufacturing process. So they're perfluorochloro
22 polyether carboxylic acids, so we call CLPFECAs, and then
23 they have a variety of internal linkers here. So they
24 were seen in both soil and water in a mix of polymers.
25 And we see both the chlorinated and the de-chlorinated

1 analogs.
2 Like in North Carolina, we're unable to do
3 quantitation. So in the domains where they asked us to
4 give the estimated concentrations, we quantify it as PFNA,
5 because it's something that is regulated, they have a
6 standard for it, and their predicted physiochemical
7 properties are fairly similar. So all the figures that
8 I'll show are either estimated concentrations or they're
9 just based on raw NTA abundance in the mass spectrometer,
10 which again is just a loose parallel for concentration.
11 --o0o--
12 DR. McCORD: So in the water, we are able to show
13 that 99 percent of the abundance and the estimated
14 concentration is associated with a single isomer. And
15 it's found in both the tidally influenced surface water,
16 which is everything that connects to the Delaware River.
17 Because it's tidally influenced, you get back-flushing up
18 even minor tributaries, but that there's also groundwater
19 contamination in a lot of these sampling locations. And
20 their exact locations don't matter very much. But the
21 general trend is that things that are close to the
22 factories that are using this compound are highly
23 contaminated.
24 --o0o--
25 DR. McCORD: In the soil, we see a very distinct

1 trend. So if you quantify and estimate the concentration
2 of all of these different compounds in soil and then you
3 do some GIS based mapping and modeling, you can show this
4 almost bullseye pattern around a specific fluorochemical
5 user in the location.
6 So Chemours was the factory in North Carolina
7 that was responsible for most of its contamination, here
8 Solvay is using a different product that we were able to
9 associate very specifically with them. And we have reason
10 to believe that it's emitted on an air basis, or at least
11 this pattern is from air deposition, even though there's a
12 substantial amount of effluent that's going directly into
13 the Delaware River and impacting it.
14 --o0o--
15 DR. McCORD: So just like in North Carolina,
16 because there's groundwater contamination, they're
17 interested in human exposures. So because there are PFNA
18 contaminant levels that are regulated in the state, many
19 of the people who live in the neighborhoods and areas
20 around these factories, they have these point-of-entry
21 treatment systems for water treatment of drinking water.
22 So they have these two-stage POET systems, where
23 it's either granular activated carbon or an ion exchange
24 resin. And we were able to do sampling in 2019 of both
25 the ground influent water that's going into these POET

1 systems, as well as the effluent water that's being
2 delivered to drinking. And we could show that PFNA is
3 reduced by the anticipated amount. It's not 95 percent or
4 more.
5 And then doing non-targeted analysis you can show
6 that the abundance or estimated concentration at these
7 influent steps decreases a similar amount. So the same
8 treatment technologies that have been applied for PFNA in
9 this region also seem to be good at reducing the levels of
10 the emerging contaminants.
11 --o0o--
12 DR. McCORD: So in this particular instance, we
13 were able to show that those in-place treatment systems
14 are protective for both PFNA and the emerging compounds.
15 And there's ongoing litigation to try to obtain similar
16 stock materials for quantification -- real quantification,
17 like was done in North Carolina.
18 There's also litigation about the level of
19 liability for cleanup, and the actual amount of emissions,
20 and a number of other legal issues that's still ongoing.
21 Unlike in North Carolina, we haven't yet been
22 able to institute any biomonitoring. However, it's been
23 discussed that it will be added to an ongoing serum
24 monitoring that's being proposed in that region. And it
25 would also be a non-targeted serum screen.

1 --o0o--
2 DR. McCORD: So overall, what I hope you've taken
3 away from this is that non-targeted analysis allows us to
4 investigate all sorts of different media. I've shown
5 soil, water, serum. We've also done air and other
6 matrices, and that it's critical in the discovery of
7 emerging contaminants, as well as the characterization of
8 things that aren't located in reference libraries. The
9 non-targeted data can support early stage monitoring by
10 identifying potential targets for follow-up experiments.
11 And even when it doesn't provide absolute
12 quantification, you can still do relative quantification
13 experiments that can be help you track things like
14 treatment of water, or the effectiveness of air handlers.
15 However, ultimately, due to the current
16 regulatory environment, chemicals standards and absolute
17 quantification are necessary. And if you don't have a
18 standard, it can be very difficult to perform risk
19 assessment, unless Jon solves the problem.
20 --o0o--
21 DR. McCORD: So I have to acknowledge all of the
22 State and regional partners who are responsible for
23 getting us all the samples and helping us set up all these
24 studies.
25 --o0o--

1 DR. McCORD: And then I will end at approximately
2 at the same time as my one minute warning.
3 CHAIRPERSON SCHWARZMAN: Thank you so much,
4 James. Yeah. And we have permission to slightly shorten
5 the lunch break, so that we make sure we get your
6 questions answered. So questions from the Panelists for
7 James.
8 Jenny.
9 PANEL MEMBER QUINTANA: Hi. Thank you for that
10 really great presentation and showing the power of what
11 chemical analysis can do to really clean up, in effect,
12 real-world problems. Thank you for that.
13 I had a question about the biomonitoring and how
14 you felt the results communication went to the population
15 that was biomonitored and how people interpreted their
16 results, and do people vary in how they reacted to them,
17 or just that whole experience that you had.
18 Thank you.
19 DR. McCORD: So in the case of the biomonitoring,
20 there was a packet that went out, provided people with as
21 much context as they felt was appropriate. So we tried to
22 show, in the case of these chemicals, there's no health
23 effects data associated with them. So we are trying to
24 show people what their levels look like relative to the
25 whole population.

1 There were a number of community meetings.
2 People are always unclear on how to handle data like this
3 when it's inherently uncertain. And so most of the
4 discussion sort of came back to we can't say very much
5 about a lot of the emerging contaminants. And I don't
6 necessarily think that inhabitants of Wilmington, North
7 Carolina, where we did the study are particularly pleased
8 with the amount of information that they've been given.
9 There's always a lag in the actual like risk
10 assessment for these emerging contaminants compared to
11 their detection and even our ability to monitor them,
12 because the chemistry progresses faster than you can do
13 biology studies. So for GenX specifically, we were in a
14 slightly better position, because it wasn't detected in
15 anyone's serum. And it's the one that there is actual
16 health effects data for. These emerging contaminants were
17 kind of something that no one was expecting when they got
18 their results back initially. So there's not as much
19 community pressure about them, because they sort of came
20 out of nowhere.
21 People were expecting to see GenX in their blood
22 and to be upset about that. But knowing that there are
23 other things in their blood and that the levels are
24 decreasing, there was not as much of a -- sort of an
25 uproar about it.

1 We are, both at EPA, and at the State level in
2 North Carolina doing the follow-up risk assessment on the
3 other emerging contaminants. But to a certain extent, the
4 cleanup is already being done and it's going to be a very
5 long process before we really know what the long-term
6 effects are to know how to explain to people what their
7 results actually meant or if there are any long-term
8 consequences for them. So it's a -- sort of a fraught
9 situation. I'm not sure if I can give any strong answers
10 beyond that.
11 PANEL MEMBER QUINTANA: Well, you're at the
12 frontlines of how to do this, so thank you to -- thank you
13 very much.
14 CHAIRPERSON SCHWARZMAN: Tom.
15 PANEL MEMBER McKONE: Thanks. That was a really
16 fascinating presentation, very interesting. I guess the
17 question I have is about the portability of the whole
18 process. I mean, admittedly this was like a -- I mean,
19 the whole thing was a wonderful learning experience, but
20 I'm expecting that eventually people at EPA and other
21 places are going to say, oh, this is great. Can you do
22 this for us, you know, Boston at the Charles River, or
23 Midland, Michigan? I mean, you could name dozens of
24 places where people would like to start applying this sort
25 of more comprehensive analysis to really answer questions

1 about what's -- what's in the water and what's getting
2 into people. So my question is do you think this will
3 be -- like you can set up a guide book of protocols, so
4 that it can be transported elsewhere?
5 DR. McCORD: So we have a team in RTP where I
6 work that's exclusively dedicated to this type of system
7 for PFAS analysis in particular. And we have about seven
8 different states where we're doing this sort of thing.
9 And it's, you know, Michigan, and New York, and West
10 Virginia, and all these places. And there's more sort of
11 queuing up all the time.
12 My hope is that we can develop a guide book where
13 this could be applied in any state or area where people
14 are interested in doing non-targeted analysis to really do
15 this type of thing. I sort of infamously, when I had
16 first joined the agency, in a conference call said that
17 you could apply this technique to essentially any outfall
18 for any industry and find something probably that was not
19 on anyone's radar that they were exposing the sort of
20 local area to, and so I would never be out of a job.
21 But we actually tried to move this into the
22 State's arena. Here in North Carolina we tried to do some
23 technology and methods transfer to the State laboratory.
24 We helped them write a PR to get a QTOF to do the analysis
25 themselves. We offered to like ship me over there for a

1 few weeks to train them and teach them how to do
2 non-targeted analysis. And it was initially sort of
3 tentatively approved by the State legislature, and then
4 ultimately shot down, because it was deemed to be too
5 aggressive of an environmental monitoring system.
6 So I don't know how much broad scale interest
7 there is in applying these really like aggressive cutting
8 edge monitoring approaches nationwide, but I definitely
9 support the use of techniques like this for interested
10 parties, if they are able to support the actual scientific
11 effort to do so. And we have tried it in the past and
12 we're willing to support it going into the future. That's
13 sort of my -- my hope.
14 CHAIRPERSON SCHWARZMAN: Great.
15 Oliver.
16 PANEL MEMBER FIEHN: So before we had another
17 interesting presentation that said, well, the problem is
18 two-fold, we don't have these qualification criteria and
19 performance criteria to know if a laboratory or a method
20 is really good in non-targeted analyses, right?
21 So if you now say, you know, you would like to
22 see that non-targeted analysis would be used in other
23 states, what is your take on guide -- guidelines or
24 qualification criteria, accreditation almost for
25 non-targeted analyses?

1 DR. McCORD: So it depends on what your end goal
2 is in the approach that you're applying what sort of QA
3 and QC you need to apply. So I think Jon is trying to
4 solve a much harder problem.
5 So in our case, in this particular instance,
6 we're associated with a class that's high visibility, high
7 interest, and people are generally of the opinion that
8 anything that falls into the PFAS category is something
9 that's worth following up on.
10 So we have the easy job of focusing on a
11 relatively-ease-to-characterize class of chemicals and
12 identifying novel compounds, which is difficult from an
13 analytical perspective to do the like elucidation and
14 everything. But once you do an identification, everything
15 that falls out of that basically shunts back into the
16 standard workflow. You get standards. You do risk
17 assessment. You do quantitation. And the discovery is
18 the sort of hard part.
19 In the case of doing non-targeted analysis,
20 generally like Jon is saying, I think that there is a need
21 to focus on like he says the accreditation and being sure
22 that what you are finding is defensible. And I think
23 right now in a lot of cases, just any consistent approach
24 applied broadly is better than an inconsistent approach.
25 So if you come up with some process of doing validation

1 and you can sort of show your work, then that's a good
2 starting point and it's a point where you can build from.
3 So just the fact that people can use, for
4 example, the Schymanski Scale to talk about the confidence
5 of their identifications and then store their data, I
6 think that's a good starting place, because like Meg said
7 as well, if you've done the analysis and you've assigned
8 confidence and made identifications, you can always go
9 back and improve them later.
10 So as long as you have a good handle on the
11 limits of your methodology, going forward that data is
12 always useful. So collecting the data, even if the
13 results that come out initially aren't always optimum, you
14 at least are in a starting point and you can improve over
15 time.
16 CHAIRPERSON SCHWARZMAN: Thank you so much for
17 that. Veena, I know you had a question. We need to break
18 for lunch. And we have a discussion section later this
19 afternoon. And so I want -- I just have note that you
20 have something you want to add. And if it's a question
21 for James, we can return to this. That's no problem.
22 Does anyone else want to get on the queue for
23 later. Carl, you had one. Okay. And Ulrike. Okay.
24 Great. So this will start off our discussion after the
25 afternoon presentations. And I have the queue.

1 Thank you so much, James, for the very
2 interesting presentation and we'll obviously return to it
3 a little bit later, when we have a discussion.
4 So I want to wrap-up the morning session.
5 There's also no -- sorry just to note that there were no
6 audience questions also, that we checked for those.
7 Okay. So before we break for lunch, I just need
8 to provide the usual informal Bagley-Keene reminder, which
9 is that as for the -- directed at the Panel members,
10 please comply with Bagley-Keene requirements and refrain
11 from discussing Panel business during lunch or the
12 afternoon break. We'll break for lunch now. We reconvene
13 at 1:30. But I want to make sure that everybody is aware
14 of returning no later than 1:25, so that the technical
15 issues can be resolved and we can start right at 1:30.
16 Thank you very much to all our morning presenters
17 and the staff who have been keeping this going and we'll
18 come back at 1:30
19 PANEL MEMBER McKONE: Quick question.
20 CHAIRPERSON SCHWARZMAN: Yes.
21 PANE MEMBER McKONE: So my computer will probably
22 shut off, because it goes to sleep. And I -- can we
23 re-sign in the same way we did this morning? It's a
24 technical question.
25 CHAIRPERSON SCHWARZMAN: Technical question of

1 staff.
2 PANEL MEMBER McKONE: I assume I'm going to have
3 to sign out. I mean, my computer won't likely keep this
4 open, unless I sit here and keep it from shutting down.
5 MS. HOOVER: This is Sara. I can tell you from
6 my own experience earlier when no one could hear me, I
7 actually shut everything down, re-signed in using the same
8 link and it was fine. So my understanding is that during
9 the session, the links will remain live. I'll just pause
10 for a second to see if Elizabeth or Marley want to comment
11 on this. I think that that is the case.
12 MS. ZALAY: You'll be able to rejoin, if you have
13 to restart or reboot from sleep mode.
14 MS. HOOVER: Thank you. Thank you, both
15 Elizabeth and Marley who have just confirmed that that is
16 the case. So please feel free to sign-off and rejoin at
17 1:25. Thank you very much.
18 CHAIRPERSON SCHWARZMAN: Okay. So I'm concluding
19 the morning session now.
20 Thanks.
21 MS. HOOVER: Okay. Bye.
22 (Off record: 12:42 p.m.)
23 (Thereupon a lunch break was taken.)
24
25

1 A F T E R N O O N S E S S I O N
2 (On record: 1:30 p.m.)
3 CHAIRPERSON SCHWARZMAN: Okay. We're going to
4 start the afternoon session. And I will just begin by
5 introducing the next speaker.
6 Dinesh Barupal is an assistant professor in the
7 Department of Environmental Medicine and Public Health at
8 the Icahn School of Medicine at Mount Sinai, New York.
9 He's leading the Integrated Data Science Laboratory for
10 Metabolomics and Exposomics. His research focuses on
11 developing, integrating, and implementing novel
12 computational methods for metabolic epidemiology,
13 computational metabolic -- metabolomics, and chemical text
14 mining, blood exposome, and metabolic bioinformatics.
15 Dinesh will present on, "Data Science and
16 Chemoinformatics Tools to Support Exposomics and
17 Metabolomics".
18 (Thereupon an overhead presentation was
19 Presented as follows.)
20 DR. BARUPAL: Thank you, Meg. So I want to say
21 some -- a few discussant points, and ideas, and data
22 science for metabolomics and exposomics that could be
23 interesting for the Biomonitoring Program.
24 --o0o--
25 DR. BARUPAL: So I will cover three topics in

1 this discussion. One is what are the opportunities in
2 non-targeted analysis with a focus on data science;
3 chemical to publication mapping. You know, build a
4 resource for chemical to publication mapping; and
5 prioritization some more chemicals for hazard assessment.
6 --o0o--
7 DR. BARUPAL: So opportunities in non-targeted
8 analysis.
9 --o0o--
10 DR. BARUPAL: I see NTA as the great potential in
11 disease prevention strategies. We have -- on the left
12 side, we have -- on the left side, we have primary
13 preventions that we're interested in on risk factors. And
14 as you go towards the right side, secondary and tertiary
15 prevention, where we're interested in the -- in the
16 tertiary prevention, we're interested in finding new
17 biological pathways or metabolomic reactions.....that can
18 be targeted by therapeutic options.
19 And if we fill in exposomics and metabolomics
20 NTAs, we can see that exposomics fits more on the
21 risk-factor side and prevention. And metabolomics fits
22 more on tertiary prevention, where we're interested more
23 in internal biochemistry and metabolomic pathways that can
24 be tinkered by drug targets.
25 And the question is how do we prioritize

1 different NTA assays? So as you know, that a combination
2 of different chemistry or computational approaches, we
3 have a battery of NTA assays that can be explored. And we
4 need -- that is a need to prioritize that which assay --
5 NTA assay fits best for identification of risk factor in
6 exposomics view, or which NTA assay fits best for
7 identification of new metabolomic pathways when we want to
8 have tertiary prevention strategies.
9 We can also think, and this -- in a single
10 prevalence way, that in genomics, a rare variance carries
11 more risk. We see this often in common diseases. We have
12 a similar situation for NTA assays, that sample frequency,
13 as we go more from lower to higher, we are capturing more
14 internal biochemistry and metabolic pathways. And it also
15 more fit with metabolomics assays. Whereas, if you go on
16 the lower side of the -- on the lower sample frequency or
17 single prevalence, we are starting recovering exposures or
18 fine, or precise sub-type, or group of population they're
19 exposed to only specific type of chemicals.
20 And this way, exposomics fits on covering the
21 chemicals that may occur with the low frequency, whereas
22 metabolomics fits more on that. We cover more and more
23 component of high prevalence.
24 In my view, that we should avoid just holding
25 single prevalence when we generate metabolomic NTA

