MEETING

STATE OF CALIFORNIA

ENVIRONMENTAL PROTECTION AGENCY

AIR RESOURCES BOARD

SCIENTIFIC REVIEW PANEL

ON TOXIC AIR CONTAMINANTS

CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY

SIERRA HEARING ROOM, 2ND FLOOR

1001 I STREET

SACRAMENTO, CALIFORNIA

TUESDAY, JANUARY 23, 2018

9:01 A.M.

JAMES F. PETERS, CSR
CERTIFIED SHORTHAND REPORTER
LICENSE NUMBER 10063

A P P E A R A N C E S

PANEL MEMBERS:

Michael T. Kleinman, Ph.D., Chairperson

Cort Anastasio, Ph.D.

Jesús A. Araujo, M.D., Ph.D.

Paul D. Blanc, M.D.

Alan R. Buckpitt, Ph.D.

Stanton A. Glantz, Ph.D.

S. Katharine Hammond, Ph.D.

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

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

REPRESENTING THE AIR RESOURCES BOARD:

Mr. Jim Behrmann, Panel Liaison

Mr. Vernon Hughes, Chief, Community Assessment Branch

REPRESENTING THE OFFICE OF ENVIRONMENTAL HEALTH HAZARD ASSESSMENT:

Dr. Lori Lim, Senior Toxicologist

Dr. David Ting, Chief, Pesticide and Environmental Toxicology Branch

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

REPRESENTING THE DEPARTMENT OF PESTICIDE REGULATION:

Dr. Terrell Barry, Lead Exposure Assessor

Dr. Shelley DuTeaux, Chief, Human Health Assessment Branch

Dr. Svetlana Koshlukova, Senior Toxicologist, Risk Assessment Section

Dr. Eric Kwok, Senior Toxicologist, Exposure Assessment

Mr. Randy Segawa, Special Advisor

Dr. Marilyn Silva, Lead Risk Assessor

Dr. Marylou Verder-Carlos, Assistant Director

I N D E X

P R O C E E D I N G S

CHAIRPERSON KLEINMAN: Good morning. We're going to call this meeting to order, but we're going to delay about five more minutes while everybody's getting settled. And we are waiting for two of our panel members, who may be delayed. So we will be back on in about, let's say, in five minutes.

(Off record: 9:31 a.m.)

(Thereupon a recess was taken.)

(On record: 9:34 a.m.)

CHAIRPERSON KLEINMAN: Good morning. Now that our panel is assembled I'd like to call this meeting to order. I want to welcome you everybody to this meeting of the Scientific Review Panel on Toxic Air Contaminants. And I want to just -- also we are going to have viewers on the webcast watching. So welcome to them as well.

A couple of administrative items. For the people in the room, there are restrooms and drinking fountains outside of the room to the left. Should there be a fire alarm, please exit down the stairs and proceed outside the building.

Most importantly, the panel will really appreciate it if you set all your communicators to a silent mode.

And now I'd like to just go around the table and

have the panel members introduce themselves, starting with Alan.

PANEL MEMBER BUCKPITT: Good morning. I'm Alan Buckpitt. I'm retired from the School of Veterinary Medicine at UC Davis.

PANEL MEMBER GLANTZ: I'm Stan Glantz. I'm a professor of medicine at UCSF.

PANEL MEMBER HAMMOND: I'm Kathy Hammond, Professor of Environmental Health Sciences at UC Berkeley School of Public Health, and associate dean for academic affairs there.

PANEL MEMBER ANASTASIO: I'm Cort Anastasio. I'm a professor in the Department of Land, Air, and Water Resources at UC Davis.

PANEL MEMBER LANDOLPH: I'm Joe Landolph, Associate Professor in Microbiology and Pathology and Toxicology at USC and a member of the USC Norris Comprehensive Cancer Center.

PANEL MEMBER ARAUJO: I am Jesús Araujo, Associate Professor of Medicine and Environmental Health Sciences at UCLA.

PANEL MEMBER RITZ: Dr. Beate Ritz, Department of Epidemiology, Environmental Health Sciences and Neurology at UCLA and a member of the Center for Occupational and Environmental Health at UCLA.

PANEL MEMBER BLANC: Paul Blanc, University of California at San Francisco in Department of Medicine and Chief of the Division of Occupational and Environmental Medicine.

CHAIRPERSON KLEINMAN: Thank you. And I'm Michael Kleinman. I'm at University of California Irvine. And I'm the Chair of the Panel.

So this morning, there are two agenda items that we'll be going through. The first item will be a short briefing by the Air Resources Board to the Panel about implementation of Assembly Bill 617. And then the second item will be the Panel's review of the draft evaluation report on chlorpyrifos from the Department of Pesticide Regulation.

The Assembly Bill 617 requires that the Air Resources Board, among other things, develop a monitoring plan and emission reduction strategy for California's most polluted communities. The Panel's one of several groups to be consulted in the implementation of this significant legislation signed by the governor last year.

Today, Vernon Hughes, Chief of the Community Assessment Branch of the ARB's Office of Community Air Protection will brief of on ARB's plans.

Mr. Hughes, thank you very much for being here today; and I'll turn it over to you.

MR. HUGHES: All right. Thank you. Thank you very much for having us today. Again, we'll be giving an overview of the implementation status to date.

As you all are probably aware, AB 617 passed in the summer, authored by Assembly Member Cristina Garcia, and it fundamentally transforms how we do community-level planning for air quality, especially in communities that experience a greatest, highest cumulative exposure burdens. Specific the legislation sets out a number of planning framework elements including community-level air monitoring; the development of a monitoring plan; a State strategy and community-specific emission reduction plans; an expedited schedule for the installation of the cleanest controls on facilities, so that goes back to BARCT and TBACT type of controls; enhanced requirements for the reporting of emissions; and increased penalty provisions for polluters, as well as grant -- mix available grant funds for communities and for early action items.

To implement the program, the California Air Resources Board has established the Community Air Protection Program in the Office of Community Air Protection, which I'm a branch chief there. And the legislation sets ambitious implementation schedules to be achieved by October 1st, 2018; and that includes identifying impacted communities, establishing the

criteria for air monitoring and local emission reduction plans, as well as developing statewide strategies for reducing emissions.

It also gives air districts specific roles, so it's not only Air Resources Board implementing; the air districts play a very important role especially in implementing the action plans called for in the bill. And today, we've been working very closely with the air districts, with CAPCOA and air districts on working through as partners how we move forward with the implementation.

We've also had a significant level of outreach to community groups, environmental groups, and regulated industries. So lots of meetings. And I'll touch on the scale -- or our scope of outreach that we've done to date as well in a minute. But based on the outreach to date, we've put together two documents that provide staff's initial proposals on forming the program elements. The first one is called the Community Air Protection Program framework document as a concept paper. And then also a process and criteria for 2018 community selections. So part of the bill requires a process for identifying communities for action plans and monitoring; and that document covers the process for selecting the communities.

The program framework is still in the early

stages, so these documents are -- it's really designed as a mechanism to seek continued feedback once we release them. They'll go out early February, both the documents will go out for review and feedback. And we'll discuss these papers also in three summit meetings that we're going to be having in -- all-day summits that we're going to be having in February. And those summits will be essentially a morning session that covers the broader program and then break-out sessions that cover more specific elements of the programs. We plan to get into a fair amount of detail in those summits.

AB 617 also prescribes a certain level of outreach in terms of consultation by requiring CARB to consult with specified stakeholders. Those stakeholders include this panel as one of the groups; air districts; office of Environmental Health Hazard Assessment, or OEHHA; environmental justice organizations; affected industries and others.

In response to those requirements for the consultation, CARB's put together a multi-stakeholder consultation group of more than 20 stakeholders. And we'll seek input from the consultation group through the consul -- through the consultation group we'll seek consultation. Just because of the short time frames that we're under, that's an efficient way to bring all these

folks together and get their input and feedback.

Dr. Kleinman is one of the members of the consultation group, and it's going to be chaired by Dr. Balmes, one of CARB's board members.

And the first meeting of the group is scheduled for the end of this month. So we look forward to this committee's and the other members of the consultation group, their feedback on our program.

As I mentioned, we've had a significant amount of outreach to date in the program. We've had a core starting with the board meeting in October. Afterwards we had a series of four informational meetings throughout the state on the program and over 50 discussions with community residents, air districts, environmental justice organizations, and other stakeholders.

Some of the themes that we heard during this public outreach process, they're certainly reflected in the concept paper and the papers that are going out early February. But we've heard an interest for a ground-up community-based approach. The communities really want to be involved as these programs are put together, both for monitoring and emission reduction programs. They're interested in steering committees, being involved in steering committees. Also a desire for increased monitoring, just to better understand what's happening of

course at the neighborhood level.

And establish criteria -- the criteria for setting up both the monitors in communities, so that they're run in ways that the community certainly understands the results, and it can be used -- the results can be used for actions directly.

They're interested in data transparency and really understanding -- again, being able to interpret the data themselves, if there are any sort of adjustments to the data, for corroborating the data say against federal reference methods, et cetera, they want to understand that and just be aware of how the data's processed. So a very transparent data stream is of interest.

And they've mentioned, you know, the term -- or coined the term "democratization of data." They're certainly interested too in being involved in deploying the networks based upon methodologies that can be standardized.

They also want to focus on immediate -- in terms of emission reduction programs, communities that the nature of the problem is well understood. There's been a lot of studies to date and in certain communities, and they're very interested in getting action, where action could be taken and the data support those actions.

Incentive funding programs. They're interested

in programs that can help small businesses that are part of the community to support their efforts to reduce emissions. Some of those businesses have a hard time turning over older equipment; and so having a funding mechanism to facilitate turning over the equipment for those small businesses is of interest.

And then of course, along with emission reduction strategies, typical of statewide strategies and air districts, they're also interested in best practices transportation strategies and routing of vehicles. So engaging local, city, and county governments as well; they're very interested in bringing not only state and local air districts but also the city and county governments together.

In terms of outreach moving forward, the community meetings, workshops, and all-day summits, they're going to continue in the future here. In February the 22nd, we're going to have a -- one of the summits that I mentioned earlier in Oakland. The 27th in Bakersfield, and the 28th in Riverside. So again, those summits will focus around these concept papers, having some very detailed discussion of the contents of the papers. We're looking for public feedback in their summits.

In March we have an informational board update where we're going to go over the status of the program and

community selection, et cetera.

Release of the draft framework document will come in May. So the concept papers we'll -- and feedback we get from the public will feed into the broader, larger concept paper, and that framework document in May they'll pull all the information together to develop a statewide strategy and monitoring plan.

And in June we'll have workshops to workshop that larger document.

And then in September, of course, we have the board meeting to consider adoption of the framework.

That ends the status I guess to date on implementation. So thank you.

CHAIRPERSON KLEINMAN: Well, thank you very much, Mr. Hughes.

I'd like to just ask if the panel has any questions.

All right. I just want to mention that this whole idea of the community involvement I think is terrific. There's a lot of opportunity to both, you know, get a better understanding of what is happening in key communities and community perception of air quality and other issues will feed back to, you know, both the regulators and the scientific community so that we have a better feeling for what is really important to people.

MR. HUGHES: Um-hmm.

CHAIRPERSON KLEINMAN: -- out there at the ground level. So I'm very happy that this program is stepping up, and I'm looking forward to participating in it.

Thank you.

Kathy.

PANEL MEMBER HAMMOND: I have just one quick thing. I appreciate this very much -- the presentation very much and the work you're doing. That's great. I'm just wondering if we can get some of those dates and some of that information in writing.

MR. HUGHES: Sure. Yeah, I can send it to Jim Behrmann --

PANEL MEMBER HAMMOND: Great. Thank you.

MR. HUGHES: -- with a list of dates, sure.

PANEL MEMBER HAMMOND: Thank you.

CHAIRPERSON KLEINMAN: All right. Well, again thank you very much, Mr. Hughes.

MR. HUGHES: You're very welcome. Thank you for having us.

CHAIRPERSON KLEINMAN: Now we'll move on to our second agenda eye, which is the evaluation of chlorpyrifos as a toxic air contaminant.

The Department of Pesticide Regulation distributed a draft evaluation of chlorpyrifos -- or it's

easier to say CPF -- as a toxic air contaminant to the Panel on December 11th of 2017, and then followed it with an orientation presentation at our December 13th SRP meeting. DPR followed up that meeting by providing the panel with a bibliography of 308 references and the complete 2014 and 2016 U.S. EPA risk assessments. And if you look around the table, you'll see that we're all burdened by many hundreds of pages of documentation.

DPR staff have also met with several individual panel members and they'll be reporting back at this public meeting later.

The next step in the evaluation of C -- sorry.

The next in the evaluation of chlorpyrifos as a toxic air contaminant is a peer review by the Scientific Review Panel, or SRP. The Toxic Air Contaminant Act is a statutory framework for identification, evaluation, and control of chemicals identified as toxic air contaminants. And the SRP today will review the DPR risk assessment to determine if it's seriously deficient based on a review of scientific data, the procedures and the methods used to support the assessment's conclusions.

Today we'll hear the technical presentation from DPR. Then OEHHA will present their findings of the draft TAC doc evaluation. And this will be followed by a discussion of six charge questions that DPR specifically

asked the Panel to address.

Because of the complexity of the CPF database and the risk assessment, which as you can imagine goes on for -- in great detail, the Panel may take more than this meeting, and in all likelihood will take more than one meeting, to discuss all six charge questions and to decide whether the report is not seriously deficient, which is the requirement of the State law.

If the Panel decides that the report is not seriously deficient, we'll then submit written findings to the director of DPR, and here she will -- or he will decide -- sorry -- if chlorpyrifos will be listed as a toxic air contaminant. If the Panel finds serious deficiencies, then we will return the report to the DPR director for revision.

As a reminder to everyone, including me, please speak directly into your microphones; and this is for the benefit of the court reporter and also for the listeners on the webcast.

And with that, I'd like to turn the meeting over to Dr. Shelley DuTeaux, the Branch Chief for Human Health Assessment at the Department of Pesticide Regulation, who will begin the presentation.

And we're going to have a short recess while we're configuring the various communication devices.

(Off record: 9:54 a.m.)
(Thereupon a recess was taken.)
(On record: 9:56 a.m.)
CHAIRPERSON KLEINMAN: Thank you very much for your patience. And I think we're now ready to begin the presentation.
(Thereupon an overhead presentation was
Presented as follows.)
DR. DuTEAUX: Thank you, Chair Kleinman and members of the panel. Again, my name is Dr. Shelley DuTeaux. I'm the Branch Chief for Human Health Assessment of the Department of Pesticide Regulation. We're very pleased to be here today to continue on our discussion of chlorpyrifos following the overview presentation of the December meeting.
As you mentioned, Dr. Kleinman, we have a huge database. This is a big undertaking. So I realize there will be a lot of questions. But I did want to ask the Chair prior to starting our presentation, if you wanted to delay discussion and questions until after we talk and OEHHA gives their findings, and then open the discussion, or did you want us to take questions during this presentation?
PANEL MEMBER GLANTZ: I'd like to make an alternative suggestion.

I think it would be -- I mean, if the Panel doesn't want to do this, it's okay. But I think it would be useful to just go around the panel and hear what questions we have so that you can focus the presentation on the big issues, you know. I think that -- because in reading through all of this, I mean I had some fairly foc -- I mean, you know, I think the issues are pretty clear at least from my perspective. So, you know, there's a lot of issues in here that are probably not controversial. And, you know, to just have them know kind of what we're wondering about so they can be, you know, kind of focusing on those issues in the presentation. That would be my preference of that's okay.

I mean we already -- I was one of the people who talked to the DPR people in advance, so they kind of know what I'm going to ask them anyway.

But I mean what do people think about that? Bad idea? Good idea?

Doesn't work?

Okay. Never mind.

CHAIRPERSON KLEINMAN: Yeah, I think that because there is also -- not only the people on the Panel but there's a wider audience involved, I think it would be best to have -- leave them on the table --

PANEL MEMBER GLANTZ: Okay. Never mind.

CHAIRPERSON KLEINMAN: -- and then go from there.

But in terms of I think the best flow would be to have the DPR presentation followed by the OEHHA findings, which puts everything out there, and then we will start to focus on the charge questions.

PANEL MEMBER BLANC: Well, actually I would say that you should trust us that if we have a question that makes it impossible to understand what it is you're presenting, that we'll break in with those questions. Because 120 slides later, for us to remember what the question was that we just lost you on, is probably a disservice to everybody.

DR. DuTEAUX: You'll be grateful then that we only have 50 slides.

PANEL MEMBER BLANC: OEHHA probably has 50 also.

(Laughter.)

DR. DuTEAUX: 20 slides.

PANEL MEMBER BLANC: Right. But you get the point?

DR. DuTEAUX: Yes. Thank you.

CHAIRPERSON KLEINMAN: Well, I think, you know, in terms of this if there are burning questions as the presentation comes up, I think it would be best to deal with those, you know, as they arise. But hopefully we'll still be able to get through this.

DR. DuTEAUX: Great. Thank you.

Okay. Then we'll go ahead and proceed.

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DR. DuTEAUX: Joining me today I have a distinguished group of colleagues joining me from the Department of Pesticide Regulation. Several of the scientists will be aiding in answering questions and clarifying, as well as some executive staff that are also here. So let me go ahead and introduce them.

First of all is Dr. Marilyn Silva. She's the lead risk assessor for this document.

Dr. Terrell Barry is the lead exposure assessor.

Carolyn Lewis is a research scientist III with our department.

Dr. Svetlana Koshlukova, our senior toxicologist in the risk assessment section.

Dr. Eric Kwok, our senior toxicologist with the exposure assessment section.

And also aiding us with additional questions if need be is Dr. Andrew Rubin, staff toxicologist; Mr. Randy Segawa, special assistant; and Mr. Jesse Cuevas, our Assistant Director.

Thank you all for being here.

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DR. DuTEAUX: So today's presentation I'm going

to start by giving a background on pesticide toxic air contaminants. Because this panel hasn't had one of these come in front of them for about eight years or so, it's good again to go over some of the information had we shared in December.

Then I'll go over the steps in evaluating chlorpyrifos as a toxic air contaminant, or otherwise known as TAC. I might use that acronym throughout the presentation. We'll give an overview of DPR's assessment, which you received, 278 pages plus additional documents.

And start with discussion of questions from the Panel and charge questions 1 or 2. And as Chair Kleinman said, if we get through the rest, then that will be great.

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DR. DuTEAUX: But first of all a background on pesticide toxic air contaminants, or pesticide TAC.

DPR's authority is cited in the Food and Agricultural Code and, as mentioned before, requirements for the TACs are in sections 14021 and 14027. And it is defined much like a regular air contaminant in that it's an air pollutant that may cause or contribute to an illness -- oh, sorry -- an increase in mortality or an increase in serious illness which may pose a present or potential hazard to human health.

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DR. DuTEAUX: In consultation with OEHHA and ARB, DPR shall -- sorry, let me spell those out for you -- the Office of Environmental Health Hazards Assessment and the Air Resources Board -- DPR, the Department of Pesticide Regulation, shall evaluate the potential hazards and health effects of pesticides that may be determined to be a TAC.

And in consultation with OEHHA, DPR prepares a report of health effects on the pesticide, which you have in front of you. This report addresses the availability and quality of the data on health effects, potency, mode of action and other relevant biological factors, an estimate of the levels of exposure that may cause or contribute to adverse health effects, and the range of risks to humans resulting from current or anticipated exposures.

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DR. DuTEAUX: To date - this is a timeline of the steps we've taken thus far - we first released a draft chlorpyrifos risk assessment document, or RCD, in December 2015. Then we received technical comments from OEHHA, ARB, and Dow AgroSciences. We evaluated and assessed chlorpyrifos as a toxic air contaminant based on this 2015 draft. We incorporated pertinent technical comments. And we included expanded analyses of new and additional data,

including developmental and cancer epidemiology, in vitro and in vivo results, human exposure and illnesses, pesticide use, mechanism of the pesticide, PBPK-PD modeling, air draft modeling, and so on and so forth.

Then in August 2017, we released our revised draft evaluation for chlorpyrifos as a toxic air contaminant. And we also released formal responses to the technical comments we received from OEHHA, ARB, and Dow.

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DR. DuTEAUX: In September, just four months ago, we presented a draft evaluation overview to our Pesticide Registration and Evaluation Committee; and we opened a 45-day comment period.

During that time, the public comment period, and the months following, we released a revised draft of the Evaluation of Chlorpyrifos as a Toxic Air Contaminant. It now incorporates pertinent technical comments received during the public comment period and an expanded analysis of new and additional data including developmental neurotoxicity in vivo results in animals.

We also released responses to the technical public comment and additional comments we received from Dow.

And we distributed the latest evaluation, with all of those comments, to this Panel.

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DR. DuTEAUX: We received, as did you, OEHHA's findings in December. Then we followed up with an orientation presentation on December 13th. And we followed up with the Panel with supporting -- additional supporting materials that were requested. On the 17th we released our response to OEHHA's findings.

And all of these documents that I mentioned are available on line.

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DR. DuTEAUX: So here we are at the first SRP meeting to review the data. And as Chair Kleinman mentioned, the Panel shall review the scientific data on which the report is based, the scientific procedures and methods used to support the data, and the conclusions and assessments on which the report is based; and determine if the report is seriously deficient.

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DR. DuTEAUX: So on to the evaluation of chlorpyrifos as a toxic air contaminant.

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DR. DuTEAUX: So chlorpyrifos is a very old chemical. We have data going back -- I think one of the earliest reports we saw was 1948. It is a chlorinated organophosphorus ester, and it's manufactured by Dow as an

insecticide, acaricide, and miticide in the structure as shown here.

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DR. DuTEAUX: It was first registered in 1965, meaning that there was plenty of data on its R&D prior to that.

In December 2000, EPA reached an agreement to halt manufacture of chlorpyrifos for nearly all residential uses.

And in March 2001, EPA registration was canceled for indoor residential products except those that are containerized baits in child-resistant packaging.

Outdoor residential products were canceled except for fire ant mound treatment by licensed applicators or mosquito control by public health agencies.

And in December 2002, all retail sales were stopped.

However, there's currently a large amount of agricultural uses in the United States that are registered by EPA including on fruits, vegetables, tree nuts, and grain crops.

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DR. DuTEAUX: In California specifically we have 48 products that are actively registered. And the major uses in California also mirror those of the United States,

including nut trees, fruits and vegetables, and grain crops.

We also have several non-production agricultural uses allowed in the State including golf course turf -- excuse me -- industrial sites, greenhouse and nursery production, see treatments, sod farms, and wood products.

We also allow it to be used for cattle ear tags, again roach bait in childproof containers in homes and sewer manholes, for fire ant control, and again for public health control of mosquitos.

We also have additional restrictions than EPA does, so we have it listed as a California restricted material.

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DR. DuTEAUX: The major geographic use areas in California include the Central Valley, the Central Coast, and Imperial County.

It's used year-round, but peak use is usually in the summertime, depending on weather.

Allowed applications include aerial, air blast, ground boom, chemigation, and others.

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DR. DuTEAUX: So this is the total pounds of chlorpyrifos used in California agricultural production since 2011. You'll see that the draft number here for

2016, which needs to be finalized in our PUR report, our pesticide use registry database report; so 2016 is a draft number, but you can see a trend in downward use of chlorpyrifos across the State.

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DR. DuTEAUX: For human illnesses and exposure reports, California Department of Pesticide Regulation has a robust program, and they track these reported incidents. From 20 -- 2004 to 2014 there were 246 cases of pesticide exposure from 84 episodes involving chlorpyrifos. And the majority of those cases were either due to drift, residue exposure, or ingestion - which was largely intentional unfortunately. Only 5 percent of ingestion was accidental.

PANEL MEMBER BLANC: That's an error on the slide?

DR. DuTEAUX: No, ingestion -- the majority of cases includes ingestion. Only 5 perc -- oh, you're absolutely right. I apologize. 5 percent of the majority of cases was ingestion, and it was largely accidental. But there are cases of intentional ingestion as well for suicide -- attempted suicide.

The --

PANEL MEMBER HAMMOND: I'm sorry. I don't understand what you just said. Could you say that again.

DR. DuTEAUX: Okay. Thank you. I will clarify.

Ingestion cases made up 5 percent of the total cases. Of those ingestion cases, they were largely accidental. Usually that comes in the case of a pesticide being poured into a nonlabeled container, sometimes a water bottle or something else.

But there are cases of intentional ingestion as well.

PANEL MEMBER HAMMOND: And then I have another question, just a clarification of what you're talking about here.

You keep calling these cases of exposure. Are they cases --

DR. DuTEAUX: Yes.

PANEL MEMBER HAMMOND: Are they cases of illnesses or...

DR. DuTEAUX: There's a definition that our Worker Health and Safety Branch uses to define what a case -- an illness report and an incident and an episode is.

I don't have those definitions right with me. But I can ask Randy or Jesse if they'd like to clarify.

DPR SPECIAL ADVISOR SEGAWA: Good morning. I'm Randy Segawa, special advisor with DPR.

So, yes, DPR has a pesticide illness surveillance

program, has had one for several decades now. And so we track illnesses due to pesticides. And so in this case we are talking about actual acute illnesses. And that's what we're referring to when we say cases.

PANEL MEMBER HAMMOND: Okay. So I think that that's another error in the slide. It's not 246 cases of exposure but of reported illness; is that correct?

DPR SPECIAL ADVISOR SEGAWA: Correct.

PANEL MEMBER HAMMOND: I think that's an important distinction.

CHAIRPERSON KLEINMAN: So each case is an individual or a group --

DPR SPECIAL ADVISOR SEGAWA: Correct. And so there are two -- in this case there are 246 individuals that became ill due to chlorpyrifos exposure that were reported and those 246 individuals were exposed in 84 different incidents or episodes.

CHAIRPERSON KLEINMAN: And then following that, when you say majority of cases, those are the -- those add up to the 88 percent and those are just bystanders?

DPR SPECIAL ADVISOR SEGAWA: No, this would -- well, illnesses are reported both for bystanders as well as occupational exposure.

PANEL MEMBER HAMMOND: So how -- and if I'm jumping ahead, stop me. But how many of these cases were

bystander and how many were workers?

DR. DuTEAUX: That's actually -- if I hit the next slide --

PANEL MEMBER HAMMOND: No, no, I'll wait. Let's just don't go forward --

DR. DuTEAUX: It's right there.

PANEL MEMBER HAMMOND: Oh, okay, okay. So --

DR. DuTEAUX: And "bystanders," Randy, if you could add a definition of bystanders, because it's not just residential bystanders, occupational bystanders.

DPR SPECIAL ADVISOR SEGAWA: Yeah. And so what we refer to occupational exposures is the people who are handling and applying the pesticide.

PANEL MEMBER HAMMOND: So you had relatively few, only 12 perc -- less than 12 percent of the cases that were reported.

But again, the cases are not cases of exposure, they're cases of reported illness?

DPR SPECIAL ADVISOR SEGAWA: Correct.

PANEL MEMBER HAMMOND: Okay.

PANEL MEMBER BLANC: I just want to point out for those of you who are less familiar with the pesticide illness reporting system, it's a passive surveillance system that relies on reports being filed with the county ag commissioners usually, or county health commissioners.

There's been a component expanded wherein cases are solicited from the California Poison Control System, but that does not span this entire period, I do not believe. But I could be wrong about how long you've had that arrangement with the --

DPR SPECIAL ADVISOR SEGAWA: Yeah, I'm not sure either. Yeah, but you're correct, that we have been consulting with Poison Control to get their data. We also consult with worker compensation to get their information as well. And so we -- we try to get as complete amount of data as possible.

PANEL MEMBER BLANC: But it's a -- it's an incomplete surveillance system. So one of the things that would be important since the inconsistencies in the system are fairly stable over time, would be to get a sense of the temporal trends in the 10-year period in question.

So is there -- the next slide have the temporal trends perhaps?

Good. Thank you.

DR. DuTEAUX: Thank you, Randy.

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DR. DuTEAUX: Okay. So again, here are the temporal cases, plotted out cases and episodes from 2004 to 2014. And much like the plot of chlorpyrifos use statewide, these reported cases have generally trended

down over the same amount of time.

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DR. DuTEAUX: And the next plot is illnesses caused by agricultural use. And in blue is the non-occupational or the non-handler cases, illnesses; and in the green are the occupational. And again there's a trend over time of less of these with less chlorpyrifos used across the State.

PANEL MEMBER HAMMOND: I have a question on that.

I thought you said more than 88 percent were non-occupational? That doesn't look like that's true looking at that figure.

DR. DuTEAUX: I think that --

PANEL MEMBER BLANC: Kathy, you have to understand, if I'm a farm worker and a plane flies over me and sprays me with chlorpyrifos, and I get ill and go intensive care, that's not occupational in their system; that's bystander. I have to be the pilot applying the material to be ill to be occupational, or the person formulating it.

PANEL MEMBER HAMMOND: Okay. So we --

PANEL MEMBER BLANC: Some of these people are, you know, the kid playing at the school, but some of them are the farm workers but they're not occupational in this system.

Randy, correct me if I'm wrong on that.

PANEL MEMBER HAMMOND: But I think that -- it's like we have two different definitions than on this slide and two slides back that are confusing. I hear what you're saying, Paul. I get it. But...

DR. DuTEAUX: And I apologize for any confusion. This report and the graphics from it are generated from a report from our Worker Health and Safety Branch, and it is referred to as one of the first references in the back of your risk assessment document. And it's available on line. And if the Committee would like to have copies of it, we'd be happy to make copies during the lunch break and distribute them.

CHAIRPERSON KLEINMAN: Yeah, I think that would be a good idea.

DR. DuTEAUX: Okay. We will do so.

PANEL MEMBER GLANTZ: I do think just that the point Kathy's raising, if you'd just look at the slide, and you just add up the occupational numbers, that looks like that's more than 12 percent.

DR. DuTEAUX: Agreed. And it does look confusing. And I wish I could explain the numbers more, but it was generated in a different branch.

PANEL MEMBER HAMMOND: Yeah, if -- one way that could perhaps help on this is -- I hear Paul's point that

under non-occupational -- I mean under occupational here are people that are bystanders in the other 88 percent.

DR. DuTEAUX: Occupational bystanders.

PANEL MEMBER HAMMOND: But you could perhaps make a third color here that were bystanders who -- people who were occupationally exposed but not --

DR. DuTEAUX: Sure, that -- I absolutely understand what you're saying, Dr. Hammond.

PANEL MEMBER HAMMOND: Yeah.

DR. DuTEAUX: Just occupational bystanders, residential bystanders, and then occupationally -- occupational ag handler exposures; those three colors would make a tremendous difference in this graph. And knowing that that would clarify, we will certainly move forward with a suggestion to the Worker Health and safety Branch for their subsequent reports that come out annually to perhaps make the graphics that way.

PANEL MEMBER HAMMOND: And also I would be interested in a graph that breaks it into different age groups.

DR. DuTEAUX: Different age groups.

PANEL MEMBER HAMMOND: I mean how many of these illnesses are among children, for instance?

DR. DuTEAUX: Okay. So that would be the residential bystander?

Got it.

PANEL MEMBER HAMMOND: Unless there are children in the fields.

DR. DuTEAUX: Wow. Cal/OSHA might have an issue with that. Although I realize that there are restrictions were lifted on the federal level for who can use pesticides, age-wise. I think that goes down to age 16 or that was -- that was somehow changed.

Well, we'll have some complicated numbers coming out in next year's report. But I appreciate the chance to try and clarify. I appreciate Randy coming up. And we will certainly make an effort as a department to come out with a more clarified assessment of the data for future year reports.

PANEL MEMBER HAMMOND: I appreciate your efforts there too. Thank you.

DR. DuTEAUX: Thank you.

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DR. DuTEAUX: Okay. Moving on to the fun stuff. Symptomology.

Acute poisoning of chlorpyrifos can result in human death. Doses generally over 300 milligrams per kilogram in humans would be required to cause death. But it also can result in unconsciousness, convulsions, cyanosis, and uncontrolled urination.

Lower doses are those less than 300 milligrams per kilogram, can result in hypersalivation, respiratory distress, muscle tremors, and the general range of symptoms seen with other organophosphate poisoning.

For chronic toxicity in workers. Workers who have reported higher exposures reported impaired memory, some speech difficulties as well.

But there were no consistent reports of effect in workers exposed to lower levels.

And this is from Albers, et al, 2004.

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DR. DuTEAUX: So moving on to the Toxicology Profile.

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DR. DuTEAUX: As I mentioned, there's -- chlorpyrifos has a classical mode of -- classical target, a toxicity associated with being an organophosphate in that it binds and inhibits the enzyme acetylcholinesterase in both insects and mammals. The effect on insects is why it is used in this state and elsewhere as an insecticide.

In mammals, chlorpyrifos results in an accumulation of the neurotransmitter acetylcholine. And this results in excessive stimulation of the cholinergic pathways in central and peripheral nervous systems. And it requires metabolic activation of chlorpyrifos to the

oxon to inhibit this cholinesterase activity.

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DR. DuTEAUX: Acetylcholinesterase hydrolyzes acetylcholine in some non-neuronal cells such as red blood cells.

And RBC, red blood cell, inhibition is commonly used as a surrogate of the inhibition in other target tissues, including brain.

The threshold dose for red blood cell acetylcholinesterase is approximately one milligram per kilogram per day including for immature organisms. And these are in a mammalian system. And this number will come up several times throughout our discussions today with you.