1 matrices. We see this all of a sudden during a quality
2 control process or during the element generation that our
3 thresholds applies on data matrices that ignore all the
4 compound, if they don't occur in 50 percent sample or 10
5 percent of samples. I think those signals thresholds
6 should be avoided and dropped for NTA assays. All the
7 signals that we detect, even in one sample, that should be
8 stored in a proper way in a database, so we can mine them,
9 the way we mine electronic.....records.
10 --o0o--
11 DR. BARUPAL: And that can be achieved if we
12 start indexing raw LC-MS and GC-MS data into enterprise
13 databases. So enterprise database system -- enterprise
14 database systems need to be developed for indexing raw
15 spectral data. And once we have that all the data,
16 whatever -- even if it takes from one terabyte to going
17 from 100 terabyte. Because enterprise databases have
18 original scalability, we can index all the data, and this
19 way we can query directly on the database. We can
20 generate tables directly through the databases, exactly
21 the same way we mine literature data, chemical data, or
22 electronic health data in a medical system. And these are
23 all -- it's stored in an enterprise database system.
24 And NTA assays that needs improvement. Well, we
25 need to work on indexing raw spectral data into enterprise

1 databases. That way, we will have better tables and we
2 can do better analytics to find risk factors as well as
3 finding new metabolomic pathways.
4 The other serious issue we have, the annotation
5 of LC-MS and GC-MS peaks is we know that compounds still
6 remain unknowns. My view is we need an integrated
7 holistic approach. So if we focus only on expanding mass
8 spectral library, we will have a increment of progress
9 that only small personal chemicals will be annotated.
10 However, if we combine the best innovation in all
11 these four domain, like instrument, sample processing, and
12 .....in workflow in mass spectral library over progress
13 multiplies and so we cannot see good progress. If we
14 combine all these four domains and the best innovation,
15 the best ideas in a logical way, and then we have a
16 notation approach, that will have a better -- more impact
17 and that way we can annotate a lot of peaks that have
18 MS/MS spectra. And also, if we have better instruments,
19 we can get a lot of MS/MS spectra for peaks which lack
20 MS/MS spectra, then the issue will be that how do we rank
21 experimental or in silica evidences for peak annotations?
22 These are open-ended questions that need more discussion
23 when we process data or when we design NTA studies these.
24 I'll jump to the biological interpretation part.
25 NTA data cover way more number of compounds. And these

1 days, they can easily have 1,500 to 2,000 compounds. And
2 it has been absorbed regularly that many of these
3 compounds are not covered in current biochemical databases
4 such as KEGG, Reactome, or MetaCyc. That creates a
5 problem when bioinformatics or statistical approaches that
6 you utilizes -- that were adopted from genomics and
7 utilizes a hypergeometric test that depends on a
8 background database. So in genomics this is clear, the
9 total number of genes we know.
10 But for metabolomics this is not clear. And
11 quite frankly, a background database does not exist for
12 NTA. And if we use existing bioinformatics approaches
13 that use a hypergeometric test, we're introducing
14 interpretational bioassay for NTA data. And
15 interpretation is focused to only compound that are
16 covered in the background database.
17 Assuming the statistical independence of chemical
18 is false, it's false solution. And in applying FDR on raw
19 p-value for individual chemical, and for metabolomics and
20 exposomic data sets, I think it's inappropriate, because
21 we do know that there are mixtures that are chemical
22 groups and there are metabolomic pathways. And there's a
23 correlation between these metabolite group. So it is
24 inappropriate to apply FDR or by assuming the statistical
25 independence on unusual metabolite level.

1 --o0o--

2 DR. BARUPAL: One way to visualize NTA data is in
3 a chemical similarity graph. So idea is that we have two
4 chemical structures, xanthine and hypoxanthine as shown
5 here. They're 90 percent similar. We could
6 computationally map them using a coefficient called
7 Tanimoto Similarity Coefficient that uses a -- utilizes a
8 substructure decomposition metrics.
9 That similarity data can be visualized in
10 Cytoscape software and we can overlay statistical results.
11 We have used those natural graph in several studies that
12 works great for 100 to 200 chemicals. However, today's
13 NTA data can have more than that, so -- and I seem -- we
14 can easily have thousand compound in non-targeted
15 metabolomics data set. And it become harder to visualize
16 that many chemicals in a single network plot and become
17 even harder that how do we interpret those large-scale
18 network visualization.

19 --o0o--

20 DR. BARUPAL: So other approach that we developed
21 is called ChemRICH, which uses medical subject ontology.
22 It takes chemical structure by chemical detected in NTA
23 data. And then it uses Tanimoto similarity coefficient
24 formula to map them to MeSH ontology.....
25 So in this plot, we have lipophilicity on X axis

1 that chemicals groups that are polar are shown on the left
2 side, non-polar are shown on the right side. And on Y
3 axis we low -- a negative log or p-value that we get from
4 Kolmogorov –Smirnov test that is done on set level one
5 using observed p-value for assay and comparing against a P
6 uniform -- uniformed distribution of p-value. That way,
7 we can rank the sets by their association strength.
8 And I was reading this paper last week by a
9 biomonitoring program identifying chemical groups for
10 biomonitoring in EHP. I think.....will be a great tool to
11 be used for NTA data coming from biomonitoring studies.
12 And that way we -- it can prioritize and show the chemical
13 classes that can be put into prioritizing some process.
14 That's still an open-ended question that how do
15 we include unidentified metabolite into chemical set
16 analysis. So this is all non-compound. We know the
17 chemical structures, but I would include unknown compound,
18 which is a large majority of peaks are still unharmed.
19 There are ideas like substructure or correlation
20 modules or correlation modules that can be explored to
21 include those unknown -- include those unknown in the
22 chemical set analysis.
23 --o0o--
24 DR. BARUPAL: So in summary, we have several well
25 known issues with NTA data processing. That a large

1 number of signals remain unknown. We have a slow signal
2 processing for large batch of samples. So whenever we're
3 trying to process 1,000 or more number of samples, it's
4 hard to -- it gets really slow. And then we have errors
5 in peak grouping and deconvolution. We have correction of
6 retention time drifts, for batch to batch. The presence
7 of missing values are there. Low frequency signals are
8 often ignored. We have presence of artifacts and
9 background signals, issues with data normalization,
10 challenging biological interpretation. There are ethical
11 issues in data sharing for sensitive analytes such as
12 illicit drugs.
13 So these are well-known issues. We just need to
14 know them. And there are ways to overcome several of
15 them. But this need to be addressed and bring to the
16 table when we're trying to process the data, as well as
17 when we're trying to design -- do a new NTA study.
18 So those were my thoughts on NTA, and what new
19 opportunities we can have, and what new ideas we can bring
20 in for processing data and interpretation and what are the
21 challenges on it.
22 I'll switch to now chemical to literature
23 mapping.
24 --o0o--
25 DR. BARUPAL: Why -- we need a resource in a

1 public domain where chemicals are connected to publication
2 in an electronic way -- electronic way.
3 So we report chemical names in a different
4 section of our paper, like abstract, tables, figure, and
5 paragraph, and supplemented data, and again converted to
6 PDF or in XML, and they can have in a database. But there
7 is no table where that this chemical was reported in this
8 literature in public domain. So we wanted to have this
9 resource, because it will allow us to build next
10 generation tools for metabolomics data interpretation, as
11 well as chemical prioritization. Because right now, the
12 approach is we take one chemical and then we do -- run
13 manual queries and it gets laborious. And if you have --
14 if you detect 1,700, 2,000 identified compounds, we're
15 talking about easily million paper in -- to review for
16 a -- just a single study. So to over -- to make it
17 efficient, we need a chemical to literature mapping.
18 --o0o--
19 DR. BARUPAL: We undertook such exercise, where
20 we mined one million publications on measurement of a
21 chemical in a blood specimen. And we learned that we
22 could have almost 42,000 two-dimensional structures. And
23 out of those, at least 15,000 have five or more number of
24 publications. And those 15,000 can be utilized for
25 expending mass spectral libraries as well as to prioritize

1 candidate structure for peak annotations.
2 --o0o--
3 DR. BARUPAL: And there is a -- there's a great
4 potential for non-targeted metabolome studies for blood to
5 expand the blood exposome database. So in 2008, there
6 were 150 identified compounds a typical metabolomics data
7 set generated by Metabolon Company. And now, there is a
8 12-fold increase that they can generate data sets with
9 1,700 identified compounds. Those are all known targeted
10 analysis.
11 All those identified compound goes to this subset
12 D, which is NTA metabolomics studies added 1,250 specific
13 compounds to the blood exposome database. There is a
14 great potential for NTA assays in this approach. We need
15 to make sure that existing mass spectral libraries have
16 all these compounds in the public domain, so other people
17 can use it.
18 --o0o--
19 DR. BARUPAL: Now, it's chemical prioritization
20 for hazard assessment.
21 --o0o--
22 DR. BARUPAL: Why chemicals?
23 Because most exposures are for individual
24 chemicals, whether they come from diet, drugs, or water
25 pollution, or other sources. In fact, IARC monograph,

1 which is one of the best character -- characterized
2 exposure database. Eighty-two percent are individual
3 chemicals. And there are mechanisms in place to identify,
4 monitor, and regulate exposure to a specific chemical.
5 --o0o--
6 DR. BARUPAL: IARC monograph(inaudible) it will
7 weighting evidences and based on -- based on a systematic
8 review of the evidence by the working group a
9 classification scheme for in this is proposed. For
10 example, Group 1 has 120 agents.
11 And we took exercise to prioritize pesticide
12 structure using chemical similarity, chemoinformatics, and
13 text mining. So in this plot, we see organophosphorus on
14 the upper panel, organochlorine in the bottom panel. And
15 the size represent the number of(inaudible)papers on
16 pesticide and cancer, and thickness of the blood -- this
17 dark represent number of papers on cancer epidemiology.
18 So this way we can see that in organophosphorus
19 which chemical pest -- which pesticides have literature
20 evidence availability on cancer, epidemiology. And that
21 lead to IARC Monograph meeting 112 and 133 on
22 organophosphorus and organochlorine pesticides.
23 The idea is that chemically similar agents can be
24 well weighted together, as they might have a similar
25 toxicological profile. And I think we can develop a

1 similar approach for chemicals in the California
2 Biomonitoring Program list. And we can overlay text
3 mining -- to text mining, if there are any available
4 literature data for different chemicals in the list and if
5 they can help in the priorities.
6 --o0o--
7 DR. BARUPAL: So in conclusion, non-targeted
8 analysis assays are a great potential for detecting
9 high-priority chemicals exposome research and
10 biospecimens. However, proper combination of analytical
11 chemistry and data science need to be planned ahead. And
12 indexing raw data into enterprise databases and avoiding a
13 signal threshold prevalence -- threshold are needed for
14 exposomic assays. Computational text mining can improve
15 the prioritization process by linking chemicals to
16 publications.
17 And hopefully, in the future, we can mine full
18 text data for expending the chemical to publication
19 linking. An interpretation bias remains a major challenge
20 in mining NTA data, that utilizing existing biochemical
21 databases, which are proven and complete for NTA.
22 With that, I want to thank my current and former
23 collaborator at IARC, UC Davis, and Icahn School of
24 Medicine at Mount Sinai. A special thank you to NIH for
25 funding these two initiatives.

1 And thank you. Happy to take any questions
2 CHAIRPERSON SCHWARZMAN: Great. Thank you so
3 much. We have a little bit of time for Panel questions
4 for Dinesh and we'll check for audience questions as well.
5 DR. BARUPAL: Hi, Oliver.
6 PANEL MEMBER FIEHN: Thank you. That's, of
7 course, very interesting. What do you think about using
8 large repositories, like the GNPS or massive resources for
9 mapping non-targeted spectra to compounds, to similar
10 compounds, to exposome compounds, do you know anyone who's
11 tried that?
12 DR. BARUPAL: Let's do it.
13 PANEL MEMBER FIEHN: Can you explain?
14 DR. BARUPAL: So it need to be done. It's a
15 great idea. And we know the GNPS people are actually
16 importing data from other repositories and they're
17 indexing those data. And they are mining -- reanalyzing
18 the data in their platform. But it is their platform and
19 it's their computational approaches. And there are other
20 computational approaches in other groups. Like you have
21 your own ideas to mine and annotate. I have my own idea
22 to mine and annotate.
23 And I think it will be complimentary, if those
24 data sets are mined with multiple annotation schemes and
25 annotation of algorithms. But the -- but I don't know

1 anyone who's actually pooling those data, except GNPS and
2 mining it.
3 CHAIRPERSON SCHWARZMAN: Other questions from the
4 Panel.
5 Eunha.
6 PANEL MEMBER HOH: Eunha Hoh from San Diego State
7 University. It's a great presentation. Lots of
8 information. A lot of work. One question I always have
9 that, you know, the exposome study that measuring
10 metabolites untargeted. But in the non-targeted analysis
11 of environmental chemicals in the same biospecimen, there
12 is always a challenge because of the concentration, it's
13 very -- like environmental chemicals are at concentration
14 much lower than the metabolites, or nutrients, or, you
15 know, other chemicals that humans are exposed to. Is -- I
16 kind of want to hear your thoughts about that. You know,
17 I mean I know that you're doing a lot of data mining and,
18 you know, informatics, but if you have any thoughts on
19 that.
20 DR. BARUPAL: It's -- I think it's a well -- it's
21 a known issue of analytical chemistry, the sensitivity of
22 an instrument. And so if you start with a hundred
23 microliter plasma sample and so -- and you have your
24 sensitivity by LC-MS, of course, there are peaks that will
25 be below the detectional limits.

1 And so if you give me 500 microliter, we gave
2 five times. And so it's a combination that starting
3 material the sample preparation, and the sensitivity of
4 the instrument, that what compounds will be above the LOD
5 and what will not be. But then it's the same time
6 exposure itself, because you can have some population in a
7 cohort that exposed to five times more to a chemical than
8 other, then we will be able to see it.
9 But the way I think is that it should be by a
10 database approach, that we index everything. And even if
11 a single subject is exposed to it five times more, I think
12 it's important that we highlight that.
13 PANEL MEMBER HOH: Um-hmm.
14 CHAIRPERSON SCHWARZMAN: Other questions?
15 And, Marley or Sara, are there any questions from
16 the audience for Dinesh?
17 MS. HOOVER: This is Sara and there are no
18 questions in the Biomonitoring California email and
19 there's no questions via the GoToWebinar platform either.
20 CHAIRPERSON SCHWARZMAN: Okay. In that case, I
21 suspect we'll be returning to this information in our
22 afternoon discussion as we continue to pull all of this
23 together. And thank you so much, Dinesh for that
24 presentation and I will introduce our next speaker.
25 DR. BARUPAL: Thank you.

1 CHAIRPERSON SCHWARZMAN: Doug Walker is an
2 assistant professor in the Department of Environmental
3 Medicine also at the Icahn School of Medicine at Mount
4 Sinai. His research focuses on advanced analytical
5 strategies for measuring the occurrence, distribution, and
6 magnitude of previously unidentified environmental
7 exposures, and assisting in delineating the mechanisms
8 underlying environment-related diseases in humans.
9 He also leads the high-resolution exposomics
10 facility at Mount Sinai, which was established to provide
11 high-quality non-targeted screening of biological samples
12 for nutrition, precision medicine, and environmental
13 health research. Doug will present on, "A Multi-Platform
14 Non-Targeted Framework for Measuring the Human Exposome".
15 (Thereupon an overhead presentation was
16 presented as follows.)
17 DR. WALKER: Great. Thank you. Can you see my
18 slides okay?
19 CHAIRPERSON SCHWARZMAN: Yes, we can.
20 DR. WALKER: Okay. Great. Excellent.
21 So today, I'm really delighted to talk about our
22 work using multiple high-resolution mass spectrometry
23 platforms to provide better measurement of the human
24 exposome. I've been really impressed by everything that
25 I've heard so far, you know, but describing both

1 environmental sample analysis and human sample analysis.
2 I'm going to do kind of a deeper dive into how we're using
3 non-targeted analytical strategies to provide better
4 measurement of human exposures and link those to disease.
5 --o0o--
6 DR. WALKER: So just briefly today in my
7 presentation, I'm first going to describe a critical role
8 for untargeted or non-targeted assays in characterizing
9 the human exposome. I'll next describe how we're using
10 untargeted high-resolution mass spectrometry to generate
11 new insight into understanding more classical exposures,
12 such as persistent organic pollutants and volatile organic
13 compounds.
14 And then next, I'll describe how we're
15 incorporating these untargeted assays to study exposures
16 of emerging concern, including things like microplastics,
17 and also develop different strategies for assessing
18 exposures in population studies.
19 --o0o--
20 DR. WALKER: So I'd just like to briefly describe
21 why we're really interested in using these untargeted
22 methods and why we have a focus on the exposome. We know
23 from a number of different studies, and, you know, of
24 course, by speaking to environmental health scientists
25 we're all aware of this, but we know that genes, or your

1 genetics, alone do not describe your disease risk. And
2 this was shown -- you know, this is another example of how
3 we can demonstrate this, and this is from a paper by Steve
4 Rappaport that was published in 2016.
5 But what this graph is showing is the population
6 attributable fraction for a number of common disease
7 phenotypes, if we account for gene or gene-by-environment
8 risk factors. Now, the population attributable fraction
9 is the percent reduction in a disease that would occur, if
10 we could eliminate some risk factor.
11 So what this is showing us is that for most of
12 the common disease phenotypes, if we remove gene or
13 gene-by-environment risk factors, the prevalence of a
14 disease is only being reduced by, you know, at most 30 to
15 40 percent. And so what we're really interested in is
16 identifying what is driving the disease risk, what is that
17 other 65 to 70 percent, and how can we develop new
18 analytical methods to better characterize that?
19 --o0o--
20 DR. WALKER: Our current estimates suggest that
21 only about five to 15 percent of diseases can be
22 attributed to heritability alone. The other 85 to 95
23 percent of diseases are derived from environment,
24 lifestyle, or their interaction with the genome. So
25 therefore, if we're considering heritability alone, we're

1 taking an unbalanced view of human health and disease.