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DR. DuTEAUX: In terms of --

PANEL MEMBER GLANTZ: I just have a question.

DR. DuTEAUX: Yes.

PANEL MEMBER GLANTZ: So when you say mammalian systems, is that all mammals including humans? Or are you talking about, you know, rats, and people are different?

DR. DuTEAUX: Mammalian. So it spans the kingdom of mammals.

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DR. DuTEAUX: In terms of toxicokinetics, we'll

break this up into absorption first.

Oral absorption is complete approximately 70 to 90 percent in rats and humans.

Dermal absorption is much lower though, at only 3 to 10 percent, as found in urinary metabolites.

There's also evidence that through inhalation absorption that acetylcholinesterase can be inhibited.

In terms of distribution, the highest levels of chlorpyrifos are found in fat. It also tends to bind to plasma proteins. It's also been detected in rat and human milk. And there's also evidence of transplacental transfer.

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DR. DuTEAUX: Metabolism is generally handled by liver cytochrome P450 enzymes.

It -- chlorpyrifos can be oxidated desulfur -- oxidatively desulfurated to the oxon.

And it can be dearylated into 3,5,6-trichloro-2-pyridinol, or TCPy, as well as diethyl thiophosphate, or DETP.

And it can be hydrolyzed into TCPy and diethylphosphate, or DEP.

Elimination is generally rapid in mammalian systems. The biological half-life in humans is between 10 and 27 hours.

Urine is the main route of elimination. And you will find TCPy as well as the other two metabolites mentioned, and also glucuronide and sulfate conjugates in urine.

And urinary TCPy is commonly used in human biomonitoring studies.

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DR. DuTEAUX: The targets of toxicity have been looked at extensively in multiple systems across animal models. And this was actually a requirement of FIFRA registration. So we have multiple data volumes showing the results from the various targets of toxicity.

So first in terms of developmental and reproductive toxicity, there's no evidence that chlorpyrifos is a teratogen or that affects reproduction. I did come across one paper recently that showed that 35 milligrams per kilogram per day in a mouse model affected spermatozoa. But that's significantly above the level that causes acetylcholinesterase inhibition.

And no fetal toxicity was observed without the presence of maternal toxicity. Or to say another way, as this slide bullet says, fetal toxicity is only observed in the presence of maternal toxicity. We're talking over toxicity in the pups.

Immunotoxicity doesn't seem to be a target for

chlorpyrifos.

And there are studies for genotoxic effects. Those are mostly negative. However, DNA damage has been shown in assays with yeast and bacteria, as well as cell culture from treated laboratory animals.

PANEL MEMBER BLANC: Let me break in here just so I'm clear about your terminology.

By inference, I'm taking it that you exclude from developmental toxicity on this slide developmental neurotoxicity.

DR. DuTEAUX: Absolutely, yes.

PANEL MEMBER BLANC: So I think that's rather important to say. And the slide is actually quite misleading in a very critical and crucial way. Not that you intended it to be. But I think we have to call -- call that out right now that in future slides you're going to get to neurotoxicity; but most of us on this Panel would consider developmental neurotoxicity as a developmental subset of developmental toxicity. So if I were editing your slides, I'd put a big parentheses say "except for," you know.

DR. DuTEAUX: Thank you for the clarification. You're absolutely correct. In this case, it would be ossification cleft palate, those sort of gross malformations that we look for. But you're absolutely

right though.

Right. So Svetlana's reminding me that this -- how I'm going through this is actually following the table of contents of the risk assessment document that you've received.

But you're absolutely right. We don't want to mislead by implying in any stretch of the imagination that chlorpyrifos does not potentially affect neurodevelopment.

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DR. DuTEAUX: In terms of carcinogenicity, in animals studies there's been no evidence of tumors in chronic feeding studies of rats and mice.

In humans there have been recorded associations between chlorpyrifos use and non-Hodgkin's lymphoma, lung and rectal cancer in pesticide applicators and farmers. This is largely from the agricultural health study.

These associations are based on relatively small numbers of cases - large numbers of controls though - and concomitant exposure to other chemicals happened in many numbers of these cases.

The exposure is based on questionnaires, either as recall with occupational -- it's not handlers, it's actually farmers, or questionnaires with the family members if those farmers had been deceased. So it's a recall on what they might have used when they were

farming.

According to U.S. EPA, chlorpyrifos is not likely to be carcinogenic in humans, and that's based on the lack of evidence of carcinogenicity in animal studies and the absence of mutagenicity.

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DR. DuTEAUX: Okay. Neurodevelopment toxicity, in animals first. There are many studies where females were dosed throughout pregnancy and through lactation, or that the pups were dosed after weaning and repeated dosing. So again, the females being dosed throughout pregnancy and into lactation so that the pups were exposed in utero and through milk, or the pups when they were a certain age were then dosed after they were weaned. And it was repeated dosing, generally through gavage.

The animals were evaluated for their motor activity, auditory startle response, spatial orientation, social behavior, cognition, anxiety in young pups as they matured.

We have many results in our December 2015 and 2017 draft risk assessments, and here's a summary of some of those findings.

That developmental neurotoxicity occurs at doses that do not alter pregnancy or the general health of the offspring.

And there's evidence of long-lasting impairment on locomotor activity, deficits in cognitive function, and social interaction at doses equivalent to the threshold for cholinesterase inhibition, or one milligram per kilogram per day.

There's also evidence of a decline in anxiety shortly after weaning associated with doses below those that inhibit brain cholinesterase, or levels approximately 0.5 milligrams per kilogram per day.

In addition, chlorpyrifos has been shown to inhibit neuronal growth in vitro on concentrations well below those that cause acetylcholinesterase inhibition. And Dave Eaton did a nice review of this in 2008.

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PANEL MEMBER BLANC: Can you just clarify one usage of terminology here.

When you use the term "at the threshold of as acetylcholinesterase inhibition, do you mean at the threshold of 10 percent inhibition or do you mean at the threshold of zero inhibition?

DR. DuTEAUX: It's not zeroed out. It's just a 10 percent decrease.

PANEL MEMBER BLANC: Yeah. Okay. So I mean that's important to be clear about that.

DR. DuTEAUX: Correct.

PANEL MEMBER BLANC: Since the 10 percent is what you use for other endpoints; is that correct?

DR. DuTEAUX: Right, correct.

PANEL MEMBER BLANC: So therefore, the interpretation of this is a mixed bag, where some of the effects are at the 10 percent threshold but some of them are well below those -- that the in vitro are well below those at which any inhibition whatsoever can be detected.

DR. DuTEAUX: Right. And the second thought, a bullet from the bottom. The anxiety effect happens without the cholinesterase inhibition, at doses that don't cause cholinesterase inhibition.

PANEL MEMBER BLANC: And it's not even 3 percent, just 0 percent. Is that correct.

DR. KOSHLUKOVA: So many of the new studies that measure dose low level effect, they do not concurrently measure cholinesterase in their assays. So we are going by the general threshold for cholinesterase inhibition.

PANEL MEMBER BLANC: Right. But that wasn't exactly my question. My question was -- yes, it's below the 10 percent. Is it 1 percent or 0.1 percent inhibition or no inhibition that could possibly be measured?

DR. KOSHLUKOVA: So in general, for cholinesterase inhibition 10 percent is considered the limit of detection -- the detection limit.

PANEL MEMBER BLANC: I see.

Okay. Thanks. That's helpful.

PANEL MEMBER BUCKPITT: I think it would be very difficult to measure 1 or 3 percent inhibition. I mean you're measuring small differences in large numbers.

PANEL MEMBER BLANC: I suppose this is a statistical question. If you had enough samples, you could certainly measure 3 percent inhibition reliably if you had enough observations. But I don't know what the variability is, but assuming you had enough observations.

DR. KOSHLUKOVA: Yeah. So in 2006 or '08, U.S. EPA and NTP conducted a large data set analysis of cholinesterase inhibition in brain and RBC. In the red blood cell, the 10 percent was determined as the threshold for detection. Not the threshold. Detection limit.

DR. DuTEAUX: Meaning -- and just for my clarification, meaning that it's difficult to quantitate levels of inhibition less than 10 percent.

DR. KOSHLUKOVA: Yes.

DR. DuTEAUX: So between 1 and 9 percent, it's very difficult to quantify analytically, correct?

DR. KOSHLUKOVA: (Nods head.)

DR. DuTEAUX: Yeah. Enzymatic issues are hard to quantify at times.

PANEL MEMBER BUCKPITT: Do you happen to remember

what the number was? How many analyses they did in that NTP study?

DR. KOSHLUKOVA: We'll get back to you on this. I recall 100 data sets. And at least for brain cholinesterase. I don't recall -- I don't remember the RBC.

PANEL MEMBER HAMMOND: Another question on that.

DR. KOSHLUKOVA: We'll get back.

PANEL MEMBER HAMMOND: So just another quick question. This is just my lack of knowledge in toxicology. Is there a linear relationship between chlorpyrifos and the inhibition, or is that -- is that sigmoidal? Or what's the relationship there? On, say, 10 percent inhibition going up, is that a linear relationship?

DR. KOSHLUKOVA: It looks like.

PANEL MEMBER HAMMOND: And what concentration gives you 10 percent inhibition?

DR. DuTEAUX: One milligram per kilogram per day is generally the dose that causes 10 percent inhibition.

PANEL MEMBER HAMMOND: 10 percent inhibition?

DR. DuTEAUX: Right.

PANEL MEMBER HAMMOND: Okay. Thank you.

DR. DuTEAUX: So, again, we will follow up with the Panel on the NTP report.

Additional questions before moving off this slide?

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DR. DuTEAUX: Okay. So we have expanded and looked further into additional data on neurodevelopment toxicity in animals. And those results are shown in our 2017 draft, which is the one that you have. And we will also follow up with subsequent drafts, any additional data and findings that we have.

Most of these additional data were found in abstracts of presentations or published papers from 2014 to 2017. And those reported developmental neurotoxicity that is in pups or neurotoxicity in adults at low -- LOELs of 0.1 to 0.5 milligrams per kilograms per day. So that would be approximately one order of magnitude lower than the amount that causes 10 percent inhibition in acetylcholinesterase.

So there were three domains that were studied in this small group of research from 2014 to 2017. And the domains that were studied are cognition, behavior, and motor activity again in animal models.

There were two rodent species tested, both rats and mice. And the treatment was largely by gavage for dams during pregnancy and lactation, or pups; or indirect exposures to the pups in utero and through lactation; or

subcutaneous treatment of adults. So that's simply the neurotoxicity and not developmental toxicity.

Exposure was either fully gestational or only postnatal or both, and it consisted of either single or repeated doses.

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DR. DuTEAUX: And this is a table of some of these results, including Carr, et al., 2015. And Professor Carr was on the SAP panel that was asked to talk about biomarkers in the April 2016 meeting with EPA about chlorpyrifos.

Silva, et al., is one of the most recent papers, as well as Gomez-Gimenez. And Lee, et al., also has data on chlorpyrifos and carbamates.

And Muller was I think one of the only papers that we -- the new papers that we looked at that looked at adults only. And that was the subcutaneous testing.

So just in terms of a summary table here, you're given a large slide of it. But if I could point your attention to, when you have an opportunity to look at in the risk assessment document, tables 12, 13, 15, and 16, have additional data besides these to look at.

So in general, looking at all of the new data and the older data, behavior and cognition are relatively difficult to assess and quantify in animal models. You

can't ask the mouse how they're feeling. It's really hard. But it's complicated in that some effects don't show a dose-response. It's really hard to do a dose-response on a startle effect. How do you quantify that?

And others are equivocal. Sometimes the response goes up, sometimes it goes down.

Also, of course, you would think that the neuronal pathways involved in regulation of motor and behavioral behaviors are not all known. And I'm sure that they somehow work with each other. We haven't completely elucidated all of those pathways.

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DR. DuTEAUX: And as Svetlana -- Dr. Koshlukova was mentioning, cholinesterase activity or inhibition was generally not concurrently measured in these studies. So it's hard to know what the level of inhibition was occurring with the other effects that were being measured in terms of motor startle reflex, et cetera.

And another complicating factor with published literature, as opposed to contract laboratory reports we received through the FIFRA requirements, is that individual animal data are generally not available. Sometimes we do go back to the researchers and ask for individual data to be able to perform further analysis.

But for these particular six or seven publications, we weren't able to get individual data to perform further analysis.

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DR. DuTEAUX: So --

PANEL MEMBER HAMMOND: Excuse me.

DR. DuTEAUX: Yes.

PANEL MEMBER HAMMOND: Were you not able because of time, because these papers just came out and there just hasn't been time, or have you asked them and they've said no?

DR. DuTEAUX: Largely it's been a matter of time. But I'll defer to Marilyn as to -- yeah, we haven't.

There's -- occasionally researchers are happy to give us the information. We have a recent call-out to a researcher in Sweden for carbaryl who was willing to share the raw data with us. It's not always the case.

PANEL MEMBER HAMMOND: So if I'm hearing you correctly, you sometimes do ask for those data and then do a further analysis.

DR. DuTEAUX: Yes.

PANEL MEMBER HAMMOND: So it would seem use -- I certainly understand. This is 2017 data, just a month, you know -- so, is that something you have asked for or you're going to ask for, so you're going to include them

in the next iteration?

DR. KOSHLUKOVA: We did ask for individual -- for raw data one of the groups. This was from -- which group was --

DR. DuTEAUX: By Lee?

DR. KOSHLUKOVA: By Lee, yeah. And they did -- we did receive the data.

No, no, can you go back to...

The 2015 paper, the brain.

DR. DuTEAUX: That is the one paper we received individually -- or individual animal data.

DR. KOSHLUKOVA: So we requested this for carbaryl, not for chlorpyrifos, because that's -- that's when we started -- that's why we started looking at this paper. But we can get the chlorpyrifos data. They're willing to share.

DR. DuTEAUX: And, Dr. Silva, did you mention that you wanted to try to get the Muller data as well.

DR. DuTEAUX: She said no.

DR. SILVA: No.

DR. DuTEAUX: And she hasn't requested those data.

But if we do get individual data and can do our own analysis independent of the manuscript, we will certainly do so for either a subsequent draft of this

document or the final draft.

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DR. DuTEAUX: Okay. Moving on to developmental -- neurodevelopmental epidemiology. There are several ongoing prospective cohort studies and multiple observational studies that have investigated the associations between markers of chlorpyrifos exposure and effects on neurodevelopment, learning, and behavior in humans.

Some of the studies included biomarkers of exposure such as chlorpyrifos measured in plasma, TCPy, or nonspecific OP metabolites lights in maternal or child urine.

One of these studies was conducted by the Columbia Center for Children's Environmental Health at the University of Columbia. It's also known as the CCCEH cohort. So if you see that acronym, that's referring to the Columbia cohort.

In this study they quantified chlorpyrifos in maternal or cord blood plasma around the time of birth.

They also are unique in that they did personal air sampling for the mothers in and around the time of one month prior to birth.

And in this they evaluated associations between plasma concentrations of chlorpyrifos around the time of

birth and attention problems, attention-deficit and hyperactivity disorders, pervasive developmental disorder, working memory, and full scale IQ in the offspring of the mothers.

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DR. DuTEAUX: So Columbia -- the Columbia study is actually not the only study that tried to quantify maternal or cord blood plasma levels of chlorpyrifos at the time of birth. Digging into it further, we found several studies that have done the same thing. So the study from Columbia, Wyhatt, et al., 2003, that most people refer to is highlighted up in the light blue at the top of the table. And in addition, there have been other studies from 2010, 2012, and 2015 and '17 that have also done the same type of quantification of the parent compound in cord blood plasma around the time of birth.

They all differed in the number of samples, their limit of quantitation or detection, the median level of chlorpyrifos detected, and their methodologies.

I realize this is the first time you've seen this data. This is not in the draft. These are -- these are -- this is a brand new assessment. So I'd like to show or point out some of the information here that might be interesting to you.

First of all, there was a difficulty in finding

samples that were above the limit of detection. In restating that, it would be to say that chlorpyrifos was difficult to detect in samples. The rate was less than 68 percent, and some studies only 1 or 2 percent of the samples were above the limit of detection or quantitation. And that doesn't mean that the sensitivity of the analysis was difficult. It's just chlorpyrifos is difficult to find in the blood and it's rather reactive and it has a pretty short half-life.

The limit of detection or quantitation ranged from 0.001 parts per billion - in other words one part per trillion - up to 21 parts per billion. So several orders of magnitude between the analytical limits of detection and quantitation.

The medians also ranged as well as significantly. Some of these studies did not report median levels and simply reported a range. So, for instance, the median range for Wyhatt, et al., the Columbia study, was 0.026 parts per billion or 2.6 parts per trillion.

However, if I may point out, in their methodology, the last column, their standard curve was between 21 and 6400 parts per billion, meaning that the low end of the standard curve was three orders of magnitude higher than the median of the samples that they tested. So it's difficult to know with accuracy if those

measurements were precise or accurate.

I also would like to note that the recovery of those -- of chlorpyrifos from those samples was only 18 to 21 percent; meaning that if exposure was attributed to these samples, it was underestimated. By how much, we're not quite sure since the recovery was so low.

In other studies, the limit of detection, such as in Neta, et al., 2010, the next line, the limit of detection was actually above the highest max -- the range of the samples they tested. So it's difficult to have confidence in a number which is supposed to be the maximum concentration of chlorpyrifos in blood when the limit of detection was actually higher than that number.

And in Huen, et al., 2012 - so the CHAMACOS study - that was also the case, that the median levels of both the cord and maternal plasma sampled were below the limit of detection. And in that paper, the authors note that they do not have confidence in using -- in using the results from those studies to do any further analyses.

So I'll let this information percolate again. It was -- we did this brand new between the time that we released this information to you and this meeting, and we can certainly add this as additional information to the revised risk assessment. So we'll be coming out.

PANEL MEMBER RITZ: So this is the parent

compound, not the oxon or TCPy?

DR. DuTEAUX: Right. This is parent.

PANEL MEMBER RITZ: Right. So we would expect very little of that, right?

DR. DuTEAUX: Actually, the -- what I understand - and perhaps Dr. Kwok can weigh in - is that only about 40 percent of chlorpyrifos goes to the oxon. The rest goes through other metabolic pathways. So if you're measuring the oxon, you're actually measuring even less of the component.

So, Erik, do you need -- would you like to clarify anything further on that?

DR. KWOK: I don't have anything to add. It's the -- this one I'm not very familiar with the branching ratio, how actually different pathways -- if you have a same parent compound that you have multiple pathways on it. To be able to accurately characterize that, we would actually need to consider the kinetics of each pathway, and then it become a natural branching ratios.

I haven't actually done this analysis. I haven't seen anybody actually done this type of analysis. So at this point I really have nothing to add.

DR. DuTEAUX: Thank you.

CHAIRPERSON KLEINMAN: Kathy.

PANEL MEMBER HAMMOND: This -- thank you very

much for bringing this new material here. And I share your concerns about the limits of detection and some of that.

Do you -- is there information that you -- that would help us interpret this - I know there is, I'm sure -that relates the plasma concentration to percent inhibition?

DR. DuTEAUX: That's a really good question. In fact, your colleague, Dr. Isaac Pessah, asked the same question at the April 26 Scientific Advisory Panel meeting. And --

PANEL MEMBER HAMMOND: And did they give him an answer?

DR. DuTEAUX: And he thought with a part per trillion quantitation in plasma, that that would range to even a part per quadrillion, or that would be pico femto levels of molecules hitting the target. And I know there's a direct quote in the transcript from that meeting. But from my recall, I believe he said that that -- if chlorpyrifos actually acted at that level, at that concentration, it would be more potent than the most potent pharmaceuticals that we've engineered to this point.

But to be able to quantify what this means in terms of inhibition, it's very difficult to do, because

like some of the animal studies, acetylcholinesterase was not measured at the time these samples were taken.

PANEL MEMBER HAMMOND: Oh, darn. Right. Okay.

So they're just -- they're -- no one has -- not necessarily even in these studies, but in other studies, no one has actually measured both the plasma level of chlorpyrifos and the percent inhibition?

DR. DuTEAUX: Not in terms of developmental neurotoxicity.

PANEL MEMBER HAMMOND: Well, I'm just asking even just at a higher end of the dose-response.

DR. DuTEAUX: I actually do believe that there are some occupational studies --

PANEL MEMBER HAMMOND: Yeah.

DR. DuTEAUX: -- and maybe even agricultural health study perhaps. And I'm not sure if --

PANEL MEMBER HAMMOND: I guess it would be worthwhile piecing together what data are there and just seeing --

DR. DuTEAUX: Sure.

PANEL MEMBER HAMMOND: -- what the picture looks like.

DR. DuTEAUX: That's a very good question.

PANEL MEMBER HAMMOND: Might be occupational here and something else here. And just seeing what we could --

how they could come together.

DR. DuTEAUX: Right. And I know that there are occupational monitoring programs where they have measured it. And so that would be very interesting to look at, indeed.

PANEL MEMBER HAMMOND: Okay. And then -- stop me again if I'm jumping the gun. Sorry.

But do we have a time period in gestation that we think is most important for neurodevelopmental toxicity? I thought it was earlier there, so -- I mean I --

DR. DuTEAUX: Right.

PANEL MEMBER HAMMOND: And this is -- we should keep in mind that this exposure determination is made at birth, right?

DR. DuTEAUX: Correct.

PANEL MEMBER HAMMOND: And if the mother's been in la -- we have something that has a half-life of what, 27 hours. And a mother's probably been kind of more removed from most of the exposures, you know, that -- it may be that this is an underestimate. I don't know.

DR. DuTEAUX: Right. And --

PANEL MEMBER HAMMOND: It's really hard to know what's happening there.

DR. DuTEAUX: And you're absolutely right. Several of the studies in their discussions have talked

about what is that critical window vis-à-vis an organophosphate or chlorpyrifos specifically in terms of neurodevelopment. For most chemicals, as you know, it would be in the first trimester; into the second trimester where you have the neuronal tube development, et cetera; and then most of the growth and development happening in third trimester.

The difficulty that the studies have pointed out is there's inconsistencies with what the plasma level at birth are and the quantitation of urinary metabolites. Those don't always seem to line up in some of these studies.

Interestingly, with the Columbia study we also had personal air sampling of the mothers, 48-hour time-weighted averages.

PANEL MEMBER HAMMOND: I'm looking at those, yes.

DR. DuTEAUX: And they were not correlated well with the blood samples at birth either.

So when we move from a measurement at birth, I'm trying to figure out, is that similar to the exposure over a nine-month period? We have very little data to allow us to figure that out unfortunately.

PANEL MEMBER HAMMOND: The Columbia population were inner city, right?

DR. DuTEAUX: Right.

PANEL MEMBER HAMMOND: So they probably don't have agriculture. But they were also near the turn of the century, so they could have had the residential pesticides.

DR. DuTEAUX: Right. And it's interesting that that study as well as the home study in New Jersey, that cohort spanned the time of indoor use and banned or restricted indoor use. And so you have -- I believe there might be a discussion in that in our current risk assessment where it talks about the enrollees prior to the ban have quantifiable measures of various things, urinary metabolites, et cetera. But after that ban it's virtually impossible to detect chlorpyrifos either in plasma samples or in urinary samples as well.

PANEL MEMBER HAMMOND: So in addition to these biomarkers, I think it would be very interesting to see those airborne concentrations, those 48-hour concentrations, because those could be informative, especially if we know what year those were happening. But people could have residual, could still have the pesticides in their homes. Right?

DR. DuTEAUX: Right.

And, Terry, did you want to speak to any of the -- I know you looked at it. But if you're not prepared to talk about that now, that's okay too.

DR. BARRY: So we looked at I think it was Wyhatt 2003. And she has a table in that paper that presents the air concentrations. And the one particular table, 5 maybe --

DR. DuTEAUX: I think it's Table 5.

DR. BARRY: -- it splits out the air concentrations. If you look at the air concentrations from all the preten -- and all these -- in these studies, the correlation between the cord blood and the mother maternal blood is not very good if it's all lumped together. The air concentration correlated with the blood levels. But if you split it out between more than a month before delivery and the month prior to delivery, then --

PANEL MEMBER HAMMOND: They weren't just --

DR. BARRY: They were 48-hour samples but they --

PANEL MEMBER HAMMOND: But not --

DR. BARRY: -- were taken at different times.

PANEL MEMBER HAMMOND: I was thinking it was 48 hours before delivery.

DR. BARRY: Yeah, they're 48-hour --

PANEL MEMBER HAMMOND: But that would be crazy. Of course, you can't do that.

DR. BARRY: -- samples but they were taken at different time periods. So you've got samples air samples that were taken more than a month before delivery and then

samples that were taken during the month of delivery. And the samples that were more than a month for delivery don't correlate with the blood levels.

But the month prior to delivery, just like you're saying, there's -- it's a statistically significant correlation but we're talking R.45, R.3, you know, so it's a small R value but they're statistically significant. So you'd have to argue a biological significance for those values.

But then it sort of fell out, you know, that month before. But then all of the analysis done after that, they lump everything back together. And they don't control for whether it was the month -- you know, more than a month or a month -- within a month of delivery.

So the question would be, if you analyze that data in a time frame, whether you could, you know, dial down a little more on that effect. And I couldn't tell you that because they didn't do it.

PANEL MEMBER HAMMOND: Yeah. I think that there are ways one could pursue that. I think there's some very interesting thoughts there. But this is probably going too deep in the weeds at this point of the presentation --

DR. BARRY: Right. Yeah.

PANEL MEMBER HAMMOND: -- to talk about that.

DR. DuTEAUX: And just one more note on that. I

think -- and Dr. Barry and I talking about this before today's presentation, what would have been probably the most powerful analysis they could have done is a pairwise analysis of each individual mother's air sampling and her plasma sample. And because they grouped all the data together and did that kind of analysis, it's really difficult to see if mothers with high plasma concentrations had high personal air sampling or vice versa.

PANEL MEMBER HAMMOND: Yeah. Probably don't want to go into this in too much detail right now. But I actually think you provided some very interesting insights in how you looked at that, and I think that that suggests some pathways to analyze those data that we could talk about later.

PANEL MEMBER RITZ: So I would warn against making these correlations, because we know that there's a lot of dietary intake as well. And you can get it through dermal absorption as well. So whether or not the air levels correlate with the plasma, I would actually doubt.

So -- but the other note I had on neurodevelopment, it's not just the early pregnancy, because part of the mechanisms might be neurite outgrowths, axonal and dendritic outgrowths, and that's especially at the end of pregnancy in early life. So we

don't really know when the most vulnerable periods are. They could be very different, and they could extend into childhood definitely as well.

PANEL MEMBER BUCKPITT: I'll make one comment at this point. I went back looking at some of those human epi studies, and went back to some of the method that were published earlier. And I think there's -- I have some very serious concerns about whether those are even close to being on target. Those standard curves were generated out of water. There was a subsequent publication by the same group where the limits of detection why now 20-fold higher than what they had originally reported.

So I think we should have some serious concerns about whether the data published by Wyhatt, quantitative data, is really accurate.

PANEL MEMBER RITZ: Well, but any inaccuracy would not produce effects; it would achieve -- hide effects.

PANEL MEMBER BUCKPITT: I think based on what I see, the levels were actually probably quite a bit higher than what they reported.

PANEL MEMBER BLANC: If you do retain this table, I would suggest that you provide the 95 percent confidence intervals around the percentage of detectable chlorpyrifos. I actually think the only thing that really

is relevant here is that they could actually detect any at all. And so -- and since each of these proportions of case -- of participants in whom values were above the level of detection would have a distribution incidence -- these are relatively small samples, we should be provided with those data, if you might -- it's pretty simple calculation.

DR. DuTEAUX: But you'd ask that we do that analysis on these data or report if the authors did? Because if the authors did, I think we would have included it.

PANEL MEMBER BLANC: Yeah, I -- you simply can do it. It's, you know, 0.68 of 150 as a confidence interval. That's easy to calculate. It's related to the square root of 160.

And Dan can back me up on that.

DR. DuTEAUX: So, we'd be happy to. I just would make clear that if we are doing any analysis of independently authored data, that it doesn't appear like the authors published those data.

PANEL MEMBER BLANC: Put a footnote.

PANEL MEMBER RITZ: Just one more clarification question. So this chlorpyrifos level is singular chlorpyrifos, not attached to anything, not protein bound, not whatever? So could there be other types of

chlorpyrifos in that plasma?

DR. DuTEAUX: Well, you bring a good point. And I think this is what Dr. Buckpitt was alluding to, is that the samples taken were plasma -- were blood. Then they were spun down, and then -- it actually was serum, not plasma. But there is a lot of matrix happening in a plasma sample that makes it a complex system.

I realize that one of the papers that you sent us showed adducts. And none of these studies tested for chlorpyrifos adducts. However, when you have a standard curve made in water, and you're matrix samples collected from the subjects is plasma, there a distinct difference in what your recovery will be and what the sample actually looks like.

And to both Wyhatt and Perez's benefit, they tried to receive serum and plasma samples from the American Red Cross and use those to spike and use to develop the standard curve. However, the samples they received from the American Red Cross blood donation program had enough residual pesticides in it, again from usually dietary sources, that they couldn't use them to develop their standards. So I thought you might find that interesting to note.

PANEL MEMBER RITZ: Yeah.

PANEL MEMBER BUCKPITT: I do believe that they

did denature those samples though. So they precipitated proteins, which would knock anything off that was non-covalently bound.

PANEL MEMBER RITZ: Yeah.

DR. DuTEAUX: Okay. Anything else?

Okay. Moving on.

So some summaries about the developmental -- neurodevelopmental epidemiology in humans.

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DR. DuTEAUX: Again, it's difficult to quantify associations between chlorpyrifos exposure and effects in humans because of all the issues that we have been discussing. So there's potential exposure to multiple OPs in the environment. And several of those OPs have similar urinary metabolites.

And as Dr. Ritz mentioned, measurement of chlorpyrifos -- and Dr. Hammond -- or its metabolites at birth do not indicate what exposure might have occurred throughout pregnancy. And we do not know what the critical window of susceptibility is for neurodevelopmental effects with chlorpyrifos. And as others have mentioned, there's some inconsistencies with the analytical methods.

But as stated, in both our August 2017 and the latest draft risk assessment, we conclude that the

epidemiological data alone are not sufficient to derive a point of departure for chlorpyrifos as a toxic air contaminant, but the data are compelling.

PANEL MEMBER ANASTASIO: Can I ask you a question about that.

This is what EPA did in 2016 though, right? They used the epidemiological data to model a time-weighted average concentration and use that to determine a point of departure?

DR. DuTEAUX: They did a complicated and very novel approach of dose reconstruction and back calculation.

Eric, would you like to give a synopsis of what that methodology was?

DR. KWOK: Actually, in 2016, U.S. EPA did adopt two different approach. First, I would like to talk about the April approach.

So they assume a certain ex -- they actually tried to, you know, using the PBPK model, and then based on the exposure input, that problem at the time corresponded to our Columbia study, and then you calculate actually what the cord blood level look like.

Now, but the actual point of departure was -- if I understood correctly - and Dr. Koshlukova can help me with that - they actually using the cord blood measure and

then using the benchmark dose analysis to come up with a target. And then using the PBPK model to see what would be the exposure in order to achieve their target in the cord blood. That's what they did in 2016 April.

In 2016 November, they actually -- at that time, they came up with another revision. So what they did is they again using -- built on the spirit of the Columbia study, meaning actually the people that are in the Columbia study experience a certain type exposure, and then using the U.S. EPA standard residential protocol, the procedure to come up with exposure value, and then determine what would be the blood level look like, as a starting point. And then assume that blood level in the associated way with developmental effect in the Columbia study.

And then using the same PBPK model, but this time it's called reverse dosimetry using the cord blood, and then to see what would be the exposure and -- not the cord blood, I'm sorry -- the blood level -- the blood level, what would be the exposure corresponding to the blood level.

So they start with -- so let me clarify. They start with one exposure, a scenario called the crack and crevice exposure scenario. So they use that -- use that exposure. And then using the PBPK model, and then to

calculate what the blood level looked like, and then use that as a target. And then based on this target they using the reverse dosimetry by PBPK model, and then to back calculate what would be the other exposure scenario. Like, say, for instance, like the dietary exposure. What kind of a dietary exposure would achieve the same blood level that correspond to when they're using the crack and crevice exposure scenario, come up with a blood concentration.

I hope that clarify what they did. It's a little bit complex. But during that two U.S. EPA document they did something very different.

So is there any further clarification that I can --

PANEL MEMBER ANASTASIO: Yeah, I just have a question, sir.

I mean the November points of departure then were very low.

DR. KWOK: Yes. Because that actually -- because of the way that it calculated. So the November one actually because they using the 21-day time-weighted average. The concept actually built on the fact that based on the animal study, they couldn't actually determine the so-called window of susceptibility in terms of neurodevelopment. So I think that's the main reason

according to the U.S. EPA 2016 document, that they use a time-weighted average over the 21-day period. And because of you taking average of the 21 day. And also each day the exposure level is not as -- not assumed to be the same. Each day there's a 10 percent degradation, and the exposure is only for like two hours. So in the document is said shower, but what they really mean in terms of modeling is they cut off the exposure after two hours.

So every day you have a peak and then you drop, another peak but it's 10 percent less than the previous peak. And then you go on for 21 days and then you average everything out for 21 days. And because of that, the number turns out to be very low.

PANEL MEMBER ANASTASIO: I guess my question is, why didn't DPR use a similar approach?