2 --o0o--

3 DR. WALKER: However, there's a discrepancy
4 between our ability to characterize environment and our
5 ability to characterize biology. We have incredible
6 technologies that allow us to very thoroughly characterize
7 different aspects of biology from whole genome sequencing
8 through transcriptomics, or epigenetics, or proteomics.
9 They allow us to provide deep characterization or
10 phenotyping of different levels of biology.

11 However, even some of our best analytical methods
12 that we currently have only allow us to characterize about
13 ten to a hundred exposures in an assay or in a series of
14 assays. So therefore, in order to make the measurement of
15 environment or exposures more consistent with its
16 importance to human health, there's a critical need to
17 develop analytical frameworks that allow us to provide
18 universal screening for measures of the exposome.

19 --o0o--

20 DR. WALKER: We've approached this through
21 measurement of the human metabolome, which can be defined
22 as the complete collection of small molecule metabolites
23 found in the human body. As was mentioned previously and
24 has been discussed in the other presentations, this
25 includes a very diverse series of different types of

1 chemicals. These range from things like the core
2 biological metabolites that are needed for proper
3 biochemical functioning and for life, microbiome related
4 chemicals, nutritive chemicals in diet, as well as
5 exogenous compounds like supplements and pharmaceuticals,
6 commercial products, and environmental chemicals.
7 --o0o--
8 DR. WALKER: One of the advantages of measuring
9 the human metabolome is that it allows a -- the ability to
10 characterize both that endogenous contribution, which is a
11 measure of biological effect, as well as the exogenous
12 contribution, which is a measure of exposure or internal
13 dose to these different compounds.
14 Our current estimate suggests that if we wanted
15 to have the ability to characterize a reference human
16 metabolome, we would have to have the ability to detect
17 roughly one million chemicals. I'm not trying to imply
18 that if I were to take my blood sample and run it, you
19 know, using multitudes of different platforms, we would be
20 able to detect a million chemicals.
21 But if we want to assemble a reference metabolome
22 that includes metabolomic measures from very diverse
23 populations, collectively, we would have to have some
24 system to categorize, catalog, and detect a very large
25 number of compounds. Our estimates suggest that exposure

1 is likely to contribute to 400,000, or approximately half,
2 of these compounds or more.
3 --o0o--
4 DR. WALKER: So therefore, to really embrace and
5 understand the complexity of the human exposome, there is
6 a critical need to adopt analytical strategies and study
7 designs that incorporate untargeted measures of exposure.
8 There is no way we'll ever be able to develop
9 panels that allow us to characterize or biomonitor for
10 compounds on that scale. So we have to really start
11 thinking about how we can incorporate these data-driven
12 methods for detecting exogenous molecules in human
13 populations.
14 --o0o--
15 DR. WALKER: The measure of the human metabolome
16 provides us a comprehensive measure of the continuum from
17 exposure to disease. And we can use this information to
18 really understand the biological effects of exposure, and
19 start developing new hypotheses to study about the length
20 between exposure to disease. So we know that by measuring
21 exogenous compounds, we have a measure of exposure or
22 biomarkers of exposure in a biological sample.
23 Because we're characterizing the metabolome in
24 our assays, we also able to characterize endogenous
25 metabolites and how those are associated with those

1 exposure markers. So we have intermediate biomarkers of
2 effect. And if we're looking at certain disease
3 populations, we can also identify physiological
4 manifestations of disease within the metabolic phenotype.
5 When we think of ways of combining those, we can
6 essentially develop a framework for what we like to think
7 of as systems toxicology.
8 So as I mentioned just previously, we can use
9 measures of exposure and to identify exposure to
10 phenotyping and biological effects. If we work with
11 disease populations, specifically nested case control
12 studies, we can look at how metabolic or exposomic
13 alterations are associated with the disease phenotype.
14 And we can link these exposure and biological effects to
15 start identifying hypotheses that we can study and model
16 systems, and use more informed approaches for describing
17 mechanisms linking exposure to disease.
18 --o0o--
19 DR. WALKER: The way we've operationalized this
20 concept of measuring the exposome is through a
21 multi-platform approach that relies on both gas
22 chromatography and liquid chromatography high-resolution
23 mass spectrometry.
24 By combining these, we have a framework for doing
25 a comprehensive exposome by metabolome-wide association

1 study of disease. Using the gas chromatography or gas
2 phase analysis, we've really focused our methods towards
3 detection of volatile and semi-volatile organic compounds.
4 Many of these are the environmental exposures that were
5 interested in studying.
6 Our extraction method is really optimized to, you
7 know, isolate these compounds from either tissue or blood
8 samples. And we're primarily characterizing these on the
9 gas chromatography system.
10 At the same time, every sample that we're
11 analyzing on the gas chromatography mass spectrometer,
12 we're also analyzing using liquid chromatography with high
13 resolution mass spectrometry. This allows us to
14 characterize biological response markers, as well as more
15 polar metabolites, and environmental chemicals, and also
16 just more polar exogenous compounds such as drugs and
17 their metabolites.
18 By combining these two platforms, it gives us the
19 ability to detect more components of chemical space and
20 improve what we're measuring in our exposomic assays.
21 DR. WALKER: The gas phase or gas chromatography
22 analysis is based upon the thermo GC orbitrap instrument.
23 We've established a, you know, very robust and relatively
24 high throughput workflow that allows us to do simplified
25 sample extraction and then analysis in a fully untargeted

1 manner.
2 As I mentioned previously, our sample extraction
3 has been more focused towards non-polar, volatile and
4 semi-volatile compounds. And so this allows us to target
5 environmental compounds. We found that the sensitivity of
6 the instrument is excellent, so even operating in full
7 scan mode, we have similar sensitivity to what we would
8 see with a GC triple quad. And we're able to routinely
9 detect very low abundance environmental chemicals at the
10 subnanomolar or subnanogram per ml range.
11 These include things kind of like the
12 polychlorinated biphenyls, brominated flame retardants, as
13 well as some of the new phosphoester flame retardants and
14 other compounds that are relatively volatile.
15 Our workflow is completely untargeted, in that,
16 we don't have any specific targets or MS/MS that we're
17 trying to collect during the initial analysis. We've
18 optimized the method to detect as many signals as
19 possible. Once we've run samples from a study, we then go
20 back and do our peak picking and data extraction. We run
21 our bioinformatics and then do our metabolite annotation
22 followed by identification.
23 Identification, of course, is based upon
24 confirmation by comparison to standards or high confidence
25 annotation by matching to databases or in silico data.

1 --o0o--
2 DR. WALKER: The liquid chromatography high
3 resolution mass spectrometry platform, which again we use
4 for exposure of biomarkers and biological response
5 measures is, you know, relatively traditional untargeted
6 metabolomics platform. We use a Q Exactive HFX orbitrap
7 mass spectrometer that's interfaced to a liquid
8 chromatography system that has dual chromatography
9 capabilities.
10 So every sample we're analyzing, we're actually
11 analyzing two different modes. One is with positive
12 electric spray ionization. The second is with negative.
13 Similar to the GC, we're operating in a
14 completely untargeted framework, where we're collecting
15 our data in full scan mode. And then after we perform our
16 biostatistics and bioinformatics, we go back and do our
17 annotation and identification using standards.
18 --o0o--
19 DR. WALKER: I'm just going to go through a few
20 of the studies that we're applying these methods to and
21 how we're using this untargeted data to better
22 characterize exposures that are being experienced by human
23 populations.
24 One of the demonstrations of the usefulness in
25 this technology was an initial study that we did to

1 characterize metabolome of Chinese workers occupationally
2 exposed to trichloroethylene, which they were using in
3 degreasing operations in a manufacturing plant.
4 So within this study, we had collaborators who
5 went to different regions of China and identified
6 factories that were using -- only using trichloroethylene
7 in the degreasing process as well as control factors that
8 weren't using any volatile organic compounds in any of the
9 processes that are ongoing in that factory.
10 After identification of these workers who were
11 exposed and unexposed, they did an extensive shift
12 monitoring of personal exposure levels, and collected
13 blood and urine samples for characterization using, you
14 know, a number of different assays.
15 We received blood samples from 95 unexposed
16 workers ad 80 exposed workers and analyze them using the
17 high-resolution mass spectrometry platform -- or framework
18 described in the last slide.
19 We performed our metabolome-wide association
20 study. And as a last step, we also tried to compare our
21 metabolomic data to independently measured bioeffect
22 markers that have previously been characterized in this
23 population, and include things like immune, kidney damage,
24 and exposure biomarkers.
25 --o0o--

1 DR. WALKER: So the initial metabolome-wide
2 association study identified 188 features at this -- they
3 were features. These were not identified compounds that
4 were associated with this exposure. We characterized
5 these used in a number of approaches. But one thing that
6 became very evident is we saw a high degree of features or
7 high number of features that were very highly correlated
8 with the exposure, but they didn't match any known TCE
9 metabolites.
10 When we characterized them further, we found that
11 all of them had very consistent chlorine isotope patterns,
12 suggesting that they could be arising from the
13 trichloroethylene. But again, they weren't matching any
14 of the known metabolites.
15 To characterize this further, we just looked at
16 the biological response profiles associated with the
17 exposure in these different metabolites. We found that a
18 number of pathways were associated with the exposure that
19 we would expect to see. For example, methionine and
20 cysteine metabolism and bile acid biosynthesis were both
21 associated with the exposure, which is what we would
22 expect since these were -- these are the detoxification
23 routes for this compound.
24 However, there is a number of other pathways that
25 we weren't expecting, such as carnitine shuttle, which is

1 related to mitochondrial function, as well as purine
2 metabolism and a few other immune-related pathways.
3 Where the results really became interesting was
4 when we started looking at the correlation with these
5 other biological response measures, including immune
6 responsive biomarkers, renal damage biomarkers, and TCE
7 exposure biomarkers that were previously measured in
8 urine.
9 So what we found first is that, you know, we were
10 able to detect and identify a number of known TCE
11 metabolites. This included trichloroacetic acid as well
12 as a trichloroethanol. These were positively correlated
13 with the urinary biomarkers that were again measured using
14 a targeted lab. This is great, but it's exactly what we
15 would expect. If we didn't see these correlated, I would
16 be more concerned. So that in itself isn't exciting.
17 But what did become interesting is when we
18 started looking at these compounds that we knew were
19 halogenated chemicals, but they did not match any of the
20 known TCE metabolites. And what we were able to see from
21 this correlation network is that these identifiable
22 metabolites were linked to the biological response markers
23 that have previously been associated with
24 trichloroethylene exposure. However, we didn't see any of
25 these relationships with the known TCE metabolites.

1 So it suggests that there could be alternate
2 pathways or relationships between these unidentifiable
3 metabolites in these outcomes. And we're trying to
4 explore this further and identify what some of these
5 metabolites were using both MS/MS and cell culture
6 studies.
7 --o0o--
8 DR. WALKER: We've also been applying these
9 methods in case control studies of different diseases. So
10 this is an example of a study where we were examining how
11 the exposome and metabolome was associated with primary
12 sclerosing cholangitis and primary biliary cholangitis,
13 which is a liver disease that really is un -- of unknown
14 etiology. There is a few studies showing that there is
15 some genetic risk factors for this disease, but the
16 majority of the disease variance is really unknown.
17 So in this study, we wanted to apply the exposome
18 assay, which is based upon gas chromatography and the
19 liquid chromatography platform to characterize biological
20 response and see how those were linked.
21 --o0o--
22 DR. WALKER: The initial analysis using the gas
23 chromatography platform allowed us to identify a number of
24 different exposures that were correlated with the disease
25 status, both for PSC and PBC. And for most of these IBD

1 status, which is a comorbid condition with primary
2 sclerosing cholangitis really didn't impact the exposure
3 levels.
4 In addition to the identifiable metabolites that
5 we were able to detect, and these were identified by
6 comparison to standards using retention times and
7 fragmentation patterns, there was also a number of
8 features, which had spectra, and they were consistent with
9 chlorinated or brominated compounds that did not match
10 anything that we could find in our database.
11 So again, these are very interesting molecules,
12 but we're trying to follow up with those and study them
13 further to see what they are.
14 --o0o--
15 DR. WALKER: The metabolomics analysis was able
16 to identify a number of biological alterations or changes
17 in biological pathways that were associated with the
18 disease. It's very important to mention that these
19 individuals were very, very early in the disease process.
20 And so they had very minimal, you know, measurable changes
21 in their phenotype, but we were still able to see very
22 large differences in metabolic pathways for these
23 individuals.
24 One of those was bile acid metabolism. And we
25 were actually able to take our untargeted results and see

1 which metabolites were associated with the disease and
2 with severity, and then we developed a targeted assay or
3 used the targeted assay and were able to replicate many of
4 the findings in both this population and a much larger
5 independent PSC population as well.
6 So that was a good example of how we can use the
7 untargeted methods to, you know, guide our biomarker
8 selection and use that for clinical characterization.
9 And finally, when we looked at linking these
10 pathways that were associated with the disease to the
11 exposure, we were able to find a number of different
12 relationships. And what was most interesting about this
13 is we kind of grouped our pathways based upon overall
14 disease process. So we had bile acid pathways, oxidative
15 stress pathways, and immune-related pathways.
16 And when we looked at the correlation between
17 exposure and biological response measures, we were able to
18 group those into different clusters. And they were
19 largely consistent with the process itself. So we saw two
20 clusters that were really enriched in bile acid metabolism
21 and then we had a third cluster that was more enriched in
22 oxidative stress and immune response.
23 --o0o--
24 DR. WALKER: And so really what these untargeted
25 assays allow us to do is provide a functional measure and

1 sensitivity needed to perform exposome by metabolome-wide
2 association studies of human health and disease. There's
3 always been this question about whether the metabolomic
4 approaches provide the sensitivity to measure very low
5 level environmental chemicals. But by using the gas
6 chromatography platform we've really been able to
7 demonstrate that we do have that sensitivity and it really
8 expands what we're able to detect in some of these
9 untargeted assays.
10 --o0o--
11 DR. WALKER: And very briefly, I'll just spend a
12 few minutes talking about what are some of the new
13 exposures and new sample types that we're characterizing
14 using these methods.
15 So one of the things that we want to be able to
16 do better is measure exposures that have a relatively
17 rapid half-life. And we can't necessarily characterize
18 these in biological samples. So one of the things that
19 we're working with are the silicone wristbands and badges
20 that were initially developed by Kim Anderson's labs.
21 We've shown that you an apply the untargeted methods to
22 characterize these, and with a high degree of sensitivity
23 actually isolate different microenvironment exposures even
24 in different rooms in the same house. So they provide a
25 high degree of sensitivity and they're relatively cheap to

1 mail out and distribute.
2 We're also working on micro-needle patches that
3 can be worn for up to 24 hours. These patches were
4 vaccine patches that were essentially re-engineered to
5 withdraw interstitial fluid rather than deliver a vaccine.
6 And we can use these for biological response monitoring or
7 internal dose monitoring.
8 The hope is to get these developed to the point
9 where they can be delivered to participants in a cohort.
10 They can apply them, where them for 24 hours, and ship
11 them back.
12 --o0o--
13 DR. WALKER: And finally, one of the things we're
14 really starting to focus on now is developing these
15 untargeted analytical strategies to measure microplastics
16 in biological samples. There's been a lot of interest in
17 characterizing exposures to these micro and nanoplastics.
18 However, most of the work to date has been in
19 environmental or food samples. And there's really no good
20 methods for biomonitoring of these microplastics in human
21 populations.
22 --o0o--
23 DR. WALKER: So we're really trying to leverage
24 all of our high resolution mass spectrometry capabilities
25 and strengths into measuring these. We're using pyrolysis

1 high resolution mass spectrometry for quantifying known
2 particles, as well as screening for a very wide range of
3 different polymers and particulates that could be
4 contributing to this burden.
5 We're using depolymerization methods with liquid
6 chromatography that allow us to characterize bound
7 additives as well as screen for known particle monomers.
8 So we're essentially destructing the monomers and trying
9 to look for the -- or the polymers and looking for the
10 building blocks of those particles. And we're also doing
11 small molecular profiling to look for free plastic
12 additives or things that could be absorbed and
13 co-transported on these particles.
14 --o0o--
15 DR. WALKER: And a lot of the projects we're
16 focusing on now relate to early life exposure including
17 studies where we're trying to measure these in both
18 placenta and amniotic fluid from pregnant women. And this
19 is in a collaboration with researchers in Europe at
20 Utrecht University and Deltares.
21 --o0o--
22 DR. WALKER: So just in conclusion, untargeted
23 assays that allow us to profile the human metabolome have
24 the potential to provide key insight into exposure and
25 biological response and how that's associated with disease

1 outcomes by combining a gas chromatography and liquid
2 chromatography high resolution mass spectrometry platform.
3 We really tried to establish a unified framework for
4 expose via metabolome by an association study of disease.
5 And these technologies can be leveraged for developing new
6 methods to better characterize emerging exposures, such as
7 microplastics. And as we saw in the previous
8 presentation, some of the PFOS.
9 --o0o--
10 DR. WALKER: I'd just like to acknowledge my team
11 at Mount Sinai and all the excellent collaborators I've
12 had over the years, specifically Roel Vermeluen at Utrecht
13 University and Dean Jones, Gary Miller, and Karan Uppal at
14 Emory University.
15 Thank you very much.
16 CHAIRPERSON SCHWARZMAN: Thanks so much, Doug,
17 for that. And we have a few minutes for questions. And
18 we are going to break right at 2:30 for 15 minutes. So
19 anything that we don't get to now, we can -- let's
20 bookmark for the later discussion today.
21 Questions from panelists to begin with and then
22 we'll turn to the audience.
23 Jenny.
24 PANEL MEMBER QUINTANA: Hi. Thank you for that
25 excellent presentation. And you showed the power of this

1 approach when you had applied it to very carefully
2 characterized subjects. So one case exposure was
3 extremely well characterized, TCE, you know, with good
4 selection of subjects, and excellent exposure
5 measurements, air exposures. Another case, you had a
6 carefully characterized group of diseases -- people
7 affected by a disease.
8 And I'm just wondering if you could comment or
9 give your thoughts about whether it's better to --
10 directly -- to use your resources on these kind of very
11 targeted groups or to look like California Biomonitoring
12 is doing a larger population that's not carefully
13 selected, if you have thoughts about that.
14 DR. WALKER: Yeah. So we've always -- and, you
15 know, both the mentors -- my mentors who I worked with at
16 Emory and, you know, something I have still envisioned
17 these platforms as is basically a universal chemical
18 surveillance and biomonitoring framework.
19 So we've initially applied these to very well
20 characterized populations with the hope of demonstrating
21 that they have the sensitivity and it's feasible to
22 measure many of these exposures. I really see the
23 ultimate application of them is kind of to -- for
24 population screening or even applying to, you know, very
25 diverse disease groups to look at, you know, groups of

exposures that could contribute to either specific or non-specific disease processes.