DR. KWOK: Well, when we drafted the document, I think at that time we using the -- we used the acetylcholinesterase inhibition as an endpoint. I -- I would say that it's something that I think -- I think it's fair to say that we will look into it because it's -- it's a lot of assumption built in, you know, for that analysis. Because the 2016, the -- one document it stated that, you know, it make the assumption that, you know, the crack and crevice exposure happened at that time, you know, associated with the developmental effect that they

observed in the Columbia study.

So the exposure really not the actual measurement; it's not an assumption. So I think that need to be critically evaluated before we can move forward. So at this point I think it is something that I think we need to look into a little bit more detail before we can make a decision whether this is something that we -- can or cannot be used for other purpose.

PANEL MEMBER ANASTASIO: Yeah, I think that would be great if DPR could critically evaluate what EPA did and say, you know, these are the good parts, these are the bad parts, and this is our -- this is why we are or are not going to use this approach or something similar.

DR. DuTEAUX: In the risk appraisal there is a section where we try to provide that critical analysis. Of course EPA are our colleagues and we would be interested in knowing more about the -- both the scientific methodology that they developed as well as the assumptions going into this. However, they're at a point right now in their risk assessment where they -- they put this out in November of 2016, so it's been just over a year. Then they entered a public comment period.

Generally what happens in the EPA risk assessment process for pesticides after that is then they have a scientific advisory panel meeting where that's their

scientific review of what they've done. So they've finished the -- we assume they finished the review over the public comments. However, nothing has been published since then, and we haven't heard whether they're going to have a scientific advisory panel anytime soon. That's where these questions would definitely come in. And we have participated in those meetings either as simple audience members or actually on panels before. And we would love to have that chance to have that discussion with them. But because their timeline for reregistration of chlorpyrifos doesn't end until 2022, I would be actually surprised to see something come out from them before that time or closer to that time. I think that if they have an SAP, we'll certainly get notified about it so that we can put it on our calendars.

Without having more information about how they developed that methodology, it's hard for us to critique it. And if you go to the Federal Register, as we have, and you try to pull down the information about it, there's not as much there that we can figure out the entire method. So we're very lucky that we have Dr. Kwok because he was able to go back through and piece together. And there's actually a figure, I think it's figure number 1, or close to that, at the very beginning of the risk assessment document you have that shows this kind of back

calculation and dose reconstruction and backwards dosimetry pathway. And that was -- Erik deduced that from what we could figure out. Other than that, I wish we had more details about their methodology.

CHAIRPERSON KLEINMAN: One of the problems with the back-calculation-type approach is that when you're starting out with these metabolites, you're not entirely sure that they were all originally from CPF. There are other chemicals out there that could have given rise to some of those metabolites. So it's very difficult to say whatever you back calculate was due to the chlorpyrifos exposure.

So that's another issue.

DR. DuTEAUX: And also because there are personnel air sampling data in the Wyhatt study, it's a curiosity to me personally about trying to model those when you actually have air sampling data -- empirical data. So putting that into the system and seeing what kind of number you get out would have been a very interesting comparison.

PANEL MEMBER HAMMOND: And I suppose that's going back to Beate's point to, is that these other routes of exposure besides airborne would be part of that.

And then the composition of the science advisory panel's been changing in the last year. So that might

also be a affecting -- I mean apparently there were people on the panel who understood these things and suggested that you U.S. EPA do certain things. But now there have been some changes in the panel, correct?

DR. DuTEAUX: Um-hmm.

PANEL MEMBER HAMMOND: So that might be changing whether or not -- how they look at this. And it might be that you might have to be a little more independent here in California for a while.

PANEL MEMBER RITZ: Just to the point of assumptions, I think all of these approaches make assumptions. The animal approaches make the assumption that you can model neurodevelopment from an animal in a human; and the human system that will be 70 years old, right? So I think what is most astounding is that all three human studies have been showing some effect on neurodevelopment and on a very complex type of neurodevelopment that we all are very proud of, right - the intelligence of humans. So -- and how to measure that in mice, we haven't figured out yet.

So I would give these human studies a little bit more credence on the level of, the complexity of the system can only be measured in humans. There were blood lead, there was cord blood level measurements. Maybe they were very low, but maybe they're an underestimate of what

there was. But obviously there's something going on in the human brain.

And acetylcholinesterase inhibition is really only one of many, many, many types of modes of action that we can imagine. And we'll probably find out a lot more about what these agents can do. They are dirty agents. They're not just doing one thing. Right?

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DR. DuTEAUX: Okay. Moving on to hazard identification.

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DR. DuTEAUX: Our risk assessment that you have in front of you addresses potential bystander effects arising from food and drinking water exposure, air and skin contact, incidental ingestion, and aggregate exposure from combined sources.

We focus on two at-risk populations: Females in childbearing years due to their potential pregnancy status; as well as children that are 1 to 2 years old because of their time spent outdoors and their potential for oral exposure due to mouthing objects and eating dirt.

PANEL MEMBER HAMMOND: Now, I'm confused about bystander again. So this bystander's different than -- so this bystander does not include the people -- the workers in the field bystanders, by the occupation, and

bystander --

DR. DuTEAUX: This should include both residential bystanders and occupational bystanders.

PANEL MEMBER HAMMOND: Both. Okay.

DR. DuTEAUX: What this doesn't include are agricultural handlers of the pesticide.

PANEL MEMBER HAMMOND: Doesn't?

DR. DuTEAUX: Yes.

PANEL MEMBER BLANC: So just to be clear. It was implicit but not actually explicit in the report. These two groups of focus are because they're essentially the worst-case scenarios. So that if you're modeling found levels that were protective for these groups, they should be protective for other groups; is that correct? That was the rationale, right?

DR. DuTEAUX: Yes.

PANEL MEMBER BLANC: These are the two -- if anybody's going to be exposed to the highest aggregate levels with the most target organ toxicity, it would be these two groups; is that -- that's the stated ration -- the implicit rationale?

DR. DuTEAUX: That is the implicit -- that -- that's the implicit rationale --

PANEL MEMBER BLANC: And it's not driven by we don't have good quantitative data for some of the other

groups who if we have the quantitative data, they might even be at more risk?

DR. DuTEAUX: I'll let Dr. Koshlukova --

DR. KOSHLUKOVA: But there is one population subgroup that showed higher exposures through dietary sources, and those are infants, nursing and non-nursing. However, nursing infants would not be exposed to the mouthing activities, the foot to mouth and the object to mouth. And so this is a significant part of the exposure, which is -- which makes the children want to -- the highest exposed population in the aggregate exposure.

PANEL MEMBER BLANC: In the aggregate exposure, right?

DR. DuTEAUX: And, Dr. Blanc, point to that -- if we protect this group, then we're likely to protect most people.

PANEL MEMBER BLANC: I just want to be sure I understood what -- because it's actually not stated as explicitly as that, I think, at least in my read.

DR. DuTEAUX: We will add that in the next revision. Thank you.

DR. KOSHLUKOVA: We do have, in the appraisal part, appraisal that infants have higher exposure to the dietary sources, so...

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DR. DuTEAUX: Okay. For the draft points of departure, for the revision that you have, the point of departure is defined as a dose that is not associated with adverse effects or that causes a low level of response. And points of departure, or PoDs are used as the starting point for determining risk. In our appraisal, we used a PoD based on 10 percent red blood cell acetylcholinesterase inhibition.

And we used human equivalent doses estimated by a pharmaco -- well, I'll just say PBPK-PD model, physiologically-based pharmacokinetic-pharmacodynamic model; and this model-derived acute PoDs for oral exposure; and a model-derived 21-day, or steady-state, PoD for inhalation, dermal, and oral exposures.

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DR. DuTEAUX: Briefly about the PBPK-PD model. It predicts a time course of chlorpyrifos metabolism in humans. It incorporates red blood cell acetylcholinesterase inhibition, reactivation, and regeneration after exposure to chlorpyrifos.

The pharmacokinetic data were derived from human studies, and both human liver microsomes and plasma that were used to represent metabolic variability across a broad range of ages, as well as inputs that attribute for life stages in infants, children, and adults.

The model is able to do multi-route human exposure parameters, including oral, dermal, and inhalation. And it's undergone numerous scientific evaluations; the most recent update we received was in September of 2017.

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DR. DuTEAUX: This is a list of the points of departure in our current risk assessment. And as I mentioned, the steady-state inhalation for children 1 to 2 and females of a childbearing age is the 21-day PoD; so just to clarity that.

The number you see here, 2370 µg/m³, the air concentration, the point of departure - or if you calculate the reference dose by dividing by an uncertain -- total uncertainty factor of a hundred to 23.7 micrograms per meter cubed - is the number that we talk about in the body of the document. However, in the risk appraisal you will note that we have an additional discussion about this particular number.

So I wanted to go into a little bit of detail about how we've changed slightly from the number as you see it here.

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DR. DuTEAUX: First of all, Dow AgroSciences commented during the public comment period that the

steady-state, 21-day, inhalation point of departure -- sorry, there's a misspelling there -- for children aged 1 to 2 years old presented in the U.S. EPA 2014 risk assessment would not achieve a 10 percent inhibition. In other words it's not enough of a concentration in air to achieve that inhibition level.

So in a separate analysis requested by our department, Dow used our default physiological parameters for children 1 to 2 years old to estimate the air concentration, which they came up with as 3,000 µg/m³, and that was the number that they found resulted in 10 percent RBC acetylcholinesterase inhibition after a one-hour exposure for 21 days.

Then we did our own independent analysis and -- to estimate a one-hour-per-day, 21-day steady-state PoD value for inhalation; and we used the latest version, i.e., the September 2017 PBPK-PD model, and the model input parameters as were specified in the 2014 U.S. EPA risk assessment, and came up with a resulting PoD of 2850 µg/m³.

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DR. DuTEAUX: So altogether you can see our previous number 2370 - and that's also the number that EPA used in 2014, and that's in two of our previous risk assessments - the number from Dow, which is 3,000; and the

resulting number, 2850 µg/m³. This is our new 21-day steady-state point of departure that will be used by DPR for finalization of the chlorpyrifos TAC document.

PANEL MEMBER BLANC: Just to clarify - and this will be something I think I will be coming back to, and other panel members - but just to be absolutely clear, your PBPK modeling -- which is based on human data, not another species, correct?

DR. DuTEAUX: (Nods head.)

PANEL MEMBER BLANC: -- is -- and which gives you a point of departure for 10 percent acetylcholinesterase inhibition -- which is the threshold at which one can be secure that it occurs, correct?

DR. DuTEAUX: Yes.

PANEL MEMBER BLANC: So the PBPK model completely does not include any of the observe -- does not take into account any of the observations from animal studies that show neurodevelopmental adverse effects at levels below which we believe acetylcholinesterase is inhibited and therefore it is as likely as not that some other pharmacodynamic mechanism is coming into play. Am I correct in those -- in that assumption of what you're assuming?

DR. DuTEAUX: So there were multiple questions in there, so I'll try and tease them out and also probably

rely on Dr. Kwok to answer some of them.

So the current model, even with its most recent updates, uses the endpoints acetylcholinesterase inhibition, not any neurodevelopmental effects.

PANEL MEMBER BLANC: Well, that's not -- actually that's not exactly my -- my question is one step removed from that.

DR. DuTEAUX: Okay.

PANEL MEMBER BLANC: It relies on acetylcholinesterase at 10 percent, and therefore presumes that any pharmacodynamic effect which occurs that is relevant is driven by detectable acetylcholinesterase inhibition.

DR. DuTEAUX: I think that's a correct assumption; that's right.

Erik.

DR. KWOK: Not so sure, because I -- I think you go back to the rationale of the PBPK model construction. Because -- I mean generally you develop a model to answer the question that you're interested in. So in that -- for this particular model, the model was designed to address the cholinesterase inhibition. So the entire model actually be around that -- you know, the kinetic portion and then how the kinetic couple with the pharmacodynamic, which the endpoint of concern is a cholinesterase

inhibition. That's all this, you know, intended for. So anything outside that, I'm not sure that's --

PANEL MEMBER BLANC: Well, I'm quite sure it doesn't take into account anything outside of that. You're just confirming what would be logical based on what you're presenting. I just want to be clear that I haven't somehow missed the boat on that. That the entire precept of the PK-PD model is acetylcholinesterase inhibition.

In fact, you bring up a good point, which is actually there are aspects of the pharmacokinetic piece of this which could be -- which also assume that what really matters is the metabolism insofar as it impacts the ability of this chemical to inhibit cholinesterase.

So, for example, if it was a downstream metabolite that was actually causing a different problem, let's say, acting as a cannabinoid receptor effect, and that wasn't from the parent acetylcholinesterase, that could be an issue.

Similarly, if that effect was driven by the parent compounds but not by the oxime compound, which we know is a more potent inhibitor, then anything with -- then you would sort of discr -- you would -- a pharmacokinetic model would have to take that into account too in a different way than the standard pharmacokinetic piece of your PK-PD model.

Is that correct? Am I understanding all of that correctly?

DR. KWOK: I'm not sure that, you know, The focus of the model cholinesterase inhibition automatically have like discount the occurrence of -- if I understood your comment correctly, discounting any other effect. It really depends on actually how you use the model, because the model in -- in addition to the cholinesterase inhibition, it can generate the chlorpyrifos concentration in the blood. So if the blood turns out to be associated with all the effective interest, that you can also actually establish to see whether there's a correlation.

So I think my question -- my answer to your question is that the intention is to look at the cholinesterase inhibition, but it doesn't mean that we -- the model kind of like discount anything, you know, outside the cholinesterase inhibition. You can always --

PANEL MEMBER BLANC: Well, on the pharmacokinetic part. Pharmacodynamic, without question, anything that's not acetylcholinesterase inhibition is not counted in this model.

DR. KWOK: Yes, that's correct.

PANEL MEMBER BLANC: And the other thing is a bit more of an open question. You'd have to delve pretty deeply into it to figure out the nuance of what's being

weighted and how. Right?

DR. KWOK: Yes.

PANEL MEMBER BLANC: Okay.

DR. DuTEAUX: Interesting questions.

CHAIRPERSON KLEINMAN: But this chart, what we're saying here is that an inhalation exposure at an average level of 2850 averaged over a 21-day period is the point of departure?

DR. DuTEAUX: Well, rather it should say that an exposure of 2850 µg/m³ for one hour a day for 21 days results in 10 percent acetylcholinesterase inhibition. Is that correct?

Yeah. And just again to underline the point that the previous inhalation concentration for our 21-day PoD of 2370 is now revised upwards slightly, based on our reanalysis since the public comment period in September.

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DR. DuTEAUX: Now, onto the Exposure Assessment.

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DR. DuTEAUX: Again, we looked at non-occupational bystanders, including residents. Short-term exposures, less than 24 hours from a single application. And there were two populations of concern again: Females in childbearing age; and children 1 to 2 years old.

And we looked at indirect exposure associated with primary spray drift, including ground boom, orchard airblast, and aerial applications.

And the routes of exposure that we assessed were dermal; oral, including non-dietary incidental ingestion by children; inhalation; exposures from food and drinking water; as well as aggregated exposures.

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DR. DuTEAUX: The exposure assessment approach that we adopted is based on the U.S. EPA spray drift methods, published by Jeff Dawson in 2012 - and that was to determine expected environmental concentrations - as well as the U.S. EPA standard operating procedures for residential exposure assessment, or their SOP from 2013, to do the exposure calculations.

In addition, we used computer simulation modeling to estimate spray drift, both the horizontal deposition and one-hour time-weighted average air concentrations.

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DR. DuTEAUX: The spray drift models that were used include AgDRIFT version 2.0.5 and 2.1.1, which are empirical, or curve-fit, models. And those were for deposition only as well as for appli -- reflects application methods for both ground boom and airblast.

And AGDISP's version 8.28. This is a well-vetted

Lagrangian First Principles model that follows the behavior of droplets after they're released from aircraft nozzles.

A Comparison of the AGDISP output with measured field data have shown that the model tends to overestimate field measurements. So it likely is an overestimation of residential bystander exposure estimates or it's a conservative approach.

It also models deposition and air concentrations.

And it can be used for application methods including fixed-wing aircraft and rotary aircraft.

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DR. DuTEAUX: We used reasonable worst-case model inputs, including that the ground boom and orchard airblast worst-case application methods were assumed as -- and, Terry, I apologize. We used aerial applications as the surrogate for ground boom and orchard airblast, correct?

DR. BARRY: Correct.

DR. DuTEAUX: Sorry about that.

But because of the data that we have, we looked at dormant apple applications, which is one of the highest rates of application, as well as high boom ground boom application.

And for the aerial application, the reasonable

worst case, it was based on the reasonable worst-case agricultural aircraft type in California, and based on a DPR Enforcement county survey. So these are kind of -- the modeling is based on actual use cases in California.