So I absolutely do believe that there is a lot of application more in population screening. I think these initial studies have demonstrated what's feasible using this technology for exposome analysis. And I think there's a lot of potential to apply them in larger populations.

Our goal has been to make the assays as high throughput as cheap and use as little sample as possible, so that there is the potential to apply these more broadly to, you know, cohort studies and other populations.

PANEL MEMBER QUINTANA: Thank you.

CHAIRPERSON SCHWARZMAN: Other questions from the Panel?

Let me check in with Sara and Marley to see if there's any questions from the audience?

MS. HOOVER: Hi, Meg. This is Sara, and I can tell you there's no question from the email, but there is one question from the audience and I believe Marley is going to share that verbally right now.

DR. ATTFIELD: Hello. Can you hear me?

CHAIRPERSON SCHWARZMAN: Yes.

DR. ATTFIELD: Okay. Hi. This is Kathleen Attfield. I'm in the CDPH part of the Biomonitoring

1 California program. I was wondering -- I just don't know
2 the background of this. Is it possible to pair
3 dose-to-animal studies with the human studies, such as the
4 TCE experiment you talked about?
5 DR. WALKER: So it's not -- that's pretty
6 challenging. And that's one of the issues that we're
7 really facing with the TCE studies. So if we go to a cell
8 model, you know, we're essentially putting the TCE in
9 solution. And that exposure isn't representative to how
10 these people are being exposed. Their exposure was
11 respiratory.
12 So, you know, there is ways to kind of correlate
13 animal dose to what we're seeing in the human populations.
14 However, you know, one thing that we're -- the reason
15 we're using these occupational cohorts is because, you
16 know, they are very high exposures. These are higher
17 levels than you would ever see in -- you know, in just a
18 regular population, but they allow us to kind of cleanly
19 define the human response to these exposures in a way
20 that, you know, couldn't characterize in an animal model,
21 and that you could never test, you know, using a
22 controlled exposure.
23 So, you know, these are very unique populations.
24 And I think applying these methods first to these high
25 exposure populations provides, you know, important insight

1 into how the exposure affects the biology or how it
2 affects the pathways.
3 I'm a -- you know, not a -- I have some
4 toxicology training, but not a toxicologist by -- you
5 know, through and through. So I would have to speak with
6 some of my colleagues about what the best way to
7 extrapolate that human exposure to an animal model would
8 be.
9 CHAIRPERSON SCHWARZMAN: Ulrike.
10 PANEL MEMBER LUDERER: Yeah. Thank you for that
11 very interesting presentation. The question I have for
12 you is you -- you know, the platforms that you -- that you
13 are using that you've talked about obviously were designed
14 to maximize the types of, you know, both exogenous --
15 metabolites of exogenous chemicals, as well as endogenous,
16 you know, metabolites that you can measure. And I was
17 wondering if you could say anything about what of the
18 universe of, you know, the metabolome in humans do you
19 think you may be missing with these platforms that you
20 have?
21 DR. WALKER: I mean, I would still say we're
22 missing the majority. You know, I think we're moving
23 forward with baby steps. You know, we're going from being
24 able to detect, you know -- I don't want to -- you know,
25 we can detect a lot of features, but, you know, when we

1 deconvolute the features and convert them into spectra and
2 do all the filtering, you know, we went through a
3 measuring about, you know, 15 to 2,000 compounds on the LC
4 to now being able to detect an additional, you know,
5 10,000 or so on the GC. And again these are not features
6 I'm talking about. These are actually, you know,
7 de-convoluted spectra that we believe are signals that
8 could be arising from the sample itself.
9 But, you know, we're still not even close to
10 measuring the totality of chemical space. I mean, it's an
11 improvement, but relative to what's out there, it's an
12 incremental improvement. But, you know, as long as we're
13 moving forward, I feel good about that.
14 I think we have pretty good detection of a lot of
15 the things that we're interested in, you know, again for
16 the GC, the semi-volatile and volatile compounds. From
17 the LC, you know, we capture really good -- most of the
18 endogenous pathways some representative -- some
19 representation from those, as well as lot of drug and
20 environmental chemical metabolites.
21 But, you know, it's challenging to really put a
22 number on that, especially when we don't know what the
23 number is in terms of how far along we are, but I think we
24 still have a ways to go.
25 CHAIRPERSON SCHWARZMAN: Great. Thank you so

1 much, Doug, for that really interesting presentation. And
2 we're going to have a 15-minute break. We'll restart
3 right at 2:45 for our final presentation of the day
4 followed by an afternoon discussion session.
5 So see you then.
6 (Of record: 2:31 p.m.)
7 (Thereupon a recess was taken.)
8 (On record: 2:45 p.m.)
9 CHAIRPERSON SCHWARZMAN: Okay. We are going to
10 restart. And just to give you a sense of where we're
11 going. We have one final presentation now and then the
12 afternoon discussion session. So I will introduce our
13 speaker -- our final speaker of the afternoon is Rachel
14 Morello-Frosch who's a professor in the Department of
15 Environmental Science Policy and Management and the School
16 of Public Health at UC Berkeley.
17 Her research examines how social determinants of
18 environmental health and environmental chemical exposures
19 interact to produce health inequalities in diverse
20 communities.
21 OEHHA and CDPH collaborated with Rachel to
22 develop and test Biomonitoring California's results return
23 template. And so she'll be presenting on that today on,
24 "Chemical Suspect Screening as a New Approach to
25 Biomonitoring: An Application in Firefighters and Office

1 Workers".
2 (Thereupon an overhead presentation was
3 presented as follows.)
4 DR. MORELLO-FROSCH: Thanks. Can everybody hear
5 me?
6 CHAIRPERSON SCHWARZMAN: We can.
7 DR. MORELLO-FROSCH: Okay. And I'm just making
8 sure. Can you see my presentation?
9 CHAIRPERSON SCHWARZMAN: We can see you screen,
10 your Word document.
11 DR. MORELLO-FROSCH: Not good. All right. Let's
12 stop showing. I'm going to have to do some adjustments
13 here.
14 Do you see anything now?
15 CHAIRPERSON SCHWARZMAN: Still see the same Word
16 document.
17 DR. MORELLO-FROSCH: All right. Okay. Can you
18 see my screen? Can you see -- do you see a PowerPoint?
19 CHAIRPERSON SCHWARZMAN: Yes.
20 DR. MORELLO-FROSCH: And am I in presentation
21 mode?
22 CHAIRPERSON SCHWARZMAN: It looks like it's
23 working on it. Yes. Although, we see your version of --
24 rather than the full screen. That is we see the one with
25 the next slide showing.

1 If you're working with an external monitor, also
2 sometimes you just have to swap them.
3 DR. MORELLO-FROSCH: Yeah.
4 PANEL MEMBER SINGLA: Or you might -- you might
5 try turning off presentation mode.
6 DR. ATTFIELD: Or choose duplicate.
7 DR. MORELLO-FROSCH: What do you see now?
8 CHAIRPERSON SCHWARZMAN: We see the same thing as
9 before, the presentation mode, but from the presenter's
10 view.
11 DR. MORELLO-FROSCH: Sorry about this. I tested
12 this and it worked before. And now it's not working.
13 CHAIRPERSON SCHWARZMAN: That's okay. And don't
14 worry about your time. We'll give you the full time for
15 your presentation and just work it out.
16 DR. MORELLO-FROSCH: No, I'm more worried about
17 your time.
18 MS. HOOVER: Hi, Rachel. This is Sara. We
19 could -- we have your slides, we could set them up and
20 advance them, if you want to say next slide, if you're not
21 able to get this to work.
22 DR. MORELLO-FROSCH: What are you seeing now?
23 MS. HOOVER: The same thing, presenter's mode.
24 DR. MORELLO-FROSCH: Okay. I don't know how to
25 fix this.

1 MS. HOOVER: Okay. So why don't you close yours.
2 (Multiple voices at once.)
3 CHAIRPERSON SCHWARZMAN: There you go.
4 MS. HOOVER: There you go.
5 DR. MORELLO-FROSCH: How is that?
6 MS. HOOVER: There you go. All right.
7 DR. MORELLO-FROSCH: Okay. I really apologize
8 for that.
9 CHAIRPERSON SCHWARZMAN: The only thing Rachel,
10 there's -- the control panel for GoToWebinar, it appears
11 to us to be in the middle of your slide. Can you move it
12 to your other monitor?
13 There you go. Perfect. Thank you.
14 DR. MORELLO-FROSCH: Okay. Thanks for your
15 patience while I work through this. So today I want to
16 talk to you about a study that I've been working on with a
17 bunch of collaborators applying non-targeted methods to
18 examine environmental chemical exposures among women
19 firefighters in San Francisco. This study originated
20 among firefighters themselves in the City of San
21 Francisco.
22 --o0o--
23 DR. MORELLO-FROSCH: Our fire department there is
24 unique in that it has the largest number of women
25 firefighters out of all urban fire departments in part

1 because of the consent decree awhile ago to desegregate
2 the fire department. And so women have been with the
3 Department for a while moved up its ranks. The last two
4 chiefs have been women. And this person on the upper left
5 Jeanine Nicholson, who is the current chief, before she
6 became Chief, actually was very public about her
7 experience going through breast cancer.
8 And so increasingly women were concerned about
9 their exposures through environmental chemicals on the job
10 and the -- trying to understand the extent to which it
11 might be linked to what's going on in firefighting.
12 --o0o--
13 DR. MORELLO-FROSCH: Most studies that have
14 looked at exposures to environmental chemicals among
15 firefighters have been conducted almost exclusively in
16 men, in part because it is predominantly still very much a
17 male dominated profession. Although, it's diversifying in
18 many areas. And a lot of those studies have shown that
19 firefighters have higher exposures to a variety of
20 compounds associated with firefighting and other aspects
21 of their jobs, including PFASs, PAHs, flame -- different
22 kinds of flame retardants, dioxins and furans as
23 combustion byproducts.
24 --o0o--
25 DR. MORELLO-FROSCH: And many of these chemicals

1 have been shown in animal toxicology studies, and this
2 review was done by my collaborators at Silent Spring
3 Institute, many of these chemicals that firefighters are
4 exposed to have been shown in toxicology studies to be
5 mammary carcinogens. And so they definitely warrant
6 further study and it presented us an opportunity to
7 characterize the extent to which women firefighters might
8 be exposed to some of these compounds that have
9 applications for Mammary development in breast cancer.
10 --o0o--
11 DR. MORELLO-FROSCH: So in collaboration with the
12 firefighters who approached our science team with Silent
13 Spring Institute, as well as UCSF, colleague Roy Gerona,
14 who was doing the initial non-targeted work, we created
15 the Women Firefighter Biomonitoring Collaborative. And we
16 also had environmental health advocates working with us on
17 this to do some of the research translation piece, which I
18 will not be talking about today.
19 --o0o--
20 DR. MORELLO-FROSCH: And together we created this
21 study. And our primary aims were to characterize chemical
22 exposures among women firefighters and compare them to a
23 control group, in this case women office workers who also
24 work for the City and County of San Francisco, but who are
25 not first responders. We are also assessing potential

1 impacts of the chemical exposures that we have
2 characterized on upstream biomarkers of effect. And I
3 will not be talking about that today.
4 --o0o--
5 DR. MORELLO-FROSCH: So our inclusion criteria
6 were we wanted women over 18 who were non-smokers. For
7 firefighters, we wanted women in the fire service who had
8 had at least five years of active duty. And we ended up
9 with 83 women firefighters and 79 women office workers in
10 our study population.
11 --o0o--
12 DR. MORELLO-FROSCH: And we collected
13 biospecimens, serum, urine, and whole blood. And we did
14 targeted and non-targeted analysis in parallel in our
15 studies. So there was definitely a focused interest on
16 PFASs, but also on legacy and current use flame retardant
17 OPFRs. Again, I won't talk about that today. We have
18 some papers in the works and the PFAS papers published.
19 And then we did in parallel non-targeted chemical
20 analysis. And the biomarkers are thyroid hormones and
21 telomere length.
22 --o0o--
23 DR. MORELLO-FROSCH: We did an exposure
24 assessment interview looking at occupational and work
25 activities, diet, personal care product use, and consumer

1 product use in the home and in other places.
2 --o0o--
3 DR. MORELLO-FROSCH: And just as a little plug
4 for potential collaborators, we have building -- in
5 addition to the samples that we've collected in the study,
6 we sought to build a bioarchive that would facilitate
7 future analyses as analytical chemistry methods improved.
8 So we have a very nice repository. And we are definitely
9 eager to collaborate with others who might want to take
10 advantage of the samples that we currently have banked.
11 And we also had added nurses which I'll talk about in a
12 second.
13 --o0o--
14 DR. MORELLO-FROSCH: So as I said, we've had two
15 papers out. And this one on the upper left, which is in
16 the list of references in your packet and on -- available
17 on the SGP website. You can read both this -- this paper
18 that I'm going to talk about today.
19 --o0o--
20 DR. MORELLO-FROSCH: So our study demographics
21 for the office workers, which is this column on the left
22 and the firefighters on the right. From a racial and
23 ethnic point of view, they were very similar. We had
24 differences in educational attainment where the office
25 workers had higher levels of educational attainment and

1 the firefighters had higher levels of income.
2 --o0o--
3 DR. MORELLO-FROSCH: And so we set about
4 developing an in-house chemical mass spectra database for
5 our project. And in this case, we were limited to
6 chemicals that would ionize in the negative mode. And
7 we -- so we started with a baseline, a chemical library,
8 of what we call environmental organic acids, which we had
9 used for another study, characterizing exposures among
10 pregnant women. And then we added to that library of
11 chemicals. Had a lot of conversation with the
12 firefighting community, but also based on that review that
13 Silent Spring conducted adding chemicals that were shown
14 in toxicology studies to affect mammary gland development.
15 And the endocrine disruptors that were an initial
16 promoters of mammary tumors. And then we added additional
17 chemicals of specific interest for firefighting. And
18 again, we focused on compounds that would ionize in the
19 negative mode.
20 --o0o--
21 DR. MORELLO-FROSCH: And so similar to the other
22 workflow diagrams that you saw in prior presentations
23 today, we ran our samples through LC-QTOF/MS electrospray
24 negative mode. And you get this -- these chromatograms,
25 which then we processed to narrow down the kinds of look

1 at -- we look at the features and then try and narrow it
2 down to chemicals, chemical compounds, and -- that match
3 formulas and then we sort through the different isomers by
4 comparing retention times.
5 And then we go through a process of prioritizing
6 which ones we want to confirm and measure using targeted
7 methods. And because of resources, we have a priori
8 criteria for deciding which ones we're going to actually
9 quantify.
10 --o0o--
11 DR. MORELLO-FROSCH: So this is an example of the
12 cumulative number of environmental chemicals that we
13 detected using LC-QTOF. Each one of these lines
14 represents an individual participant in the study. And
15 the X axis is the number of chemical hits or candidate
16 compounds. And the color coding is the different chemical
17 classes that these chemical candidates fell into.
18 And so you can see there were quite a few
19 phenols, phthalate metabolites. And a lot of this is also
20 driven by the library itself. So I think that's important
21 to point out. And we could see that the hits were fairly
22 similar although slightly higher in firefighters.
23 --o0o--
24 DR. MORELLO-FROSCH: And then we embarked upon a
25 scoring and ranking of these chemicals based on the

1 suspect screen. And as I said, we had an in-house library
2 of about 722 chemical formulas. And we were able to
3 narrow it down to isomers that were matched to 300
4 chemical formulas or -- and then with retention time
5 correction, we had about 622 putative compounds, many of
6 which were isomers.
7 Here, we applied different kinds of inclusion
8 criteria based on whether or not, for example, peak areas
9 were higher in firefighters, differences in detection
10 frequencies, between the two groups. Maybe a novel
11 compound was ubiquitously detected in the entire study
12 population. And then, of course, chemicals that were of
13 interest because of their implications for mammary gland
14 development in toxicology studies, their estrogenic
15 potential, and also chemicals that had not been previously
16 biomonitored in NHANES or Biomonitoring California.
17 --o0o--
18 DR. MORELLO-FROSCH: So this is a partial list of
19 the candidate chemicals that we sought to validate, just
20 so you can kind of get a sense of how we did this. And
21 we -- this is looking at the differences in the detection
22 frequencies of these chemicals, in terms of between
23 firefighters and office workers. And then we compared the
24 mean peak areas between the two groups, the average mean
25 peak areas. And so where you see stars and symbols, this

1 indicated a significant difference, particularly in terms
2 of peak areas.
3 --o0o--
4 DR. MORELLO-FROSCH: We then applied a scoring
5 approach, based on those criteria that I just talked to
6 you about in that workflow, so whether or not they were
7 flame retardants, differences in detection frequencies,
8 whether or not they were statistically significant,
9 whether this was a novel compound that hadn't been
10 biomonitored before, genotoxic potential, estrogenic
11 potential, whether or not that something was not found at
12 all in office workers, but found in firefighters only, and
13 then whether or not it was a mammary carcinogen. Again,
14 it's another attempt to prioritize our chemicals.
15 --o0o--
16 DR. MORELLO-FROSCH: And then we used, where
17 there were commercially available standards, we sought to
18 validate the presence of these chemicals. And so you can
19 see, you know, we had different kinds of chemicals, some
20 of which had several different types of isomers with
21 different mean retention times in our serum samples. And
22 we compared that to the lab standards. And so the ones
23 that were -- that have the check were the ones that we
24 were able to validate in the QTOF. And these ones below
25 we were not able to validate because of a retention time

1 mismatch.
2 --o0o--
3 DR. MORELLO-FROSCH: And then based on that
4 validation process, then we were able to prioritize which
5 chemicals we actually wanted to go in and measure and
6 quantify, based on targeted methods. And so this is
7 descriptive statistics of the select chemicals that we
8 measured from the NTA, and then we actually quantified
9 them using targeted methods. And as you can see here, we
10 didn't see huge -- huge differences, but we did find some
11 interesting compounds, including Dinoseb, which is a
12 banned pesticide.
13 It's also, it turns out, present in some dietary
14 medications. So we're in the process of finding out from
15 some of our participants whether or not some of them take
16 some diet medication that maybe might explain the presence
17 of this compound in some of our participants.
18 --o0o--
19 DR. MORELLO-FROSCH: So we are expanding our
20 cohort and we have been adding nurses. So we have 60
21 nurses that we recruited, additional office workers, and
22 firefighters, a subset of the firefighters in our study.
23 --o0o--
24 DR. MORELLO-FROSCH: And we are looking at them,
25 these firefighters, after a fire event. So they basically

1 contacted us 24 -- within 24 hours post-fire and were
2 collecting blood and urine temporally and conducting
3 interviews. And then for the nurses versus office
4 workers, we are collecting blood and urine from them and
5 doing a comparison between these two groups. And in this
6 case, instead of doing targeted, and non-targeted, in
7 parallel, the non-targeted analysis for both of these
8 studies is going to drive what we're going to actually
9 look at in the targeted analysis.
10 So it's providing us a method for prioritizing
11 those compounds that we want to confirm, and quantify, and
12 see if we can detect novel compounds that haven't been
13 measured before in these study populations.
14 --o0o--
15 DR. MORELLO-FROSCH: Finally, I want to get back
16 to this issue of reporting back. As I think this Panel
17 has already heard about the many ways in which we've done
18 digital exposure report back that interface these tools to
19 return study results to study participants. And we
20 collaborated a lot with the Biomonitoring Program to do
21 this kind of thing in our study populations and in
22 particular with firefighters.
23 --o0o--
24 DR. MORELLO-FROSCH: And so this is kind of the
25 screen shots of what these kinds of things look like for

1 targeted analysis, which we've already returned to our
2 participants. So this gives you examples of like
3 what's -- the information on the chemicals and then
4 participants can actually see what their levels are
5 compared to others in this study population.
6 --o0o--
7 DR. MORELLO-FROSCH: But we are now in the
8 process of doing some report back on what we found out
9 from the non-targeted analysis. And this is kind of
10 language which you can kind of study when you look at the
11 slides more carefully. But it poses some interesting
12 questions about how do we communicate how this technology
13 works to study participants, because people are used to
14 kind of traditional explanations that we think what we're
15 going to measure first and then we go and measure it, and
16 while this is a very different approach.
17 So -- and the decision amongst the group, because
18 this is a community-based participatory research study,
19 was to report aggregate results rather than individual
20 level of results for these preliminary non-targeted
21 measures that we had in the study population.
22 So in terms of thinking about how we return
23 results for non-targeted analysis to study participants, I
24 think this is going to become an increasingly important
25 thing to think through how we communicate to our study

1 participants. In other words, how do we describe this
2 method in a meaningful way? How do we explain how
3 non-targeted differs from targeted methods and what are
4 some of the advantages and disadvantages of this approach?
5 How do we explain and distinguish between chemical
6 suspects versus confirmed and quantified compounds when
7 we're trying to communicate the different steps that we
8 undertake to elucidate novel chemicals that maybe haven't
9 been studied before in these populations.
10 And do we report things, for example, you know,
11 the number of chemical suspects found in each participant,
12 because, you know, like that graph that I showed you with
13 the hits and the different chemical classes, do we provide
14 it by chemical group?
15 --o0o--
16 DR. MORELLO-FROSCH: So do we do kind of a
17 suspect profile for each participant to kind of walk them
18 through how this process works or is that information
19 overload?
20 And then how do we convey our decisions about the
21 criteria that we applied for choosing which chemicals we
22 were ultimately going to validate and quantify in our
23 study population?
24 Because I think one of the challenges that has
25 been the subject of today's conversation is, you know, how

1 do you narrow it down, and what criteria do you apply, and
2 how do you -- how are you transparent about those
3 decisions, particularly when you're doing a collaborative
4 project with your study participants or community-based
5 participatory research? How do you come up with those
6 criteria for choosing those subset of chemicals that
7 you're actually going to measure using targeted
8 approaches?
9 --o0o--
10 DR. MORELLO-FROSCH: So I will leave you with
11 that. I just want to thank our illustrious team. This is
12 definitely a community-based participatory research
13 project. It's data driven in terms of non-targeted
14 analysis, but also community driven, in terms of how we've
15 designed our study protocols and sought to analyze and
16 disseminate our data.
17 Thank you.
18 CHAIRPERSON SCHWARZMAN: Thank you so much,
19 Rachel. We really appreciate that. We have a few minutes
20 for questions for Rachel and we'll start with the Panel.
21 And just a reminder, you can just raise your hand and I
22 will call on you. And then we'll go to the afternoon
23 discussion. We can just sort of blend into that.
24 Okay. Questions specifically for Rachel?
25 Oliver.

1 We see you Oliver, but we don't hear you.
2 PANEL MEMBER FIEHN: I needed to find the panel.
3 It's like where is the Panel?
4 Thank you for that presentation. So you and
5 several other participants have stated something about
6 in-house panels. And I really wonder about why is it
7 in-house? Why -- can you make things public? Can you
8 make spectral libraries public, retention times public? I
9 mean, do we all have to buy the same compounds again, and
10 again, and again? Somebody else said something about, you
11 know, the reproducibility of spectra, you know, because it
12 is important to share information. And also, not only
13 that, but at some point also share raw data, if we can. I
14 mean, Dinesh Barupal talked a little bit about the
15 problems in sharing raw data. And I guess that's another
16 discussion. But at least for spectra, we should be able
17 to share them, shouldn't we?
18 DR. MORELLO-FROSCH: Yes, I totally agree with
19 you. And as I mentioned really quickly in my conversation
20 was we developed, you know, our own spectral database, not
21 because we were trying to keep it proprietary, but we used
22 as a baseline another spectral database at the time that
23 we had used for something else and then built upon it.
24 But it's something definitely that we seek to
25 share and expand. And it's definitely not something

1 that's proprietary. And now, for example, we -- now that
2 we've added nurses, we are collaborating with the
3 Department of Toxic Substances Control. So we're using
4 even more -- you know, a much larger spectral database
5 ionization in the positive and negative mode. So I agree,
6 these are things -- this is information that you will want
7 to share, so that other people can see, you know, how you
8 built your database and how that impacted what you found,
9 because it is limited by the database that you're
10 comparing it to.
11 CHAIRPERSON SCHWARZMAN: Yeah. Oliver, do you
12 have a follow-up?
13 PANEL MEMBER FIEHN: Follow-up question. So
14 you also presented preliminary annotations that turned out
15 not to be correct by retention time metric, right?
16 DR. MORELLO-FROSCH: Yeah.
17 PANEL MEMBER FIEHN: But still, I mean, they are
18 very likely very similar, right? I mean, they have the
19 same -- a good spectrum and it matches nicely to your
20 phenols, just not that exact isomer. How do you --
21 DR. MORELLO-FROSCH: Right.
22 PANEL MEMBER FIEHN: How do you suspect -- how do
23 you suggest we should handle those, those isomers -- an
24 unknown isomer of?
25 DR. MORELLO-FROSCH: Yeah. Well, again, this was

1 sort of a proof-of-concept paper. So just to kind of walk
2 us -- walk ourselves through this process to figure out a
3 prioritization scheme of how we might make these
4 decisions. And I think there is now kind of more
5 sophisticated statistical strategies that we could
6 undertake to make some decisions and not sort of
7 arbitrarily be eliminating isomers. I also think that
8 again this data that you generate, the raw data, can be
9 mined again and again. And so, you know, those -- you can
10 revisit those isomers and other kinds of things to redo
11 your analysis or to re-mine the data again.
12 CHAIRPERSON SCHWARZMAN: Rachel, I'm just curious
13 how -- how the study participants kind of related to the
14 non-targeted aspect of this study? Did your -- sort of
15 what did they want from it -- your expectations(inaudible)
16 with NTA in its current form? What was that like
17 including that portion of the analysis in the study, as
18 opposed to the sort of more traditional and easily
19 understood targeted analysis?
20 DR. MORELLO-FROSCH: Yeah, that's a great
21 question. So when we -- when we co-designed the study, it
22 was -- it was decided that we -- that they -- they were
23 very interested in applying this -- what was then a more
24 novel technology add now has proliferated a lot more since
25 we started. But they also wanted to make sure that we did

1 targeted analysis for chemicals that they were very
2 specifically interested in, in this case, current and
3 legacy flame retardants, PFAS, and some of these other
4 kind of usual suspects that have been studied in other
5 populations in order to compare what has been found --
6 what would be found in women to other studies.
7 And I -- but there was also a lot of excitement
8 about being able to apply this technique to elucidate
9 chemicals and to maybe discover something new. They also
10 knew the risks that maybe, you know, this -- this strategy
11 might not necessarily reveal, you know, a smoking gun, if
12 you will, of some -- something novel that's very
13 specifically related to firefighting.
14 So there's a lot of conversation, a lot of
15 description of -- really visual descriptions of how time
16 of flight technology works, how you -- how you scan the
17 samples, the challenge of the isomers, how you narrow it
18 down, all that kind of stuff. So that was a lot of
19 conversations in sort of our weekly science meetings was
20 explaining this technology and to apply it and then
21 thinking together about the kind of criteria that we
22 want -- we would want to apply to narrow down the
23 chemicals that we would measure directly, because we also
24 had -- they wanted us to measure some of these chemicals
25 that we've discovered through non-targeted analysis

1 directly. That was an important part of it for them.
2 And, of course, you're limited by resources in terms of
3 choosing which ones you're going to measure.
4 CHAIRPERSON SCHWARZMAN: Yeah. Great. Thank
5 you.
6 Eunha, you had a question.
7 PANEL MEMBER HOH: This is Eunha Hoh San Diego
8 State University.
9 It's very interesting work and I'm glad to see
10 the project and really appreciate that presentation, and
11 also very interesting subjects. Non-targeted analysis,
12 you show the results based on the LC/QTOF, and -- but I'm
13 thinking about, you know, considering that the
14 firefighters are much more exposed to combustion, you
15 know, products, you know, like more chemicals associated
16 in combustion. Do you plan to analyze the samples on more
17 GC side of analysis -- non-targeted analysis?
18 DR. MORELLO-FROSCH: Yes. We -- we are -- we
19 would definitely like to be table to do that. We are --
20 we need to get more resources in order to do that, but
21 yes, absolutely.
22 CHAIRPERSON SCHWARZMAN: And, Veena, you had a
23 question also and then we'll go into the discussion
24 period.
25 PANEL MEMBER SINGLA: So hi, Rachel. Good to see

1 you.
2 DR. MORELLO-FROSCH: Hi.
3 PANEL MEMBER SINGLA: Great presentation.
4 My question was about, you know, in terms of some
5 of the primary health concerns the firefighters had, and
6 especially breast cancer, how do participants feel about
7 the total information that they got from the targeted
8 analysis and non-targeted analysis? In relation to their
9 health concerns, did they feel they got the information
10 they wanted? And also, did they -- did the participants
11 have any suggestions for what they might want to see done
12 next or what should be done about the information?
13 DR. MORELLO-FROSCH: Yeah. So -- so one of the
14 things when they -- when they came to us with wanting to
15 do a study to try and understand the extent to which
16 exposures might be associated with breast cancer, a lot of
17 the conversation before we even sat down to write the
18 grant for this was why an epidemiological study is not
19 feasible in this population, issues around statistical
20 power, all kind of things.
21 And so it became abundantly clear that, you know,
22 an exposure study was going to be really trying and get at
23 their question more indirectly and could also potentially
24 be more efficient in terms of lifting up chemicals of
25 exposure and their sources that they could act upon now.

1 So I think there was a lot of enthusiasm. But
2 again, it took a -- it was a process to really have that
3 conversation and decide what kind of study design was, A,
4 feasible, and would also get at some of their concerns.
5 And as a result of a lot of this work, there have
6 been practices that have changed at the -- at the fire
7 department to try -- try and reduce exposures and efforts
8 to do not only education but also some standard operating
9 procedures that have changed there as a result of some of
10 the results that we've -- we've been seeing.
11 CHAIRPERSON SCHWARZMAN: Thank you so much for
12 the presentation, Rachel. And I'm sure these issues will
13 arise again as we continue the discussion. I hope you'll
14 be able to be around for it.
15 And I want to transition into discussion section
16 now. So a couple of reminders as we go through this just
17 about how to participate. So as before, Panel Members,
18 please raise your hands if you want to speak and I'll call
19 on you. Guest speakers and Program staff go ahead and
20 turn on webcams and raise your hands, if you want to speak
21 also. For attendees, who wish to speak during the
22 discussion session, please alert us by using the question
23 feature or the raise hand feature, and go to webinar, and
24 we'll call on you individually. And at that point, you
25 can unmute yourself and ask your question or provide your

1 comment. And then once you finish, please, of course,
2 mute yourself again.
3 I just saw -- oh, no, I see the view just
4 changed. We're all good.
5 Okay. And then during discussion -- so Panel
6 members, just please keep your webcams showing unlike
7 pausing them as -- as we have for the presentations,
8 unless you need to step away. For everyone else, please
9 keep the webcam off, and your -- your microphone muted,
10 once you've finished speaking.
11 So webinar attendees can also submit written
12 comments or questions via GoToWebinar as before or by
13 emailing biomonitoring@oehha.ca.gov and we'll read them
14 out loud an paraphrase them if need be, if we lack time.
15 So I want to start the discussion -- I have some
16 discussion questions that I want to highlight, but also I
17 want to make sure that we return to some questions that
18 didn't get answered before we ran out of time. And on
19 my -- please tell me if my list is correct, I have Veena
20 first, Eunha, and Ulrike.
21 And do you still -- if those questions are still
22 relevant, we can just start with Veena, and we'll go
23 through that list, and just go ahead say if your question
24 isn't relevant. It's okay. We can move on.
25 PANEL MEMBER SINGLA: Okay. Thank you, Meg. And

1 James, thanks so much for the excellent presentation
2 earlier. I had -- I had two questions. One was in
3 relation to the information we heard from John about the
4 kind of wide range of coverage that he saw with, you know,
5 different methods and different labs. And I just wonder
6 if you had any sense of the coverage of the specific
7 method you were using on -- with PFAS and if -- if you had
8 any like ideas or estimates of what you might still be
9 missing from the -- you know, the new compounds that have
10 been identified?
11 And my second question was about if we have any
12 sense of if there might be wider exposure to these new
13 chemicals you've identified beyond the specific sites, if
14 we know anything about potential long-range transport of
15 these chemicals, or if these chemicals are present as
16 contaminants or otherwise in fluoropolymer -- polymers or
17 the kind of end-use products of -- of those
18 fluoropolymers?
19 DR. McCORD: Okay. So I'll answer the easier
20 question first, which was the second one. So when we
21 start to identify these new materials, we tend to both go
22 back and look at places where we already have data that
23 we've banked for things that we might have missed, where
24 they were below a threshold that we would use for
25 examining things. And in some of these cases, we do have