And we also used real-world meteorological conditions for the San Joaquin Valley, which were chosen to produce the highest model of downwind application -- or deposition.

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DR. DuTEAUX: So putting together the risk assessment and the PoDs, we were calculating risks margins of exposure, which are the ratio of the point of departure to the estimated human exposure level. So the PoD we mentioned as 2850 $\mu g/m^3$ and the estimated human exposure derived from the modeling.

A target, more a margin of exposure of 100 is generally considered protective. And for this particular risk assessment, that target uncertainty factor allows for the following:

1 for a interspecies sensitivity;

10 for intraspecies variability; and

10 for potential neurodevelopmental effects.

The margins of exposures were calculated from route-specific points of departure that were mentioned earlier. And we also used aggregate, or combined, MOEs

calculated through exposure to skin contact, mouthing activities, breathing, eating, and drinking.

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DR. DuTEAUX: In all of these calculations we determined that two exposure scenarios had -- we estimate to have no health risks or that were above the margin of exposure of 100, and no risk to our at-risk populations of children and women in childbearing age. And those include dietary exposure only - that means residue in food and drinking water - or exposure from dermal exposures resulting from spray drift.

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DR. DuTEAUX: However, our calculations came up with results showing that exposure scenarios -- several exposure scenarios might have potential health risks or that have margins of exposures below 100. And those include:

Hand-to-mouth exposure in children, meaning that incidental hand-to-mouth activity, eating dirt, mouthing objects, et cetera.

Inhalation exposure to children and females of childbearing age.

And various aggregate exposures from combined media, including food, drinking water, and deposition from spray drift.

And it's important to note that the exposure to aerosols in the air near application sites was the main driver when the aggregate MOEs were less than a hundred. That's why this is being considered as a toxic air contaminant.

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DR. DuTEAUX: The key conclusions from our risk assessment are as follows:

That the database on chlorpyrifos inhibition of acetylcholinesterase is extensive.

It also supports the establishment of dose-response that can be re-created at specific dose levels in animals.

At this time it is not possible to determine a quantitative dose-response or dose-effect relationship based on any human endpoint. Therefore these studies cannot be used as the scientific basis for our regulatory target.

The lack of dose-response or a clear mechanism of action does not negate the results showing potential associations between in utero human exposure and human development, and new data will be evaluated as they become available.

This bullet above is the basis for why we chose a tenfold uncertainty factor for a neurodevelopmental

toxicity.

And new animal data identifying developmental neurotoxicity at doses lower than acetylcholinesterase were added in the recent version. And new data that we didn't include in the version are also being analyzed right now. We will continue to consider the suitability of deriving a point of departure specific to developmental neurotoxicity in the final toxic air contaminant evaluation document.

So those are our key conclusions.

CHAIRPERSON KLEINMAN: Thank you.

PANEL MEMBER BLANC: Can you go back to that slide for a second.

When you write the bullet number 3, "At this time, it is not possible to determine a quantitative dose-response or dose-effect relationship based on any human endpoint; therefore these studies cannot..." do you mean any human endpoint of neurodevelopmental toxicity? I mean the human endpoint that you're using is acetylcholinesterase inhibition. I mean is that --

DR. DuTEAUX: You're correct. I should have clarified that, human neurodevelopmental endpoint.

PANEL MEMBER BLANC: Uh-huh. And the last one, which is -- we're also not using any experimental animal neurodevelopmental endpoint either at this time, but we

might. Is that what you're saying?

DR. DuTEAUX: That's what we're saying.

PANEL MEMBER BLANC: But wouldn't that completely change everything that you've done if you do that?

DR. DuTEAUX: As our meeting with Stan Glantz pointed out, it would require a complete revision of this document.

PANEL MEMBER BLANC: Uh-huh. So --

PANEL MEMBER GLANTZ: Well, wait, wait.

(Laughter.)

PANEL MEMBER GLANTZ: Okay. I just want to say first for the record, all the questions I was going to ask about got asked by somebody else. So that was great.

But what I was suggesting was that one would not want to have to go do a complete revision of the whole document, okay. But I do think that -- because I -- I mean I think that the neurodevelopmental endpoints are very important. And what I was, you know, talking about on the phone call we had was whether that could be taken into account by adjusting the uncertainty factors, or something short of going back and completely revising the document. So I just want to --

DR. DuTEAUX: And we actually have a table. We developed a table to try and answer your question, to show what our current PoD is, what it would be if we use the

animal DNT study, and compared to EPA's 2016 number. And we'd be happy to bring that up now for discussion or later after OEHHA has a chance to go over the findings.

PANEL MEMBER GLANTZ: Okay. Well, that -- it's really nice that you did that. I'll leave it up to the Chair to determine when you present that. But I'm looking forward to seeing it.

CHAIRPERSON KLEINMAN: Okay. So --

PANEL MEMBER GLANTZ: So is Kathy.

(Laughter.)

CHAIRPERSON KLEINMAN: On that note. What I'd like to do is while OEHHA is setting up to discuss their findings on the document, that we take a 10-minute recess for getting everything turned over and give people a chance to deal with biological necessities if necessary.

PANEL MEMBER BLANC: Is that sufficient for our stenographer? Is 10 minutes sufficient?

Okay. Thank you.

CHAIRPERSON KLEINMAN: Thank you.

(Off record: 11:46 a.m.)

(Thereupon a recess was taken.)

(On record: 12:03 p.m.)

CHAIRPERSON KLEINMAN: Okay. I'd like to call this meeting back to order. If everybody will take their seats, please.

All right. The next thing on our agenda is a presentation on OEHHA findings on the draft TAC document. And that will be presented by David Ting and Lori Lim.

And I'll turn it over to you.

(Thereupon an overhead presentation was Presented as follows.)

DR. TING: Good afternoon. Members of the Scientific Review Panel. I am David Ting, Chief of Pesticide and Environmental Toxicology Branch at the Office of Environmental Health Hazard Assessment, or OEHHA. Sitting to my right is Dr. Lori Lim, Chief of Pesticide and for the Toxicology section.

We're here to discuss with you OEHHA findings on DPR's draft TAC document for chlorpyrifos.

Also in the room are Dr. Heather Bolstad, Dr. James Nakashima over here, and Dr. Rima Woods, and Dr. Ouahiba Laribi. They are part of the team who carried out the review.

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DR. TING: As you have heard --

DR. DuTEAUX: David, check the cord in the back screen particularly, make sure it's plugged in.

PANEL LIAISON BEHRMANN: I'll get someone.

--o0o--

DR. TING: Okay. As you have heard from the

previous presentation, DPR has developed a draft risk assessment on chlorpyrifos, and it will be used in considering whether to identify the chemical as a toxic air contaminant.

OEHHA is required by law to prepare findings on this risk assessment. Our findings have been submitted to the Panel and DPR, and they're also posted at OEHHA and DPR websites, as indicated on this slide.

Overall, we agree with the approach of using margin of exposure to quantify the risk of residential bystanders exposed to chlorpyrifos. Our primary recommendations cover: Evaluation of additional toxicity endpoints and re-examining how to address the uncertainties in the assessment.

We also agree with the determination that bystanders can be exposed to air concentrations of chlorpyrifos that exceed the health protective level.

Our findings support the identification of chlorpyrifos as a toxic air contaminant.

With that, I'm going to turn the microphone over to Dr. Lim. She is going to describe in detail some of our more important findings.

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DR. LIM: Hi. I'm Lori Lim.

Is that better?

Hi. My name's Lori Lim. I will be presenting the findings directly related to the determination of risk for bystanders' exposure to chlorpyrifos. They are toxicity endpoints, points of departure, exposure assessment, and uncertainty factors.

Next.

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DR. LIM: And my presentation will start with finding number 8, which is using the RBC acetylcholinesterase, AChE, inhibition as the critical toxicity endpoint for chlorpyrifos.

RBC AChE activity is a sensitive marker of systemic AChE inhibition. It is often used as a surrogate for AChE's activity in the nervous system because it is easy to take blood samples and the I -- enzyme is essentially the same forms in both tissues.

Toxicity studies show that with chlorpyrifos, RBC AChE is often more sensitive than brain AChE. The data in Table 1 illustrates this point.

The experiment was conducted with two groups of young rats postnatal day 11, and adult female rats given chlorpyrifos by gavage. At 0.5 milligrams per kilogram per day there was no significant inhibition for either RBC or brain AChE, indicated by the low values under each of the three groups.

At 2 milligram per kilogram more inhibition was measured for RBC, indicated as minus 36 percent, 31 percent; than for the brain, which is 2 percent and minus 7 percent for the pups.

In addition, more inhibition was detected for the pups' RBC inhibition compared to the adult RBC. So we have 36 and 31 for RBC at 2 milligram per kilogram versus 19 percent for adult female. This is one of the data sets to illustrate this point.

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DR. LIM: The next finding is on developmental neurotoxicity, or DNT, as a potential critical endpoint for risk assessment. There are numerous animal and human studies showing exposure to chlorpyrifos is associated with DNT. And I'm saying that DNT is a simple developmental neurotoxicity but encompasses many effects.

In some rat and mouse studies, chlorpyrifos exposure during gestation and postnatal periods was found to cause DNT effects on cognition, anxiety, social behavior, and motor activity.

In some studies, these DNT effects were observed at doses that show minimal or no brain acetylcholinesterase inhibition. This point was talked about with Dr. DuTeaux's presentation. This mainly referred to a study by Carr, et al., in 2017, in which the

neurobehavioral effects were observed at 0.5 milligram per kilogram per day. But brain acetylcholinesterase inhibition were 4 percent decrease at 0.5, 4 percent at 0.75, and 19 percent at 1 milligram per kilogram per day.

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DR. LIM: OEHHA's view of the DPR observations from a registrant study and those in recent published literature are presented in table 2 on the next slide.

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DR. LIM: These recent animal studies were conducted with low doses, which can provide the basis for improved dose-response relationship analysis compared to the earliest study, which are mainly conducted with either a single dose or high doses.

In this table, the first study, Hoberman, 1998, is the FIFRA guideline study, and the rest are published reports.

GD is gestational day, LD is lactational day, and PND is postnatal day.

In the Hoberman study the most sensitive endpoint was reduced parietal cortex thickness in the pup, measured on day -- 66 days old.

Note that the effect observed -- the effective dose is set at 1 milligram per kilogram. And there are no data for the lowest dose group of 0.3 milligrams per

kilogram per day.

The key points about the published studies are: All were conducted by the oral route and a range of doses were tested. The pups were exposed to chlorpyrifos during gestation and/or postnatal period but were test much later after exposure. The lowest effective dose was at the same level of 0.1 milligram per kilogram per day from four report.

Effect of the low doses were anxiety, motor activity, and spatial learning.

Next.

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DR. LIM: The human study support the consideration of DNT as a critical endpoint. They are epidemiological studies looking at organophosphate exposure and toxicity.

Three major prospective birth cohort study have shown association between exposure to organophosphates, including chlorpyrifos, during pregnancy and adverse neurodevelopmental outcomes.

The exposure level would generally measure as metabolites in the urine.

The Columbia study measured the most comprehensive measurement, in that it measured chlorpyrifos as well as TCPy, the specific metabolite of

chlorpyrifos.

Chlorpyrifos was measured in the maternal blood within one day of post-delivery and fetal cord blood at delivery as well as TCPy in the urine of the maternal and fetal -- and fetus as well as the urine and meconium.

However, it is difficult to use these exposure data to establish direct dose-response relationships using approaches for laboratory animal studies. One problem is when the chemical level is measured for a single time point while the associated effects are measured much later.

Additional evidence of DNT for chlorpyrifos comes from zebrafish studies and in vitro model for DNT. Zebrafish requires a certain level of AChE for normal development. When zebrafish is exposed to chlorpyrifos, it showed abnormal behavior and inhibition of AChE activity.

There are many possible modes of action for chlorpyrifos-induced DNT effects. But there is no definitive conclusion. This can explain the variety of DNT effects observed in human and animal studies.

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DR. LIM: Finding 13 is a summary of findings on critical endpoints. For all exposure scenarios evaluated in the draft TAC document, the critical toxicity endpoint

used was 10 percent inhibition of RBC acetylcholinesterase activity. While AChE inhibition is a sensitive toxicity endpoint, other endpoints such as DNT and respiratory toxicity effects may be more sensitive as well as toxicologically more relevant.

Next.

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DR. LIM: The next topic is point of departure for the critical toxicity endpoint. The point of departure is the starting point of the low dose extrapolation and is used to determine the health risk, calculated as the margin of exposure associated with a certain exposure level. Generally the duration of the point of departure matches that for human exposure duration.

In the draft TAC risk assessment the acute single-day inhalation dermal and incidental oral exposures were evaluated using a steady-state point of departure for RBC AChE inhibition. The use of that steady-state point of departure is said to compensate for background exposure to chlorpyrifos and cumulative RBC AChE inhibition.

OEHHA finds that this is a conservative approach but notes that it may add uncertainty to the risk estimate for this point. That is, the actual exposure is adjusted by the toxicity or point of departure rather than by a

better estimation of the exposure level.

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DR. LIM: Another point from finding 14 is that since the point of departure was derived from a PBPK model, it would be helpful to explain the factors driving the values.

For the inhalation exposure, the point of departure expressed as air concentration is about 3-and-a-half -- 2-and-a-half-fold lower for children than females. However, the point of departure in terms of dose, milligram per kilogram per day, adjusting for respiration rate but not for the one-hour-per-day exposure for the two age groups, so that they're very similar.

On the other hand, the dermal point of departure for children is more than fivefold higher than that for female group.

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DR. LIM: Finding 15 is related to the last point on the steady-state point of departure, but the uncertainty for the values.

In the inhalation component of the model, chlorpyrifos is modeled as dry particles of relatively small sizes. In contrast, the bystander's inhalation exposure to chlorpyrifos is a spray drift cloud comprised of liquid aerosol droplets of varying sizes. The

pharmacokinetics of chlorpyrifos of these two forms could be different at different deposition sites.

In addition, the steady-state inhalation component model has not been validated. There are no subchronic inhalation animal or human toxicity data suitable for this purpose.

The only human inhalation exposure toxicity was a combined acute dermal and inhalation study by Vaccaro, et al. This study will be discussed in finding 22.

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DR. LIM: Finding 16 is on exposure assessment. The acute exposure is for one- to one-and-a-half hour per day. The TAC document estimated exposure for individual routes and all routes for spray drift shown in the first row. In addition it included a spray drift in dietary aggregate exposure in the second row of the table, but only for children 1 to 2 years old, but not for female -- or adults.

While children often have the higher intake on a body weight basis, and slightly a more sensitive group, the risk of these two groups can't be compared based on exposure levels alone. The risks for the female group needs to be determined given that the point of departure for this group are different than those for children.

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DR. LIM: Finding 17 is also on exposure assessment on the use of surrogate air concentration. We agree that the use of the surrogate aerosol concentration is appropriate. The concentrations are likely conservative estimates with a ground boom and airblast applications. It is the best available method to estimate the air concentration for these applications. They're similar to air monitoring data by the California Air Resources Board for airblast applications.

However, they could be underestimates for a specific scenario when there is little or no foliage, resulting in more spray drift than predicted.

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DR. LIM: Finding 19 is on exposure, in this case the need to consider chlorpyrifos vapor exposure. The concern is for residential bystanders who also live close by. There has been several questions about what's the definition of bystander. And the way we interpreting it, a residential bystander is somebody who can be walking by the field as well as living near the area.

They can have aggregate exposure to both vapor and aerosol. Release of chlorpyrifos as vapor from deposit is possible in areas where the summer temperature is high.

The relationship between temperature and vapor

pressure is shown in this graph on the slide, where increasing the temperature from about 70 degrees to about 100 degrees causes a 14-fold change.

And this exposure to chlorpyrifos vapor may last for many hours compared to the one-hour exposure duration to the aerosol. Thus the effect of temperature on chlorpyrifos is an important factor to consider.

In addition, we want to note that the U.S. EPA added vapor pressure -- vapor exposure estimate in the 2014 revised health risk assessment.

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DR. LIM: The remaining slides of this presentation are on uncertainty factors, starting with finding 22 on interspecies uncertainty factor. This uncertainty factor is an extrapolation factor used when data from animal study are used to extrapolate to human response. The full factor is tenfold, and it is reduced to one when adequate human data are used.

OEHHA recommends that interspecies uncertainty factor of threefold because there are uncertainties in the PBPK model with simulated pharmacokinetic and pharmacodynamic of chlorpyrifos in human. The model is not equivalent to a well-conducted human study because some of the model parameters were derived from animal studies. There were limited human data from model

validation, as will be shown in the next slide. Furthermore, the model has not been adequately validated for human steady-state exposure for any route.

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DR. LIM: The table in this slide is a summary of the human studies presented in our finding. It shows the acute human studies used to validate the acute and steady-state outputs of the PBPK-PD model. The data from the first study were also used to derive model parameters.