1 far-ranging samples that we can compare to. And then as
2 we do more studies going forward, we always look for
3 things that we previously discovered.
4 So in the example of New Jersey, we have far
5 field soil samples from as far out as New Hampshire, which
6 is quite far north in the prevailing wind direction. And
7 we were able to identify that material as far north as
8 basically into another State and region. And it's not in
9 samples that we've collected from the non-prevailing wind
10 direction, where we no reason to believe that it's a
11 thing.
12 For stuff like GenX, we've only ever really found
13 them to an appreciable degree in industrial impacted
14 locations. And it seems like because of this
15 proliferation of new -- different types of materials,
16 every different manufacturer seems to have switched to new
17 things. So unlike the legacy PFAS compounds, like PFOA,
18 which is ubiquitous, because everybody had -- had this
19 convergent evolution onto a very narrow chemistry, because
20 we've proliferated to all sorts of different new things,
21 it appears like the problem is very site specific.
22 Everywhere that we go that we do an investigation
23 like this, we find a different fingerprint, a different
24 combination of chemicals. And depending on who the major
25 producer or user is in that site, they're using whatever

1 chemical is best suited for their purposes. So like I
2 said, we've got six or seven different states that we're
3 working on.
4 And in each site, there's a different major
5 driver chemical. So, you know, Michigan is dealing with
6 6:2 FTS as a replacement for PFAS. New Jersey has these
7 chlorinated compounds as a replacement for PFOA.
8 Fayetteville was -- has GenX and related chemicals as PFOA
9 replacements. West Virginia is another Chemours site
10 that's also dealing with both the GenX HFPO-DA compounds,
11 but then other things. And it does seem to be very
12 stratified in terms of what's a problem where. It's no
13 longer a universal PFOS -- or a universal PFAS question.
14 And I've Completely forgotten what your first question
15 was, if you could repeat it.
16 PANEL MEMBER SINGLA: Sure. No problem. If you
17 have any sense of the coverage of the -- your method for
18 PFAS?
19 DR. McCORD: Yeah. Okay. So we apply a couple
20 methods. So like in the previous talk, we do both sort of
21 positive and negative mode LC methods. Most of what we
22 see are negative mode compounds again because they're kind
23 of drop-in replacements for a lot of the legacy PFOA type
24 compounds. So they're frequently carboxylic acid
25 perfluorinated type compounds, especially around

1 fluoropolymer manufacturing. In specifically AFFF
2 impacted locations, there's a lot more zwitterionic
3 compounds, sulfonamides, and positively charged compounds
4 that show up only in the positive mode. So we look at
5 both sorts of modes.
6 We know that we're blind to volatile compounds
7 because we don't have a GC method that we apply. We sort
8 of just focus on water surface, water extractable organic
9 fluorine type compounds from soils and other stuff that's
10 LC-able, because that's the only high res instrument that
11 we've had for a while. But we've recently added more high
12 res GC capability and we're hoping to move into that
13 space.
14 Specifically, we know, in North Carolina and in
15 West Virginia, as well as in New Jersey that there is a
16 substantial air deposition portion to the story. And we
17 see it in soil and in, you know, surface water that's
18 impacted by things coming out. But there are volatile
19 fluorinated products that are released via the air route
20 that we can't measure at all. And some of them, we can
21 determine -- we know what they turn into environmentally.
22 We can see the end products in the water.
23 Others, they're not known to -- you can't see them by
24 LC-MS and we know that we're missing them.
25 And so that's one of the reasons that outside of

1 my group, but in the EPA in general, they're working on,
2 you know, total organic fluorine-type methods to try to
3 get a handle on everything that's perfluorinated, so that
4 we can fill in some of these gaps. So we're trying to be
5 as broad as we can in our coverages by applying lots of
6 different methods. But we do know that we're missing
7 things and we try to be aware of that.
8 I'd say we get -- I don't -- I don't know. I
9 can't speculate. But we get most of the stuff that's
10 important in water I think. Non-ionized stuff we're
11 missing a lot and I don't know how much, because there's
12 no way to know.
13 CHAIRPERSON SCHWARZMAN: Eunha, I think you're
14 next.
15 PANEL MEMBER HOH: This is Eunha Hoh. I have --
16 actually, Jon had to stop the presentation, because of the
17 time. But one of the slides that, Jon, you planned to
18 show that it was the loss of detection or identification
19 through the sample preparation or something like that. I
20 don't remember, was like solvents. You know, you added
21 the chemicals into solvent, and the next -- the other
22 stat, another stat, so we're kind of losing the detection
23 of the chemicals.
24 Jon, would you -- I think that's very important,
25 you know, for non-targeted analysis in the rear samples,

1 you know. Would you give some comments on that or, you
2 know, your thoughts on it. Yeah.
3 DR. SOBUS: Of course. And I apologize again for
4 having to basically skip those slides. I think the slides
5 are available to the Panel members and the public. And we
6 did go ahead provide some of the references of the
7 publications. So if folks want to do a deep dive into
8 that information, you should have access. If you don't,
9 please feel free to reach out to me and I'll get it to
10 you.
11 In a nut shell, that work was led by our
12 colleague Seth Newton, where we basically took that
13 SRM2585, which is a house dust -- a composite house dust
14 sample. And Seth did a number of additional experiments.
15 So he did experiments where he did multiple dilutions,
16 simply in solution. So that was basically the best case
17 type scenario, where you would expect performance to be
18 optimal. Then he did experiments where he took that same
19 spiked solution and added in dust extract basically to
20 provide that matrix.
21 Then in another experiment he spiked at a very
22 high concentration the dust and performed an extraction
23 and a cleanup.
24 And then in the final experiment, he spiked at an
25 environmentally relevant concentration into the dust and

1 then did the extraction and the cleanup.
2 So basically, that slide was showing that we
3 started with about -- let me see, I've got my notes. We
4 started with 365 spiked chemicals. The best case scenario
5 for his experiment just in the solvent spike, we
6 identified 134. So we lost 63 percent off the bat, even
7 in the best case scenario.
8 Once we took into account the matrix effects, we
9 lost ten percent of the compounds just because of matrix
10 interferences. When we took into account the extraction
11 procedures and the cleanup procedures, we lost another
12 five percent. And then when we took into account the
13 concentration issues, we lost an additional nine percent.
14 So we went from 134 that could be identified
15 under optimal conditions to 49 that could be observed
16 under real-world experimental conditions. So it's just
17 kind of making that point that, yes, the ENTACT mixtures
18 is a really good way to kind of evaluate benchmark
19 methods. But it's critical that we move into that kind of
20 real matrix, real sample appropriation space, because it
21 is going to drastically affect the performance of a given
22 method.
23 PANEL MEMBER HOH: Thank you.
24 CHAIRPERSON SCHWARZMAN: Okay. And our -- last
25 on our list of built-up questions is Ulrike.

1 PANEL MEMBER LUDERER: Hi. Thanks. Thank you,
2 again for those really interesting talks. I had a
3 question again also for James. And that was -- so a lot
4 of these new PFASs are supposed to be less persistent than
5 the -- some of the legacy ones. And I was wondering if
6 you're -- in your analyses, you were able to determine
7 whether you were finding some evidence of environmental
8 breakdown of any of these chemicals, or whether you were
9 really just -- you know, you were identifying only the
10 chemicals that were actually being manufactured at these
11 sites?
12 DR. McCORD: So as I mentioned, we know a little
13 bit about the chemistry from our discussion with the
14 companies that are there. What we are detecting in a lot
15 of cases are the terminal environmental Provex from things
16 that they're emitting via air or other sources. They
17 fairly rapidly breakdown, and so what we see are the
18 terminal products.
19 And there's really no indication thus far that
20 there's any further environmental breakdown. They are
21 designed to be less persistent. But our experiments that
22 we've done for the most part don't really bear out that
23 they breakdown substantially more than a perfluorinated
24 compound, specifically the structures that we've seen. So
25 we did a little bit of sort of top assay type

1 experimentation, where you can hit them with, you know,
2 strongly oxidizing conditions to force them to another
3 terminal product. But all of the perfluorinated ether
4 type compounds that we've seen, and even the chlorinated
5 ones, would pretty much stay as they are, even under
6 pretty harsh like top assay type conditions.
7 We've seen evidence that things like ADONA, which
8 is a polyfluorinated, and then things like 6:2 FTS
9 obviously, they have chemical breakdown pathways that you
10 can do under top assay type conditions and then also
11 biological breakdown pathways. But it seems like the
12 emerging contaminants they have the same types of general
13 behaviors as the other contaminants do.
14 Now, they drop off in the environmental matrices
15 that we're measuring, because, for instance, in the Cape
16 Fear River when you turn off the effluent, they're the
17 only source. And then the water dilution basically dries
18 the concentration way down over a very short time frame.
19 So if you remove the source, the total
20 concentration in the environment is so low that it drops
21 below the limit of detection within a month or two. And
22 then it seems like the clearance rate in humans is on the
23 order of months to years. So the exposed population
24 starts to get rid of it as well, but that just means that
25 it falls below our analytical levels, not that it's

1 necessarily breaking down.
2 And we've tried to do some sort of studies where
3 you can put them in soil and do different things, and they
4 don't really do much.
5 PANEL MEMBER LUDERER: Thank you.
6 CHAIRPERSON SCHWARZMAN: So I see there's a
7 couple questions. I saw Oliver's hand and Carl's. I want
8 to take a moment here just to go over the goals for the
9 discussion question -- the -- sort of the prompts for the
10 discussion session to make sure that we're getting the
11 Program the feedback that they need, as well as kind of
12 getting our questions answered.
13 So I'm just going to take a minute here to read
14 the discussion questions and then set us loose on that.
15 And if Oliver and Carl have questions or comments related
16 to that, we'll get to those next.
17 So some things that the Program is interested in
18 hearing from us about are, number one, possible next steps
19 for the Program in terms -- in the area of non-targeted
20 analysis. Are there pilot NTA projects that you could
21 envision that you think the Program should conduct? And
22 what are the challenges or the difficulties that you would
23 envision and sort of foresee as Biomonitoring California
24 starts to try to integrate NTA into its studies? So
25 that's the first question is next steps and potential

1 challenges.
2 The second question is looking for opportunities
3 to work with other groups that are already doing
4 non-targeted analysis or collaborate with those
5 researchers in ways that support the Program goals, and
6 specifically to some of the guest speakers, can we arrange
7 trainings with your groups for Biomonitoring California
8 staff to sort of deepen staff's understanding of the
9 methods that we heard about today?
10 And the third question from the Program is are
11 there emerging chemicals or chemical groups that NTA is
12 identifying that should be reviewed by the Program as
13 potential designated chemicals? So if they're not on the
14 chem -- designated chemical list, but they're really kind
15 of rising to the top in some of the NTA studies that are
16 being done, should we propose those to the Program for
17 consideration?
18 And finally, any suggestions for the Program
19 about returning results from NTA studies to participants?
20 And that gets back to some of the questions that we asked
21 of Rachel in her study.
22 So those -- that's what the Program wants input
23 on. Oliver, did you have a point you wanted to make with
24 regard to that? Please go ahead.
25 PANEL MEMBER FIEHN: Yes. My question was

1 related to that to some extent it's both question and also
2 comments for next steps and so on -- opportunities. So I
3 found it very interesting today. It's very much to my
4 heart, as you can imagine. But there is a problem that is
5 shared between metabolomics and exposomes research in the
6 sense of how to convey the coverage as well as the
7 confidence in annotations, when you find a chemical and,
8 you know, how sure are you, especially now when you report
9 back to participants in a study.
10 That relates to the question how we report
11 confidence. Several speakers said they would use the
12 Schymanski levels, but Jon made very clear that, in his
13 presentation, that when his -- in his ring trial, you
14 know, participants reported like they had every
15 confidence. Schymanski level one with MS/MS and retention
16 time and everything is fine, and it actually wasn't
17 correct. So that was interesting.
18 And I see this both as a question to Jon how he
19 would envision, you know, these confidence levels
20 calculated or better maybe transparent to the public and
21 to participants, as well as for us, including the
22 biomonitoring program the State laboratories, you know, to
23 think about the ring trial, because Jon specifically said
24 they would invite other lab stories to participate as
25 well.

1 And I think that would be a great opportunity
2 for, you know, our laboratories, if they want to use NTA
3 methods in the future to see, you know, how they would
4 stack up to that challenge, right?
5 Apparently, that was -- you know, it's very
6 clear -- the study design is clear. It is possible to
7 participate. It is -- the samples are ready, both the
8 chemical mixtures, as well as the, you know, spiked
9 matrices. And I think this would be a great opportunity
10 for our laboratories to see how they stack up before they
11 then dive into further, you know, resources, and further
12 studies. So that was my question, as well as next step,
13 and opportunities.
14 CHAIRPERSON SCHWARZMAN: Jon, if you want to
15 respond or add anything to that, you're welcome to.
16 DR. SOBUS: Sure. That's a series of great
17 points. And I agree with Oliver on pretty much all of
18 them. Let me see if I can remember some of the points I
19 wanted to make there.
20 First is kind of confidence levels in reporting.
21 Oliver and I had attended together a metabolomics workshop
22 as ASMS last year. And something that really stuck out in
23 that evening work group, probably attended by a hundred,
24 150 people, is how many people said how frustrating it was
25 that even when they reported the confidence levels, when

1 they passed along that information, folks that were the
2 recipients of the information didn't quite know what to do
3 with it.
4 In some cases, if they didn't know what to do
5 with it, they would just kind of leave it off. So there's
6 both the -- from the standpoint of the recipient not
7 understanding the confidence levels, and not being able to
8 interpret them and then there's perhaps something equally
9 or more troubling, which is what I've experienced is the
10 experts who are actually annotating some of these
11 compounds with the confidence levels that, in my
12 experience, are getting it wrong, right?
13 So you have some people that aren't using
14 confidence levels, some people that send the confidence
15 levels forward to have them misinterpreted or not
16 interpreted, and then some people that send them forward
17 but they're actually the wrong confidence levels to begin
18 with.
19 So I think that's something that is going to be
20 addressed through education, and through consensus, and
21 through adherence. I don't necessarily think the solution
22 is making confidence levels more refined or more complex.
23 I think that may have the effect of pushing people away.
24 But we -- we had I think and hour and a half or two hour
25 discussion exactly on that topic and there was no

1 consensus, at the time, amongst a community of experts.
2 So the confidence level reporting thing is
3 extraordinarily complex. And, Oliver, like you said, even
4 if you report something in a confidence level, it's very
5 difficult to know whether you can accept that as truth at
6 a particular confidence level. One of the things I'm
7 doing, but I didn't talk about is trying to assess
8 performance not only for a specific method or a specific
9 lab, but the performance level at a specific reported
10 confidence level.
11 So the difficulty here is is you need to answer
12 those questions because they're critical, but the more I
13 dig into these performance metrics, the more nuanced they
14 get, the less accessible they get to my target audience.
15 So it's incredibly challenging. And I think the solution
16 again is to have as much discussion as possible, as much
17 education as possible, and just transparency in what's
18 being done.
19 So that's -- that's kind of the confidence levels
20 and reporting confidence levels in terms of performance
21 review. Again, I think I understand what you're saying.
22 And if I do, I entirely agree with you that in my mind,
23 you know, for targeted analyses right now, there are --
24 there are bodies that do credentialing, right? Some
25 specific targeted methods have to be credentialed in order

1 to do work. I see that as the future for environmental
2 NTA.
3 And part of what we're trying to do through the
4 ENTACT project is put the research community on a path
5 towards credentialing. And this -- these are my opinions.
6 But in designing ENTACT the way we did, we kind of had
7 that in mind to say what would a study need to look like
8 to be able to fully and usefully evaluate performance?
9 Now, some of the drawbacks in the way that we've
10 done it is we started it in 2018. It's now 2020 and I've
11 still got a long way to go in terms of the evaluation. I
12 think the participants would agree unanimously that it was
13 more work than they thought it was going to be when they
14 agreed to participate.
15 So I think my recommendations right now would be,
16 A, this needs to happen. There needs to be some type of
17 samples that can be used for evaluation and the contents
18 of those samples need to be kept secret. I think there
19 needs to be an independent third party that is
20 appropriately resourced to manage these projects and to
21 efficiently do the data analysis that I'm trying to do
22 right now.
23 It's incredibly difficult to find the time to
24 clean the files, to process the files, to match it, and to
25 constantly shift thinking and have to redo things. So

1 whomever that third party would be that would be in charge
2 of the credentialing, again would have to have the
3 appropriate resource to be able to work efficiently and
4 get responses to these laboratories to get them
5 credentialed as soon as possible, so that they can support
6 actual experimental work.
7 CHAIRPERSON SCHWARZMAN: Dinesh, I think you have
8 something to add here?
9 DR. BARUPAL: Yeah. So I have a comment on this
10 one that to whom we'd want to communicate the result. So
11 if it's a question of development of a database or
12 publishing a manuscript, I think we can use different
13 scheme of levels for annotation. But moment we want to
14 share those with participants, or clinical decision
15 making, or some other hard decision making, they need to
16 be passed through that they will -- annotation were
17 confirmed by pure standards, because any misannotation can
18 be translated into wrong decision-making.
19 So after database development or if we want to
20 just publish some good manuscript, it's okay to use these
21 levels and discuss about that, the pros and cons about.
22 The moment we want to give it to a participant, we want to
23 be really sure that it has been confirmed by pure
24 standards.
25 CHAIRPERSON SCHWARZMAN: Carl, did you have a

1 point, suggestion, or a question? You were next on the
2 list, I think.
3 PANEL MEMBER CRANOR: Are you talking to me, Meg,
4 I'm sorry?
5 CHAIRPERSON SCHWARZMAN: Yes. I thought you had
6 raised your hand earlier.
7 PANEL MEMBER CRANOR: I have, yes. First of all,
8 I think this is a great set of presentations. I hope that
9 it is useful to us and to the State. I want to -- let's
10 see, what could be next? Well, I think the generic idea
11 behind non-targeted testing is to identify things that are
12 maybe not yet seen to be a problem and then to send them
13 through an appropriate system as quickly as possible to
14 see whether they -- people ought to be protected from
15 them. That's point one.
16 Point two though is that non- -- in some sense,
17 non-targeted testing and biomonitoring are, what I would
18 be tempted to call, legally post-market, but let's think
19 of it as not fully preventative of heath effects to
20 people, because they're already out there, and now we're
21 discovering them, and tying to do something about them.
22 So a second point I would make about our next
23 steps, is there a way to design non-targeted testing, so
24 that they can be used in a much more preventive manner?
25 Now, I thought the case study from Cape Fear was

1 very interesting in that sense, because you were looking
2 at substitutes for the perfluorinated compounds. That
3 raises a couple of -- well, it raises a couple of legal
4 questions, but also a couple of preventive questions.
5 Were those, the second- or third-generation substances,
6 something that had been properly approved by the U.S. EPA?
7 I suspect not or didn't get much scrutiny. But they're
8 out there -- the suggestion was that they're still very
9 persistent and guide -- I'd seen a few papers that suggest
10 that there's toxicity.
11 So to what extent can our non-targeted testing
12 not only pick up new things that we should worry about,
13 but can -- can be pushed into the existing legal
14 structures, for example, to hold companies accountable if
15 their substances that they're using haven't gone through
16 the appropriate EPA presumably pre-market approval that is
17 supposed to be part of the new TSCA?
18 So I do worry about both non-targeted testing and
19 biomonitoring as being -- having preventive opportunities
20 but very late in the game. And so I would urge people to
21 think about how to make them more preventive upfront to
22 the extent possible and see where we can go that way.
23 DR. McCORD: I can -- I can comment on it. I
24 don't know if I'm supposed to raise my hand first or not.
25 CHAIRPERSON SCHWARZMAN: Please, go ahead.

1 DR. McCORD: Okay. So I am not an expert in
2 TSCA, but I'm going to give some of my understanding of
3 what has gone on specifically in the Cape Fear and sort of
4 more broadly.
5 So GenX, the compound that we were able to
6 identify a standard for was sold as a product by Chemours
7 as a replacement for PFOA. There was the sufficient TSCA
8 approval and available toxicology data, both in America
9 and in Europe for that compound -- particular compound.
10 In that particular instance, the State of North
11 Carolina actually had prohibited the company from emitting
12 GenX from their manufacturing process at the facility. So
13 they made that particular compound in one of their
14 processing lines in a closed loop process that generated
15 no waste. However, it turns out, it's also produced as
16 byproduct of their polymer manufacturing process and used
17 internally within that process, in addition to the fact
18 that they make it closed loop and then ship it to other
19 places where they use it.
20 And all of the other compounds that we identified
21 in the Cape Fear are also byproducts of their mostly
22 fluoropolymer manufacturing process. And it makes sense
23 from an industrial perspective if you can use the
24 byproducts of your polymer manufacturing as your
25 processing aids and everything is internal, then you don't

1 have to make products all on their own. And they're also
2 exempt from TSCA regulation, because my understanding is
3 that TSCA does not cover intermediates and other products
4 with no sort of commercial purpose. They're simply waste
5 products and then they are byproducts and used internally,
6 because they're never designed to be sold or emitted in
7 large quantities or anything like that.
8 So the company ultimately was responsible for
9 emitting GenX, because they have a specific rule about
10 non-emitting it and were actually emitting it as a
11 byproduct, but the other compounds are not covered under
12 the same type of TSCA regulation, just because of the
13 nature of the types of chemicals that they are.
14 Likewise, in New Jersey, the chlorinated compound
15 has some toxicology studies and it has approval as a food
16 contact material under ECHA. And I don't think it has any
17 TSCA data that I have access to. It might be filed under
18 CBI, which I don't typically have.
19 So some of these compounds, they -- they do have
20 toxicity data, if it is ever anticipated that they are
21 going to be emitted. But a lot of the compounds that we
22 find fall into this sort of gray area. They're
23 intermediates and other products that they're never
24 supposed to get out. They're only ever found as trace
25 contaminants of the finished product or side products of a

1 reaction that wind up in a waste stream, and then they
2 expose 75 miles of the surrounds for a particular
3 manufacturing facility. So they fall into this legally
4 questionable area.
5 The question of how you can apply non-targeted
6 analysis to the TSCA process is something that I'm
7 particularly interested in. And we have a project that
8 we're in the very early stages of of trying to figure out
9 how we can do non-targeted analysis particularly on things
10 that are mixtures and that might have byproducts and other
11 trace contaminants within TSCA. However, I think that we
12 are a very long way away from even getting non-targeted
13 analysis data incorporated into the TSCA process for
14 characterization, because in many cases, TSCA approvals
15 and significant use rules -- significant new use rules and
16 things like that, there's no experimental data that
17 doesn't come from the company.
18 So until a consultant has a QA problem -- that we
19 can solve a QA problem, where that data can be part of a
20 regulatory like data submission package, I don't even know
21 how we can get people to look at that data. So solving
22 the QA problem and figuring out to like deal with that
23 type of data is I think the first step in getting
24 regulatory bodies to look at it and being able to
25 interpret that data.

1 And then there's the challenge of figuring out
2 how do you do rapid toxicology characterization on unknown
3 compound if you do detect them, because the goal, I think,
4 is to avoid turning environ -- and the goal, it depends on
5 who you think is really in charge of things. But the idea
6 would be that you would like to avoid having to
7 characterize every potential chemical in existence in
8 order to have approval for anything.
9 CHAIRPERSON SCHWARZMAN: Thank you for that. But
10 I want to interrupt here for -- just for a sec to say
11 that -- to allow enough time for this discussion to really
12 carry through, we're going to do a small change to the
13 agenda, which is move the public comment period from the
14 end of the day up to 4:05 p.m., and then return to this
15 discussion until 4:20, when we move on to sort of wrap-up
16 the day.
17 So just to say we have more time for this
18 discussion. If anybody -- the reason I wanted to mention
19 it now is if anybody wants to make a public comment, they
20 should please prepare it and either indicate to us that
21 you would like to speak, or send it into the email
22 address, or indicate it on GoTo meeting and we will come
23 back to that at 4:05 p.m.
24 MS. HOOVER: Meg -- Meg, let me just chime in
25 real quick. This is Sara. I just wanted to clarify that

1 there are a bunch of public comments right now that are
2 relevant to the NTA discussion, so we could call for those
3 basically now.
4 CHAIRPERSON SCHWARZMAN: Right. That's what I
5 was going to say.
6 MS. HOOVER: And the 4:05 -- just to clarify to
7 the audience. What we're saying is normally at the very
8 end of the meeting we call for open public comment on any
9 topic. And what I'd like to do at 4:05 is just hear is
10 there any open public comment, given the fact that we
11 haven't had any -- or much of any public comment all day.
12 So we'd like to keep this going, because it's such a rich
13 discussion and lots of topics. So anyway, continue.
14 Thank you, all.
15 CHAIRPERSON SCHWARZMAN: Yes. So I'm going to do
16 the comments and questions that have come in over email
17 now, but I just wanted to give people a heads up about the
18 public comment period will be at 4:05, not at the end of
19 this discussion or we'll check for public comment at 4:05.
20 So with that, I want to turn to the comments and
21 questions that are coming in on the GoToWebinar. And I
22 want to invite Marley to share those.
23 CHAIRPERSON SCHWARZMAN: We can't hear you,
24 Marley.
25 So if that's --

1 MS. ZALAY: Can you hear me now?
2 CHAIRPERSON SCHWARZMAN: Yes. Good.
3 MS. ZALAY: Okay. This is a question from Susan
4 Hurley with Biomonitoring California for Doug. Can you
5 elaborate more on the silicone badges, are they ready for
6 prime time?
7 DR. WALKER: So I would say they serve a very
8 specific purpose. You know, it makes it very difficult to
9 take what we're measuring on the wristbands and actually
10 extrapolate that to an exposure level. We use them as
11 more of a screening tool to try and identify what
12 exposures are occurring and what we can detect. I think
13 they are ready for use in that context. The nice thing
14 about them is they're very cheap to produce. They cost
15 about $0.25 to buy the wristbands. And then we have to
16 clean them to remove impurities that were added during the
17 manufacturing process. That costs about another four to
18 five dollars.
19 But, you know, they're cheap enough where you
20 could actually produce a lot of them, send them out to
21 cohorts, collect them, and then analyze subsets from those
22 that you distributed. So say you want to provide these
23 wristbands to a population and then study a certain
24 outcome, you could easily send out a thousand or two
25 thousand of them, collect them, and then re -- you know,

1 only analyze the samples from people who ended up, you
2 know, developing an outcome or a disease. So in that
3 context, they're very useful.
4 But you have to be careful about how you're
5 interpreting the data, because we can't, like I said,
6 quantify what exposure is. We can just use it as a screen
7 to identify what exposures are occurring.
8 MS. ZALAY: Thank you. There's one more question
9 and one general comment.
10 I'll read the comment first and then I'll read
11 the question. Miaomiao Wang from the Environmental
12 Chemistry Laboratory at DTSC, the Department of Toxic
13 Substances Control, commented that among the labs that
14 participated and finished the ENTACT trial, they were
15 among those -- those labs. And they also participated in
16 the EPA workshop in 2018 and they're working on a
17 manuscript and look forward to performance feedback from
18 EPA.
19 And then lastly, there's a question from Martin
20 Karozy saying NTA can be used to measure exposures, but it
21 can also be used to measure biomarkers of disease. Can
22 anyone talk to examples of this?
23 DR. WALKER: So --
24 CHAIRPERSON SCHWARZMAN: Can you just say
25 something about that relevant -- let's take it within the

1 context of what Biomonitoring California does, which might
2 be to make some of these links between exposure and
3 disease. But please go ahead, Doug.
4 DR. WALKER: Yeah. So we kind of see the disease
5 biomarkers as an intermediate between the exposure and the
6 outcome itself. You know, that's the advantage of using
7 the untargeted metabolomic platforms is you can
8 characterize all these biological processes and link them
9 to the exposure biomarkers that you're measuring. But I
10 mean that -- that is a very good point that was made by
11 the commenter question. You know, a lot of these
12 untargeted exposomic methods that we're using now were
13 kind of borne out of more traditional metabolomics
14 analysis. And those have been used in a number of
15 applications for more disease biomarkers.
16 So there's -- you know, there's that kind of
17 historical use, but another important thing to recognize
18 is that the exposome or the exposures that we carry and
19 potential development of exposome risk scores could also
20 act as biomarkers of disease once we start better
21 understanding, you know, how our exposure profiles overall
22 contribute to our health outcomes, or, you know, other
23 things that we're addressing and studying.
24 CHAIRPERSON SCHWARZMAN: Okay. Thank you for
25 fielding those.

1 Jenny.
2 PANEL MEMBER QUINTANA: In terms of the Panel
3 giving guidance, to Biomonitoring California, I was
4 wondering if we should have some discussion about the
5 benefits of non-targeted analysis.
6 So, for example, what I've been hearing is that
7 we can use it for finding regrettable substitutions. It's
8 very valuable where people are changing what's in
9 products. Another use I heard was byproducts, finding
10 byproducts, which aren't necessarily known. The third
11 might be finding unrecognized pollutants in lots of people
12 that we didn't know was a big -- very widespread. And
13 then fourth was risk from specific exposures like
14 firefighting.
15 By the way, someone has their microphone not
16 muted that's typing. Just as a -- let you know.
17 So -- and speaking about risks from specific
18 exposures, like the firefighters, I did also wonder if
19 there's a role for other samples that could really drive
20 the non-targeted analysis, like, for example, air samples
21 during a firefighting event. Maybe identifying chemicals
22 there might help drive what you might look for in people.
23 So I just thought I'd maybe bring up should we
24 talk about what would be the biggest benefit to
25 Biomonitoring California, and then we could decide how to

1 achieve that first -- second.
2 CHAIRPERSON SCHWARZMAN: Yes, Jenny. I think
3 that's excellent. What we're trying to do is sort of
4 summarize this and make recommendations to the Program
5 where relevant. So if you have thoughts to start that. I
6 mean, thank you for your -- for getting that started.
7 Did you have recommendations you wanted to add to
8 that, Jenny?
9 PANEL MEMBER QUINTANA: I wasn't sure if "you"
10 was the Panel or "you" was me.
11 My recommendation would be for substitutions.
12 Finding those regrettable substitutions would be a very
13 important use, I think, and also byproducts. So I think
14 those two things would be very important. But apart from
15 that, I think I would really vote for looking at specific
16 populations. And the specific populations in addition to
17 what's already being studied, I would say should be
18 disadvantaged populations, whether it's a community or
19 whether it's workers in a certain industry that --
20 thinking about California, what makes California unique,
21 perhaps compared to other states, is our high proportion
22 of refugees, and immigrants, our diverse industries. So I
23 think we should think about California also and what makes
24 us unique as well and our proximity to the border. In the
25 case of where I live, people exposed to pollution from

1 open burning in Tijuana. You know, there's -- there's a
2 lot of unique features in our a population and a lot of
3 agriculture, for example.
4 So thank you.
5 CHAIRPERSON SCHWARZMAN: I agree, Jenny. And I
6 think the examples of, you know, what's been done in
7 Delaware and the other examples from the same presentation
8 that are sort of site specific. And we're looking at, you
9 know, what's -- what's in this area are really interesting
10 models for us to sort of think about adapting to our
11 state.
12 Dinesh, you had something to add there and
13 then -- and then Carl, sorry. Just to let you know I've
14 seen you.
15 DR. BARUPAL: Thank you. NTA has a great
16 advantage in all -- all these -- some different scenario
17 is the number of analytes. So you -- sometimes you only
18 have hundred microliter plasma sample. And the question
19 is do you measure ten compounds using -- using a targeted
20 approach or do you measure 5,000 compounds with that
21 hundred microliters and store all the data.
22 So -- and in this setting, NTA really has a great
23 advantage that we should do NTA if it has the right
24 combination of analytical chemistry, sample preparation,
25 and the data science approaches.

1 CHAIRPERSON SCHWARZMAN: Okay. Thank you.
2 Tom.
3 PANEL MEMBER McKONE: I forgot to reach for that
4 mute button.
5 Thanks. I actually want to continue on the ideas
6 that Jenny brought up. And I think -- I was thinking of
7 it a little more broadly though, which is -- I mean, if
8 you look at the history of environmental health sciences,
9 we've always tended to look backwards and do a better and
10 better job of detecting the chemicals we already know
11 about.
12 And I think, you know, we've done some of that
13 here. We're always building our list. But to the -- we
14 want confidence and we're picking chemicals that we're
15 going to find. And we want confidence that, you know,
16 something somebody else has already done.
17 So what came up for me today, especially on the
18 non-targeted assessments, is part of a broader issue of
19 how do we really start being a little more proactive in
20 finding chemicals that we haven't quite looked at well
21 enough or don't even know about yet. I mean, there's --
22 there's this whole idea that there's -- you know, we heard
23 really big numbers, hundreds of thousands of
24 environmentally-related chemicals that might be, you know,
25 in the metabolome or the exposome. And it's just a --

1 it's kind of overwhelming.
2 So I thought, you know, in terms of strategy, I
3 think non-targeted assessments is one component of maybe a
4 broader effort to look at this is a really good tool. We
5 learned a lot about it. But I also think the Program
6 should be looking at kind of a portfolio of tools to
7 find -- to make sure we're looking forward, that we're
8 really anticipating what's in the population now or might
9 be in the population in a year, instead of really still
10 tending to look backwards about, oh, well, we just found
11 out from other people that this is an important issue.
12 I mean, it's kind of what we did with flame
13 retardants, so -- so -- and it's a funda -- I think what
14 really brought this up is when I asked Jon Sobus about,
15 oh, is this all you do or do you have a way of really
16 targeting it. And he's -- he mentioned it. He said, oh,
17 it's too much to talk about today, but that there's a
18 whole series of activities to go through to try and build
19 lists and then narrow them down, to then do their
20 non-targeted analysis, not on everything in the world, but
21 really things that show up. So there are these methods
22 for kind of triangulating among different ways of looking
23 at it.
24 CHAIRPERSON SCHWARZMAN: I'm going to use Chair's
25 prerogative here to insert a comment, that it kind of

1 connects to what Tom just said on this issue of sort of
2 finding replacements and the evolution of the market as it
3 changed. This has always been such a weakness is our
4 inability to anticipate given the sort of policy structure
5 in the U.S. where there isn't public disclosure of where
6 an industry is going and what chemicals they're putting in
7 what.
8 And so I even want to move beyond Jenny's kind of
9 depiction of regrettable substitution, because often
10 they're substituted with chemicals for which we have no
11 toxicological data and so we don't know if it's an
12 improvement or a worsening.
13 And Biomonitoring California has made such a
14 tremendous step in enabling designation of chemical
15 classes. And sometimes those classes are chemically based
16 and sometimes they are more functionally based, or at
17 least groups will -- class might be putting too fine a
18 point on it. But sometimes there's a functionally based
19 sort of group that's assessed, like where is the universal
20 flame retardants moving from, you know, halogenated to
21 non-halogenated flame retardants.
22 And so I think that's a particularly exciting use
23 of non-targeted analysis and could be sort of combined
24 with the other themes that have come up about kind of
25 place-based investigations, like the ones that James was

1 describing, and in selecting those, identifying
2 particularly hard hit communities or populations to
3 understand what they're being exposed to.
4 Those are the main things that kind of rise to
5 the surface for me. Nerissa, do you have a response to
6 that or something you wanted to add?
7 DR. WU: I do. And I agree with all of this. I
8 think this has been a really exciting discussion. And it
9 feels like the future of certainly little "b"
10 biomonitoring, if not Biomonitoring California.
11 But I do wonder how this fits into our Program in
12 terms of what our priorities are. We're small a Program.
13 We all know kind of the limits of what we can do. We have
14 a mandate to do surveillance work. And there's this kind
15 of dichotomy between really targeted, whether it's
16 community based or geographic based, studies where there
17 might be more motivation to look at a particular group of
18 chemicals, and some tolerance or some uncertainty of what
19 we're looking for versus surveillance, where we already
20 know we have -- you know, there -- there's a lot of
21 concern about giving your biological samples over to be
22 analyzed. And if there's a thought that you might be
23 looking at, you know, kind of a limitless range of
24 chemicals, people might be less inclined to participate in
25 something like that.