There's a Nolan, et al., study for the oral and dermal route; the Kisicki, et al., study for the oral route; and the Vaccaro study for dermal and inhalation combined.

The key points of these studies are there are few subjects and they are all adults. Three of the four studies use single-dose, one-time acute exposure. RBC AChE's inhibition, the critical endpoint basis for the point of departure, was observed in only one subject and in one study, and that's the one by Kisicki, et al.

It should be noted in the Vaccaro study, a slow release formulation was used. This formulation shows lower peak air concentration by about fourfold and much lower toxicity than non-encapsulated chlorpyrifos.

In this study, the subjects were exposed to chlorpyrifos by dermal and inhalation routes. So the

subjects wore suits, in which they roll around on the floor to simulate kids' activities. And that's -- and then these -- the material's cut up and measured for dermal absorption.

More importantly, RBC acetylcholinesterase activity was not measured.

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DR. LIM: Finding 23 is on intraspecies uncertainty factor, which is used to account for differences in response to a chemical between humans or inter-individual variability in the human population.

An intraspecies uncertainty factor of 30 is needed to fully account for the potential variability in both pharmacokinetics and pharmacodynamics in the human population response to chlorpyrifos.

The PBPK-PD model did not fully account for the physiological, anatomical, and biochemical changes during pregnancy and among different age groups. For PK -- pharmacokinetic considerations, sensitive parameters related to metabolic clearance of chlorpyrifos and its oxone were based on in vitro data from a small number of plasma and liver postmortem tissues as shown in this table.

Note on this table that there are no more than 10 samples per age group; and for the age group of children 1

to 2 years old, there are only one plasma sample and five liver samples.

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DR. LIM: In addition to pharmacokinetics there's a need to account for the variability due to pharmacodynamic aspect of the RBC AChE inhibition. The reported coefficient of variation for the parameters describing the inhibition are relatively small. For example, the inhibition rate was derived from all male adults. It is unclear how representative the mean CV values are for the general population. It is known that RBC AChE activity varies with age, pregnancy, and even between healthy adults.

Another consideration is whether the intraspecies uncertainty factor derived for RBC AChE inhibition would be applicable for DNT. Many factors can influence an individual's susceptibility to developmental neurotoxicants, potentially resulting in a large inter-individual variability.

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DR. LIM: The final finding is finding 24, an additional uncertainty factor. This factor is applied because the DNT may be a more sensitive endpoint compared to RBC AChE inhibition. This factor is part of the Food Quality Protection Act on the evaluation of pesticide

tolerance in food. The Act requires the U.S. EPA to apply this factor when there's potential pre- and postnatal toxicity and incomplete exposure and toxicity data for infants and children.

In the draft TAC risk assessment the tenfold factor was applied because the DNT data were considered inadequate to use -- to form the basis for a point of departure determination.

In our view, the use of this factor in a surrogate endpoint of RBC AChE's inhibition adds uncertainty to the risk characterization. Thus, in light of the more recent published report, so it's a body of evidence of human epi studies, we would recommend a thorough evaluation of these DNT studies to see if a point of departure for DNT can be directly determined.

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DR. LIM: This ends my presentation.

Any questions?

CHAIRPERSON KLEINMAN: Thank you.

So let's open this up for some brief questions by the Panel if --

PANEL MEMBER BUCKPITT: Dr. Lim, I had a question on your I think fourth slide, the finding 8. Are there any data out there in the animals -- you have inhibition here in pups and adult females. From 2 milligrams per

kilogram; that's a single dose, right?

DR. LIM: (Nods head.)

PANEL MEMBER BUCKPITT: Are there any data out there for multiple doses in a dose response?

DR. LIM: This is the dose representative what the group has is 2. And then in this same experiment another group had 0.5.

PANEL MEMBER BUCKPITT: Right. But are there any studies where they give 0.5 per day for several days?

DR. LIM: Yes, this is a multiple --

PANEL MEMBER BUCKPITT: Oh, I didn't know.

DR. LIM: These are a single day's experiment. But there are multiple-day experiment. It's quite detailed to describe in the TAC document with multiple doses.

PANEL MEMBER BUCKPITT: Okay.

PANEL MEMBER ANASTASIO: Thank you.

I have a question actually related to the OEHHA findings document. Can I ask you about that.

DR. LIM: Sure.

PANEL MEMBER ANASTASIO: So on point 25, the last page, page 14.

Okay. So the you say that the target MOE would be a thousand based -- well, actually that's based on the OEHHA analysis, right, the uncertainty factors you were

just talking about, factor of 3, a factor of 10, a factor of 30, gives you a factor of a thousand.

PANEL MEMBER GLANTZ: Which finding? What page are you on?

PANEL MEMBER ANASTASIO: 25. Sorry, these the OEHHA -- OEHHA finding document?

PANEL MEMBER GLANTZ: No, those are --

DR. LIM: It's the finding memo itself.

PANEL MEMBER GLANTZ: It's the December 2017 document.

No, that's not it.

That's DPR's response to OEHHA.

PANEL MEMBER ANASTASIO: You gave us a lot of documents.

DR. LIM: We're trying to make it short.

(Laughter.)

PANEL MEMBER ANASTASIO: I appreciated that.

Okay. So based on uncertainty factors for DPR, they came up with a total uncertainty factor of 100. OEHHA is saying total uncertainty factor of a thousand.

But then in that last paragraph, the first sentence: "Consideration of OEHHA's above findings on the uncertainty factors could result in a higher TAC target MOE of at least 10,000." Can you explain the 10,000?

DR. LIM: It is very confusing, because we have

health risk assessment, okay, which we have the standard, you know, uncertainty factors. But under the Toxic Air Contaminant Act, the criteria for it to be listed is tenfold lower. So it flips the equation to meaning that you require a higher margin of exposure.

PANEL MEMBER ANASTASIO: Oh, so this is an additional factor of 10 --

DR. LIM: Yes.

PANEL MEMBER ANASTASIO: -- over the total uncertainty factor?

DR. LIM: Yes. That's why we -- we specified as a TAC target versus a regular target. Because the MOE is the point of departure divided by the exposure.

PANEL MEMBER ANASTASIO: Right.

DR. LIM: So normally with the -- with the DPR document you want that to be a hundredfold difference. That's the hundred. But under TAC you want that difference to be a thousand. So essentially you're dividing the point of departure by 1,000 to get the reference dose.

PANEL MEMBER GLANTZ: Right. But the -- I had the same question. So I can see that. But then it -- I said, are you saying that the margin of exposure should be 10,000? Because that's what it seemed like you were saying at the end of that sentence.

So is that what you guys are --

DR. LIM: Yeah. You apply the math on what's a TAC criteria is, then it would be 10,000 from our 1,000, yes.

PANEL MEMBER HAMMOND: I think maybe it might be clearer if you laid out each of -- you know, there are so many places the uncertainty factors are coming in - intraspecies, interspecies, different ages, all of these. If you were actually to lay them out, there's this factor, there's this factor. At one point there was a 30 factor. So I'm surprised we don't end up with a 3 in the front of what -- 3 times 10 to whatever it is.

But if you were just to kind of lay each -- you know, each of the factors out, it might clarify for everybody.

DR. TING: That's a good suggestion.

Just to get back to your question, the first paragraph of our finding number 25 explain why this additional 10 is specific to the TAC program.

PANEL MEMBER ANASTASIO: And that's simply to be listed as a TAC?

DR. TING: Yeah. That's the criteria --

DR. LIM: Yeah

DR. TING: -- for that program.

DR. LIM: Right.

That's not to say that the reference concentration should have that tenfold factor. This is purely for listing criteria.

PANEL MEMBER GLANTZ: I'm now totally confused.

(Laughter.)

PANEL MEMBER GLANTZ: Maybe the thing to do, because this is clearly going to be one of the big issues in this, maybe over lunch you and DPR can make a slide with -- which is -- with each of the different elements that contribute to this. And you could have the OEHHA number and the DPR number next to each other, and then we could just see why do you think different things, because this --

CHAIRPERSON KLEINMAN: Yeah, I think --

PANEL MEMBER GLANTZ: And I can -- yeah, I mean I still don't understand where -- I mean my understanding of the way the margin of exposure worked is you have the point of departure, which is kind of like what OEHHA likes to talk as a reference exposure level. And then when OEHHA and ARB are doing it, they divide that to say "what's the acceptable level?" And what DPR does is they -- they flip the fraction and they -- so they ask like how much below that are you? But I don't see how that should make a difference -- changing a thousand to 10,000.

CHAIRPERSON KLEINMAN: But I think if you take finding --

PANEL MEMBER GLANTZ: Because it seems like they ought to be just -- just invert -- they should just be inverses of each other. Just because it's a definitional thing, I don't see why it should make such a gigantic difference in the number.

CHAIRPERSON KLEINMAN: But I think if you aggregate the recommendations from finding 22 where you're going to increase the interspecies uncertainty factor by -- to 3, and then finding 23 where you're going to have an intraspecies uncertainty factor of 30, that gives you a 90. Then the other 10 gives you 900. And then the original hundred, you get up to 9,000. And so there may be a little bit more in there as well.

PANEL MEMBER HAMMOND: I missed one of those.

PANEL MEMBER BLANC: Can I ask --

PANEL MEMBER GLANTZ: Still a pretty big difference from what DPR was saying. So I think --

DR. TING: We'll try to make that table as you have instructed.

PANEL MEMBER GLANTZ: Okay. And I -- because I think that's going to -- I mean to me, there's a couple of key issues that have come out of all this, and that's one of them. I mean to me, the two -- the two key questions

that I had going into this were the neurotoxicity endpoint versus the acetylcholinesterase endpoint. And the other one is what's the appropriate uncertainty factor. I think after reading through all of this, those -- well, and then there's the questions about the exposure model. But the -- but in terms of the biology, those are the really two keys questions that I think come out of this.

So I think in the discussion after lunch, the more we can like get those differences ventilated and explained, I think that will really help move things forward.

Because I still don't see where you get the 10,000. But we don't have -- we can do that after lunch.

PANEL MEMBER BLANC: That's assuming there is a lunch.

(Laughter.)

PANEL MEMBER GLANTZ: Kleinman said there would be lunch.

PANEL MEMBER BLANC: I want to just clarify with you in the same way that I tried to clarity with DPR some things to see if I understand and can grasp the differences and the similarities.

So in terms of the modeling that was used for pharmacokinetic-pharmacodynamic relationships, your point is that the input -- some of the input parameters in that

model are in fact derived from animal studies, not from human studies; and therefore, a value of 1 is not sufficiently conservative because you're not using a human model.

Is that -- do I understand your point correctly on that?

DR. TING: Yes. Using an uncertainty factor of 1 implies that the prediction is right on. There's very little error. And in our review, this model have certain limitations.

PANEL MEMBER BLANC: Right. But the limitations are not solely that it was validated with a small number of human observations but also that some of the parameters were derived from animal studies, not from --

DR. TING: We listed a couple of things, including the difference in nature of the particles used in the model validation and real situation, the difference in terms of not all parameters are derived from human samples --

PANEL MEMBER BLANC: Yes, okay.

DR. TING: -- as well as more number of samples.

PANEL MEMBER BLANC: All right. So that's essentially what I just -- I understood you correctly. Okay.

None of that critique addresses the

pharmacodynamics being based on acetylcholinesterase inhibition. You seem to be accepting that as an appropriate pharmacodynamic component to a PK-PD model. Or am I missing something?

DR. TING: Actually we try to separate PK from PD.

PANEL MEMBER BLANC: But you said to increase the uncertainty factor by 3 because of the PK, not because of the PD. Otherwise you would have come up with 10 instead of 3.

DR. LIM: We accept the model as a model for RBC cholinesterase inhibition.

PANEL MEMBER BLANC: Why would you accept that?

DR. LIM: But that's what it was intended for. And so --

PANEL MEMBER BLANC: But that's what's being applied here.

DR. LIM: Right. And I think it -- we were saying we cannot use this model for DNT. You would need a different model. So we wouldn't apply an interspecies for that reason.

PANEL MEMBER BLANC: So therefore, what are you suggesting for the modeling of risk here? Are you just throwing up your hands and saying there is no way to do it?

DR. LIM: No.

PANEL MEMBER BLANC: Because all of your suggestions about adding additional uncertainty factors still presume that they're using modeling of acetylcholinesterase to model the endpoint that you say they should model, which is neurodevelopmental toxicity. So it seems to be a contradiction of some sort, an internal inconsistency in your argument.

DR. TING: You are right in saying that we explore both options. In using -- keeping the RBC cholinesterase inhibition as the point of departure, we suggest a bigger uncertainty factor. However, we also realize the cumulative uncertainty factor would be relatively large, so we recommend to explore the possibility of using DNT directly.

PANEL MEMBER BLANC: Of using what? I'm sorry.

DR. TING: Developmental neurotoxicity as an endpoint directly.

PANEL MEMBER BLANC: But that's what DPR suggests by adding a factor of 10, an uncertainty -- that's where their uncertainty factor of 10 comes from, isn't it?

DR. LIM: Yes, as an additional uncertainty factor. We're actually looking to the Panel to give us some input on -- as part of your charge question to ways of looking at the epi study.

PANEL MEMBER BLANC: Okay. So I guess what you're saying is you can't answer my question.

DR. LIM: Yeah, we understand the uncertainties, we understand on what U.S. EPA did in their two assessments in 2016. And it is a really difficult question. You really need to have the raw data from the epi studies. And I think we have greater confidence in the human studies at this point. But if there are ways to look at the epi studies --

PANEL MEMBER BLANC: You mean the nonhuman studies?

DR. LIM: Yeah.

Then we certainly will explore that.

PANEL MEMBER BLANC: Uh-huh. So -- you don't mind -- could I keep going with this line of questioning?

PANEL MEMBER HAMMOND: Of course.

PANEL MEMBER BLANC: Okay. So assuming that you're saying it -- hypothetically were you to stay with acetylcholinesterase inhibition as the endpoint, even though we don't think that necessarily should be the endpoint, but you could maybe address that by adding a factor of 10 for the neurotoxicity. You've then suggested that for intraspecies, instead of using 10, you use 30, plus 10 -- another 10 for neurodevelopmental special things. And the reason why you're saying use 30 is

because of childhood vulnerability, right, in terms of cholinesterase sensitivity of effect --

DR. LIM: Yes. It's all --

PANEL MEMBER BLANC: -- or assess the vulnerability to --

DR. LIM: It's all about the RBC acetylcholinesterase inhibition, yes.

PANEL MEMBER BLANC: Right. Now, doesn't using an intraspecies factor of 10, which is a fairly -- you know, that's the high end of what's typically used, especially if you've got another factor of 10 for the specific subset of neurodevelopmental toxicity. I mean usually a 10 would be about as high as you'd go for intraspecies, which would generally take into account childhood vulnerability or a special subgroup vulnerability.

So is there a specific rationale why OEHHA suggests 30 instead of 10?

DR. TING: So some of our reasons are explained actually in finding number 23. We separate them into pharmacokinetic and pharmacodynamic considerations.

But to answer your question directly, a number of considerations:

First of all, RBC acetylcholinesterase is being used as a surrogate. So it is a little bit unusual.

And second, if we do not have specific reason, we may choose to use a smaller factor. But in this particular case we have pretty strong data to indicate there is developmental neurotox. But we see challenges --

PANEL MEMBER BLANC: That's where the factor of 10 comes from, right?

DR. TING: But we see challenges in doing quantitative dose-response. That's why we think --

PANEL MEMBER BLANC: I understand that.

So where I'm going with all of this badgering of you is, wouldn't it logically -- isn't the logical conclusion of what you're saying, that the interspecies factor which you're suggesting should be 3 rather than 1, because of your uncertainty in the toxicokinetic portion of the PK-PD model - pharmacokinetic part of it? I think that's what I heard you saying, right? It's got to be either one half or the other half that you don't believe the data are certain about. Because otherwise you'd say it's a value of 10, not 3.

DR. TING: Actually that number -- our consideration is the model uncertainty, is another way to say the same thing.

PANEL MEMBER BLANC: Which part of the model?

DR. TING: The conceptual model of the PBPK, how it's implemented, how it's parameterized.

PANEL MEMBER BLANC: Why wouldn't you have said it's 10 and not 3, given everything you've said about it, and given that's it's looking at the wrong endpoint or the wrong mediator?

DR. TING: I think it's the state-of-the-art PBPK model, and a lot of effort has gone into it. So it may not be perfect but we would like to give it some credit in trying to --

PANEL MEMBER BLANC: I think 10 is giving it a lot of credit based on everything you've said.

DR. TING: Andy, you want --

DR. SALMON: Okay. My name is Andrew Salmon, and I'm senior toxicologist with OEHHA. Some of you may recognize me, having worked on the air program for a year or two in the past.

(Laughter.)