1 So as I always sort of find myself sort of
2 thinking about how do we prioritize? We are legislatively
3 mandated to do surveillance work. We are legislatively
4 mandated to return results to people, and in a way that
5 people can understand, and are useful to them, and are --
6 you know, that are educational and how do we balance that
7 with this exciting work, which I think is really needed on
8 this more targeted community basis, either the community
9 is targeted or maybe the list of chemicals is a little
10 more targeted. So it's just not a wide open swath of
11 results that might be returned to people.
12 CHAIRPERSON SCHWARZMAN: I wanted to continue
13 this line of discussion, but I also want to stick to on
14 our promise to check for public comment at this time. And
15 so let's just put a pause on that for one sec, while we
16 check for public comment, and then continue that line of
17 conversation.
18 So Marley and Sara, is there any one indicating
19 the would like to make public comment at this point?
20 MS. ZALAY: This is Marley Zalay. There's no
21 additional questions from GoToWebinar.
22 MS. HOOVER: And I can confirm there's no
23 questions in the email either, so please continue with
24 this discussion.
25 CHAIRPERSON SCHWARZMAN: Great. Then we have

1 until 4:20 for this discussion.
2 I appreciate the -- Nerissa bringing us sort of
3 to the practicalities of the Program. And also one of the
4 things it made me think of is the one way that -- by --
5 non-targeted analysis can even increase the surveillance
6 aspect of biomonitoring work in ways that targeted
7 analysis may be even is just much more limited. But I say
8 that in the context of having heard this interesting thing
9 that Rachel said, which was that the participants were
10 less excited about NTA than they were about looking for
11 the particular chemicals that had sort of risen to their
12 consciousness and level of concern.
13 And I really appreciate the point that you're
14 making, Nerissa, about sort of the palatability of these
15 kinds of studies to participants.
16 Anyway, I'll step aside and let somebody else.
17 I think, James, did you want to respond to that?
18 DR. McCORD: Yes. So I've been associated with
19 this problem in a lot of different cases. So we've worked
20 with biobank materials and we have some ongoing studies
21 related to that where we're doing both targeted and
22 non-targeted work. And also, we've had to deal with
23 reporting to communities that are affected this, where
24 we've done targeted and non-targeted work.
25 And to also piggyback of something that Dinesh

1 kind of said earlier about choosing like when you're going
2 to do targeted and non-targeted work. In a lot of cases,
3 the work that we've done, we've sort of extracted targeted
4 information out of non-targeted experiments. You can do a
5 full scan type non-targeted experiment and also use it to
6 generate some quantitative data, if you have standards and
7 can run calcurves in conjunction, and you have the right
8 method that gives you decent chromatograph peaks and
9 things.
10 So you can process a sample in many cases the
11 same way that you would do a targeted experiment, still
12 get targeted data, and then have all this excess data
13 lying out. It depends on exactly the type of information
14 that you're looking for in your targeted data. Some
15 methods are very specific and will only -- sort of like
16 Jon said, he only makes certain chemicals all the way
17 through the process. But if you have generic enough
18 preparation methods for certain classes of chemicals, you
19 can definitely do both the targeted approaches that people
20 are used to and expect and then also collect non-targeted
21 surveillance data.
22 In many cases, when we've done this, our IRB and
23 our subject's participation agreements have basically said
24 that we hope to do this type of surveillance work in order
25 to identify new materials, but we've only ever reported on

1 specifically the targeted data back to the participants,
2 because only targeted data is associated with real risk
3 assessments where we felt like we could give an individual
4 any information related to their results or the associated
5 health risk.
6 And then we would only report the aggregate data
7 for things that are non-targeted where there's less actual
8 information. Because as I kind of mentioned when we dealt
9 with the Wilmington participants, it's very difficult to
10 make someone happy when you say we found a lot of
11 different things and you have no idea what it means,
12 because it's difficult to be comfortable with sort of the
13 ambiguity of that process, right? And you'd like to avoid
14 the anxiety associated with not knowing, if -- for the --
15 for the large majority of cases.
16 So it depends on what your exact legislative
17 mandate is in terms of what you cannot do.
18 MS. HOOVER: Yeah. Perfect seg -- perfect segue,
19 James. This is Sara Hoover. I'm just going to chime in.
20 And this is -- this is a great setup for one of our
21 questions, which is we have to return NTA results. So
22 anything we measure on participants officially, we have to
23 return.
24 Now, we've done a pilot project. I shared with
25 everyone the pilot packet that we developed. Rachel had

1 some comments about, you know, working on participant
2 returns. So that will be a fundamental part of any
3 project we do. Except for the comment about biobank
4 samples, that's definitely an opportunity where we can't
5 return the results. So we could do more broad types of
6 screening without having to think about results return.
7 But I just wanted to throw that in there, because
8 that kind of is a foundation of our Program. And so we
9 don't have the luxury of -- we have to return all results.
10 Anything that is a result we return. And you'll see how
11 we did that for the very small pilot project.
12 Again, I think someone else just mentioned too --
13 it's a very good point - I think Nerissa raised as did
14 others -- focusing in on a class of chemicals of a great
15 concern -- of a great interest -- was what we did. So we
16 didn't do actually non-targeted. Even though we called it
17 that, it was actually targeted towards just PFASs. So
18 that simplified some of the report back.
19 CHAIRPERSON SCHWARZMAN: I want to make sure that
20 we hear -- capture for the Program all the Panelists'
21 suggestions. So I want to scan who has something to
22 contribute, in our -- in our last six or seven minutes.
23 So, Veena, and is there anyone else that I should stack up
24 lined Veena. Veena and Eunha. Okay. Go ahead, Veena.
25 PANEL MEMBER SINGLA: So I really appreciated

1 Jenny's kind of overall suggestions on thinking about
2 specific populations, especially vulnerable populations
3 and also appreciate the challenge of balancing that with
4 the Program's mandate for surveillance.
5 You know, I think I'd just say in the current
6 moment when the pandemic has really laid bear the racial
7 disparities that contribute to health disparities that
8 it's really important to think about how we can better
9 understand the cumulative burden of environmental
10 exposures on vulnerable populations.
11 And I wonder if non-targeted analysis could help
12 us do that, both in terms of chemical and non-chemical
13 stressors and biomarkers of stress. And if that
14 information could be helpful in making decisions -- actual
15 policy decisions, because there is a really interesting
16 New Jersey bill that's focused on cumulative impacts and
17 integrating cumulative impacts into siting decisions
18 before making siting decisions.
19 So I think it's something to think about how
20 non-targeted analysis could help us better understand
21 cumulative exposures and also how that information could
22 be used to inform decisions.
23 CHAIRPERSON SCHWARZMAN: Great. Thank you,
24 Veena. And Eunha.
25 PANEL MEMBER HOH: Yes. I think I'd like to

1 think about the -- like what we want to do in rare
2 situation, what we can do, what is the feasible thing, you
3 know. I mean, I'm running a laboratory as well that I
4 don't -- I know how difficult it is. Like, we constantly
5 adding more, and more, and more with a limited resource.
6 It's a very, very difficult task.
7 I was thinking about the non-targeted analysis,
8 based on the biomonitoring samples like the very limited
9 amount of blood samples. It's -- I'm not sure if really
10 have a lot of resources. It's probably eventually that's
11 the way to go, but I think it's something that can be more
12 feasible, that like Jenny mentioned like something like
13 more environmental samples in a certain community, you
14 know. That could be done for the non-targeted analysis,
15 if we see the chemicals that we completely overlooked, you
16 know.
17 So that's what I kind of -- kind of can vision,
18 you know, how we may want to put it into that, you know,
19 the current Biomonitoring Program.
20 CHAIRPERSON SCHWARZMAN: Thank you for that. I
21 want to put out a question to all our guest speakers
22 about -- so the Department is -- or the Program is asking
23 us, you know, are there ways that they should be deploying
24 non-targeted analysis in realistically, currently in
25 studies? And I guess I have an open question about sort

1 of the viability at this moment of using NTA methods -- of
2 the Biomonitoring California Program, using NTA methods
3 given, for example, all of the sort of method issues that
4 Jon Sobus presented.
5 So if the Program is asking us are there pilot
6 studies that they should consider doing, I'm curious if
7 the guest speakers have any brief, because we're almost
8 out of time, input about what actually is possible right
9 now?
10 DR. MORELLO-FROSCH: This is Rachel. I think in
11 terms of addressing interests around disproportionately
12 impacted communities, the approach that was taken, for
13 example, to focus NTA strategies on chemical classes of
14 concern is a nice way to start, especially because of the
15 report-back requirement baked into the Program.
16 And so that gives you opportunities to do
17 surveillance of interest and to see what's going on with
18 chemical substitutes when you know that certain things are
19 being phased out and yet products -- certain products are
20 continuing to be manufactured. And it also allows for a
21 meaningful way to do community collaboration where
22 appropriate, either place-based or occupationally-based or
23 whatever, in terms of speaking input and people
24 understanding kind of what are the benefits and pitfalls
25 of a non-targeted analysis.

1 But your -- you have sort of a -- focusing on
2 chemical classes, your -- you have your known unknowns
3 basically. And that's probably more doable than sort of
4 completely non-targeted analysis.
5 CHAIRPERSON SCHWARZMAN: Thank you for that.
6 Doug, did you come on because you have a response?
7 DR. WALKER: Yes, I did. Thank you. You know,
8 one thing the we should also think of, whenever there's an
9 opportunity to compare targeted and non-targeted
10 platforms, I think there's a lot of advantages to doing
11 that. What we've been able to show for our assays is that
12 we do get comparable detection to a lot of the more
13 targeted platforms.
14 And so it supports using these non-targeted
15 platforms and anchoring in what we know. And then in
16 addition to that, you can start screening for, as was just
17 mentioned, you know, other compounds from certain chemical
18 classes. So in terms of pilot studies, if there is an
19 opportunity to apply a non-targeted method to samples that
20 have already been characterized by targeted analysis, I
21 think that's a really excellent opportunity.
22 CHAIRPERSON SCHWARZMAN: Great. Thank you.
23 We need to turn toward our final summary and
24 wrap-up of meeting. And I guess I would just invite, I
25 think the Program is always open for input and eager for

1 input. So if there are ideas that we haven't captured
2 today, I think the Program would welcome them by email in
3 follow up.
4 So with that, I want to turn this over for a
5 moment to Vince Cogliano who's the Deputy Director for
6 Scientific Programs at OEHHA. And he will be providing a
7 brief summary of the input and action items from today's
8 discussion.
9 Vince, please go ahead.
10 DR. COGLIANO: Thank you. Thank you very much,
11 Meg. I'm unmuted. Okay.
12 So, let's see, we heard quite a bit -- and first
13 of all, I'd like to congratulate all the speakers and
14 participants who made comments. This has been a very
15 useful meeting for me to understand this Program. And
16 there's just a lot of exciting work going on here. And I
17 think it will really help us advance risk assessment and
18 environmental protection over the next several years.
19 I guess we heard quite a few things. We learned
20 a lot of -- we heard some summaries of some of the
21 programs from California Department of Health or the
22 Department of Toxic Substances Control that are
23 contributing to this. We learned some of the activities
24 going on at the U.S. EPA about validating or coming up
25 with methods that can be used to figure out which -- which

1 new methods are suitable. We've seen some applications of
2 NTAs in exploring PFASs in North Carolina, and where they
3 found many other chemicals that are related to the PFAS
4 exposure outcomes, but which hadn't been identified
5 before. And also the New Jersey case study that came up
6 with emerging compounds we should look at.
7 We learned about some cheminformatics tools to
8 support exposomics, and metabolomics, and framework for
9 measuring the exposome. In the morning, we had a specific
10 item recommended by the Panel recommending that the
11 Biomonitoring California Program design an NTA pilot
12 project in a specific population, for example, in a
13 disadvantaged community, which we heard quite a few of the
14 comments in the last half hour, or in a specific
15 occupational group, or refugee group, or another group
16 relevant to California's unique population.
17 It would be important to examine the cumulative
18 burden of exposures, chemical and non-chemical, in these
19 heavily impacted communities and to suggest that
20 Biomonitoring California looked at ways to use
21 non-targeted analysis to address and inform these
22 decisions that we make at these -- in these populations or
23 at sites.
24 There was also encouragement during the day for
25 the Program to look for ways to use non-targeted

1 assessments to be more proactive in finding emerging
2 chemicals, including -- including regrettable
3 substitutions in chemicals which almost nothing at all is
4 known.
5 In my long career in environmental health, I now
6 have witnessed quite a few times when -- in my first ten
7 years of my career we banned or phased out some substance
8 and then ten years later we were concerned about the new
9 substance that was being used. And I think these
10 non-targeted analyses could really give us a handle on
11 what chemicals might be better or worse for substitutes.
12 We have quite a few different tools and methods
13 being developed, so we should be using a portfolio of
14 tools to find out what is in the population now and what
15 might be appearing in the future due to shifts in the
16 market.
17 So there's a focus on looking forward and not
18 looking back. You know, there's the comment made that we
19 often refine our methods to look at chemicals we know
20 about and get better and better methods of identifying
21 them, and -- instead of looking at the chemicals that are
22 actually emerging.
23 And then there was a suggestion to think about a
24 practical and feasible way to tar -- apply targeted
25 non- -- non-targeted analyses using environmental samples,

1 for example. Also, to ensure that we keep monitor
2 California's major priorities and participant feedback in
3 mind when we would consider future projects.
4 We also have to grapple with the result --
5 returning results for any project, in case -- in
6 California, based on the statutes that we have here in
7 this state. So that's another thing that whatever we
8 find, we have to disclose.
9 So I think that's my quick summary of some of the
10 recommendations and things that we've heard today.
11 And I'll turn it back to you, Meg.
12 CHAIRPERSON SCHWARZMAN: Thank you for that,
13 Vince. I appreciate the wrap-up.
14 MS. HOOVER: Meg.
15 CHAIRPERSON SCHWARZMAN: I'm sorry, Sara, what?
16 MS. HOOVER: Yeah, I just wanted to toss in one
17 morning recommendation just to capture the action items
18 and that was just the item about the Panel would like
19 OEHHA to figure out if halogenated carbazoles are already
20 captured as part of any chemical group that is already on
21 a designated list. If not, OEHHA should track this group
22 of chemicals to consider for a possible preliminary
23 screening.
24 And like I always do, I'll put up --
25 CHAIRPERSON SCHWARZMAN: Oh, we lost you, Sara.

1 You said, like I always do. So, Sara, I can't understand
2 you anymore. Do you want to try again?
3 MS. HOOVER: Let me try again.
4 Nope.
5 CHAIRPERSON SCHWARZMAN: That sounds better.
6 MS. HOOVER: Am I back?
7 CHAIRPERSON SCHWARZMAN: Yep.
8 MS. HOOVER: You guys are frozen.
9 Okay. Sorry about that. Just real quick. I'm
10 putting out a pitch for anybody who can hear me now to
11 send in emerging chemicals of interest. Anything you
12 become aware of in your work or in your NTA projects. I'm
13 having an unstable internet connection. Apologies for
14 that.
15 CHAIRPERSON SCHWARZMAN: We can hear you though.
16 That's good. So for all -- everyone who's involved now in
17 doing non-targeted analysis to keep in the back of your
18 minds, if something interesting rises to the fore to shoot
19 an email toward biomonitoring to say, you know, we're
20 seeing this new interesting thing that you might want to
21 take a look at.
22 So with that, I want to announce that a
23 transcript of this meeting will be posted to the
24 Biomonitoring California website when it's available. The
25 meeting was also recorded and I'm not clear what's

1 happening with that recording, but it may be that it's
2 being used by the transcriber.
3 The next SGP meeting is on November 12th of this
4 career. And it will also be held as a virtual meeting.
5 I want to really thank the Panel and the speakers
6 for everything that you've contributed to this meeting, as
7 well as the audience. And a tremendous thank you to the
8 Program leadership and Program staff, because there was
9 significant legwork involved in making this meeting happen
10 and transitioning it to a virtual format. And I think it
11 was shockingly smooth, given all of the potential hurdles.
12 And it's really kudos to a lot of time and effort that the
13 Program leadership and staff has put in to making this
14 work.
15 So thank you to everybody who participated and
16 I'll adjourn the meeting.
17 (Thereupon the California Environmental
18 Contaminant Biomonitoring Program, Scientific
19 Guidance Panel meeting adjourned at 4:29 p.m.)
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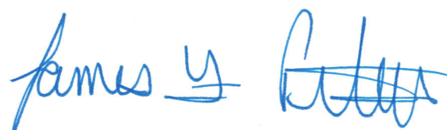
C E R T I F I C A T E O F R E P O R T E R

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 28th day of July, 2020.



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