DR. SALMON: I just wanted to add what I see as a bit of a clarification about what these various uncertainty factors are. And the way we wrote this up for the Hot Spots Program, which is the program that has the defined guidelines where this is all laid out, was that we talked about the uncertainty factors firstly for interspecies; and conventionally that overall factor has been associated with a value of 10. And within that factor of 10, there are two components, one of which is a

pharmacokinetic uncertainty of -- with a value of the square root of 10, which is conventionally reduced to 3, and the other is a toxicodynamic uncertainty that is conventionally associated with a value of root 10 as well.

So that's the -- I think in this case what we're saying is that the uncertainty which David was describing as the factor of 3 is the -- or square root of 10 is that is the toxicokinetic component of that uncertainty factor.

And the -- there's also a factor of 10 going into the toxicodynamic component because of the uncertainty of inter-individual variability. And that -- but that's a -- excuse me -- that's a component of the intraspecies, so it's a different uncertainty factor.

So we've got a -- we got uncertain -- we've got -- we've gotten residual uncertainty in both elements here. And exactly how they've assigned these various values is a -- you know, a little bit of a -- a decision that is laid out differently here.

But I think -- and the point I'm trying to make is that it --

PANEL MEMBER BLANC: Yes, yes.

DR. SALMON: -- it fits the standard model, that we've got the interspecies uncertainty covered. And that's one factor.

And then we've got the intraspecies where we've

got toxicokinetics and toxicodynamics.

PANEL MEMBER BLANC: This is interspecies?

DR. SALMON: Intra.

Well, there's a --

PANEL MEMBER BLANC: Both parts.

DR. SALMON: There's uncertainty to be accounted for in both areas, in -- both in the interspecies extrapolation and the intraspecies.

PANEL MEMBER BLANC: Right.

DR. SALMON: So that's why you've got 3, or root 10, and then you've got --

PANEL MEMBER BLANC: 30.

DR. SALMON: -- then you've got another one, so --

PANEL MEMBER BLANC: And I just don't remember you coming up -- in your brief tenure with the organization, I don't actually remember a situation - and I could be misremembering - where we had a value for 3 for interspecies and a value of 30 for intraspecies and a value of 10 for further uncertainty. I do remember a lot of examples of 10, 10, and 10 --

DR. SALMON: Yeah.

PANEL MEMBER BLANC: -- and --

DR. LIM: I think this case is very special because we're talking about a chemical which is starting

with a surrogate endpoint as the basis of point of departure.

DR. SALMON: Yeah. I think we -- that's right, absolutely.

DR. LIM: In the air program you start with the most sensitive endpoint and then you add the uncertainty factors to that. So that's why -- our main recommendation is let's get the point of departure right with the best endpoint, the most relevant endpoint, and then we'll work on the uncertainty factors.

DR. SALMON: Yeah. I think this, as you say, is a special case. In terms of modeling the cholinesterase endpoint, we probably, you know, in spite of our reservations about the PBPK modeling and all that sort of thing, we actually have a rather better coverage of that specific topic than we typically did with some things in the air program.

But the big -- you know, the big extra issue in this case is the fact that we're essentially relying on -- for that -- for this assessment, we're relying on a substitute endpoint. And the air program would -- you know, had the air program been using the Hot Spots model for laying this all out, we'd have probably put that in as the -- a data uncertainty factor. We'd have called it a separate factor of 10 because of the uncertainty about

extrapolating from a surrogate endpoint to the one we were most concerned about. So I think that's where that extra one would have been put --

PANEL MEMBER BLANC: And that's aside from the factor of 10 for neurodevelopmental?

DR. SALMON: No, that would -- that would be -- that's where that -- that's where that comes in.

PANEL MEMBER BLANC: Right. So algebraically I'm not actually that far apart in this view. That is to say, I think it should be 10, 10, and 10; and you're saying it should be 3, 30, and 10.

DR. SALMON: Yeah. There's room for debate about that.

PANEL MEMBER BLANC: And I'm still -- and I think by precedent and by clarity, my own view is were you to recommend 10, 10, and 10, it would be more elegant.

(Laughter.)

DR. SALMON: Well, it --

PANEL MEMBER GLANTZ: And it would all -- speaking as one of the people who helped develop those rules of thumb back somewhere in the Pliocene Age, I think it would be a lot clearer -- I mean you're going to get the same answer. But I think it would be a lot clearer and you would also be able to cite, you know, all of the work we did in developing those uncertainty factors and

defining them before. You end up in the -- I still don't understand where the 10,000 came from, but I'll --

(Laughter.)

PANEL MEMBER GLANTZ: -- leave that for --

PANEL MEMBER HAMMOND: Well, let me revise my request -- the initial request, to get a table that lays out each uncertainty factor. And I like the idea of doing it from the DPR and from OEHHA's point of view. But let's also do it separately for the two outcomes, the acetylcholinesterase inhibition and for the neurotox development.

So those are two different outcomes, and they each have different uncertainties in them? And I think that's what's contributing to this kind of confusion.

PANEL MEMBER GLANTZ: Yeah, I think that's a really good suggestion as a way to --

PANEL MEMBER HAMMOND: I mean I think -- and the fact that you -- the fact you can't just sit -- nobody's been able to sit there and make that table while we've been talking for 20 minutes on this says something about how complex it is to you too.

I just say that --

PANEL MEMBER GLANTZ: They're making it right there.

PANEL MEMBER HAMMOND: So make it -- make it --

And as I say, but I would -- I would suggest now that there act -- but we just need clarity, and I don't think we -- doing it orally I think is not the way to do it. But make the table and have it for each of the outcomes, as well as if the different agencies have used different factors, just so we can see.

And I have ano --

PANEL MEMBER GLANTZ: Then put it on the screen.

PANEL MEMBER HAMMOND: And then I have another question.

In other -- in other iterations of my life in different places, the intraspecies variation - so, for instance, among humans - has been a factor of 10 in workplace values. So in other words, that's all adults. And we're saying there's intraspecies variation among adults human being that relates to metabolic pathways and different aspects of that. So if that's true, I don't think 10 is appropriate if you're also going to children. And certainly fetal development, I would imagine, is something more. So I guess I don't know if the hot -- now I can't remember, because I was part of that too but I forget -- the hot spots thing. But I think that there's an adult 10 and then something else for children.

DR. SALMON: The way the hot spots default works is that the overall value for the intraspecies uncertainty

factor, the UFH, is 30, which consists by default of a square root of 10 for the toxicokinet -- well, so -- that's -- there's an uncertainty factor of 30 overall. Let's not worry about that.

(Laughter.)

DR. SALMON: Overall 30 default for the whole factor, which includes both the toxicokinetic and dynamic.

PANEL MEMBER HAMMOND: So, yeah, I -- I think for me, I'm just a little visual, it would be helpful to just see it up there. And if we could, you know, do that.

And then I have one other question that's along this line and -- and, that is, is there -- are we thinking at some level that the inhibition of acetylcholinesterase is a step towards the neurodevelopment problem? Or is it just something that is -- this is a chemical that has this effect, it has this effect, and they're unrelated to each other?

DR. TING: Well, as we pointed out, there could be many mode of actions for developmental neurotox. I think U.S. EPA counted as many as five or six. But there's no definitive answer to that question. And inhibition of acetylcholinesterase may or may be one of those. I don't know the answer.

PANEL MEMBER HAMMOND: Right. And then I -- let me just ask the question. I won't say what I think.

Do we know whether it's a direct action or a metabolite that's responsible? I didn't --

DR. TING: We don't know either. I'm sorry.

PANEL MEMBER HAMMOND: Yeah, yeah. No, I -- that's what I thought. I mean I -- so I think we -- sometimes we have to be humble; and I think that's what uncertainty factors are, humility, in the face of uncertainty, you know, of what we know and what we don't know. On the other hand, we also have these observations that in the real world we are observing among human beings and children these outcomes. That is pretty clear.

DR. TING: Right. I just want to echo one Panel member's previous comment, is that the PD part right now is based on simple chemical reaction.

PANEL MEMBER HAMMOND: I'm sorry?

DR. TING: PD, pharmacodynamic variability.

But in the neurodevelopmental toxicology -- toxicity, the variability on the PD part, pharmacodynamic part, could be much bigger.

PANEL MEMBER BLANC: So let's go back to the model.

PANEL MEMBER GLANTZ: He wanted --

PANEL MEMBER BLANC: Oops. I'm sorry.

PANEL MEMBER ARAUJO: Yeah. I just have a question just -- so you're saying that there are different

mechanisms that could be responsible for those effects. And what are those mechanisms?

DR. TING: I'm not talking about -- I'm not saying that we know the mechanism. I'm just saying that pharmacodynamic for RBC inhibition is relatively simple and straightforward. But the same cannot be said for developmental neurotoxicity.

PANEL MEMBER ARAUJO: But there's not even any -- a speculation of what could be the mechanisms or any evidences?

DR. TING: As I said earlier, U.S. EPA counted as many as five to six possible or plausible mode of actions.

PANEL MEMBER ARAUJO: And what are those?

DR. LIM: They have -- well, they describe in the TAC documents. So I don't know if you -- maybe those uncertainty -- I think DPR could probably answer that question in greater details than we can do.

PANEL MEMBER ARAUJO: Um-hmm.

PANEL MEMBER BLANC: So coming back to the pharmacokinetic-pharmacodynamic model and the point of departure which has to do with 10 percent acetylcholinesterase inhibition. And that's what that whole model is constructed around. Right? And you're saying --

DR. LIM: Correct.

PANEL MEMBER BLANC: -- that we're using cholinesterase as a surrogate for something else that we're not -- cholinesterase inhibition as a surrogate for other effects, right?

DR. LIM: Correct.

PANEL MEMBER BLANC: And you've come up with some uncertainty factors -- or the -- well, they've come up with an uncertainty factor of 10 for neurotoxicity, and you don't disagree with that uncertainty factor.

But isn't the net effect of that saying that you're point of departure is 1 percent cholinesterase inhibition essentially, or am I being too primitive?

DR. LIM: If there's a linear correlation.

PANEL MEMBER BLANC: Well, what does model presume?

DR. LIM: I think DPR would -- probably can answer that question what the 1 percent point of departure would be --

PANEL MEMBER BLANC: Well, okay.

DR. LIM: -- from the model.

PANEL MEMBER BLANC: Maybe DPR can -- who's the modeler? Is -- yeah, can you chime in and say whether that model, which was developed by the EPA I guess and then refined by you, assumes a linear response for cholinesterase inhibition?

DR. KWOK: Okay. Let me answer the question. I mean back to the notion that, you know, anything less than 10 percent cholinesterase inhibition is considered unreliable, meaning, you know, technically we cannot achieve that.

I mean in terms of the model you can actually go down to, you know, well below 10 percent, you know, or whatever percent you want. But what would be the biological meaning attached to that -- you know, the model whether, you know, 3 percent or whatever percent, you know, below 10 percent?

PANEL MEMBER BLANC: Well, let me play it out for you.

So you've got all these animal studies. Now you've got seven or eight or six, or whatever it is, reliable animal studies with the endpoint of neurodevelopmental toxicity and you have the dose that the animals got and for some of those studies you have multiple doses, right?

DR. KWOK: Um-hmm.

PANEL MEMBER BLANC: And if -- if the relationship between dose of -- of chlorpyrifos and 10 percent inhibition is such -- we heard many times one milligram per kilogram was the amount below which you didn't get 10 percent inhibition. Right? But if it's a

linear and -- relationship and if the animal models of neurodevelopmental effects show that you're -- you're low -- your LOEL was 0.1 milligram per kg, and if you thought it was a linear response, then 0.1 milligram per kg would be a 1 percent acetylcholinesterase inhibition, and then you could adjust your pharmacokinetic-pharmacodynamic modeling to give you a point of departure of 1 percent cholinesterase inhibition if it were linear of course, which I don't know that it necessarily is. But if you -- have you thought at all in that direction? Because I'm trying to think about how -- and I'd still say there's a lot of uncertainty, so I wouldn't do -- I wouldn't do that and then do away with your uncertainty factor of 10, although you may say I think it can be 5 now because we've taken part of it into account by doing this.

But is that a root -- because otherwise I'm trying to figure out even if you decide to use neurodevelopmental toxicity as your endpoint, how are you going to make that operational?

And in terms of the -- just -- this is a side comment. But in terms of this back and forth about the epi studies and we can't get the dose-response from them, in fact if there were no epi studies, or if all the epi studies were negative, I would say there's enough animal

data to have that be the endpoint. I think the epi studies are kind of the icing on the cake. I wouldn't try to use them for your dose-response, but they just underscore the biological plausibility of all the animal studies.

And add uncertainty because humans are likely to probably be more -- could be more susceptible. And certainly what they're measuring in the rodents is a more blunt measure of neurodevelopmental toxicity because they're not looking at the SAT scores of rats, you know.

(Laughter.)

DR. DuTEAUX: If I may - and if would please the Chair - this present -- this was the opportunity for OEHHA to present their findings. DPR is more than happy to come back and spend the rest of the afternoon till midnight, if it pleases you, to talk about it. But I think it might muddy issues if OEHHA's asked to respond on behalf of DPR and vice versa. So if we could allow OEHHA perhaps to finish their presentation and then invite DPR back for questioning, we'd be happy to do that.

CHAIRPERSON KLEINMAN: Yeah, I think that would -- the idea that -- it's a great idea, and I think what we will do is we can wrap up this part of the presentation and then have lunch - we'll take a 45-minute lunch recess - and then give DPR a chance to -- because

they've gone over this in detail and have given us a -- their responses to these findings, I think --

DR. DuTEAUX: And we have some good table to show too.

CHAIRPERSON KLEINMAN: And we have tables. All right.

(Laughter.)

CHAIRPERSON KLEINMAN: Let me ask, are there any other questions that we need to address directly to OEHHA on this?

Jesús.

PANEL MEMBER ARAUJO: One of my comments is not to OEHHA in particular. It's just that I have the time limitations and I will have to leave just like around -- you know, around 20 minutes.

So I will not be here for -- after you reconvene from lunch. So I don't know if -- maybe I should give my comments then to the DPR now. And --

CHAIRPERSON KLEINMAN: Yes.

PANEL MEMBER ARAUJO: -- I will not be able to be here for the discussion.

CHAIRPERSON KLEINMAN: Let's take advantage of the fact that you're here now.

So go ahead.

PANEL MEMBER ARAUJO: Will they be able to answer

or will you -- or they just comment and -- when you come back from lunch, and then you let me know?

PANEL MEMBER GLANTZ: Just go.

PANEL MEMBER ARAUJO: I just go. Okay.

So --

DR. LIM: So these questions are for DPR or for OEHHA?

PANEL MEMBER ARAUJO: Well, it's mostly for DPR.

DR. LIM: Okay. Are there any questions for OEHHA?

Okay. Thank you.

CHAIRPERSON KLEINMAN: Okay. Well, thank you very much,

And, Shelley, if you wouldn't mind.

All right. Go ahead.

PANEL MEMBER ARAUJO: Okay. So this is a, you know, very extensive presentation based on a large amount of evidence. And the majority of my comments then will go -- or focus on the pathogenesis and on the -- some on the toxicology.

So, you know, pretty good presentation in the document about and the -- you know, what the compound is and the various characteristics. And I focus on the mechanisms and -- is perhaps a little bit weaker, perhaps because there is not -- you know, most of the work has

shown just a fix on the -- this -- that it has on the cholinesterase activity. And there will be ample discussion, I'm sure, in the remainder of the afternoon. We have already witnessed some, on how to translate these and how to extrapolate like from this and effects into the actual, you know, health effects on you -- that you may -- it may have.

However, it just strikes me that either there is a possibility that there are health effects and that can be induced even in the absence of demonstrable inhibition of the acetylcholinesterase. There are going to be other mechanisms and -- as those and five other mechanisms that were mentioned by -- in the OEHHA presentation.

And so I've been doing like some searches. And I didn't find in like some alternative mechanisms, none of which were mentioned in the document. So I could suggest that one of the things that could be done to improve on the comprehensiveness of the document is of including these other pieces of evidence.

So the acetylcholinesterase inhibition again is very well documented and presented. But there was no mention about other effects such as effects on oxidation or on oxidative stress. Effects on the paraoxonase activity.

There was a good presentation in between the

relationship of the paraoxonase 1 from enzyme that metabolizes and they compound.

However, it goes in both directions. Not only do the paraoxonase detoxifies and the chlorpyrifos compound, but also this compound can alter that period of the paraoxonase 1. And there is one paper and an abstract where I saw that.

And in animals it's been described that there is like a decrease in activity of the paraoxonase, and after just one -- or low doses of -- or local concentrations of it.

That is rather important, because paraoxonase 1 inhibition or the inhibition of this activity can result in a variety of different effects. For example, they knock out animals and for the paraoxonase, so there's been descriptions of an increase in atherosclerosis, of an increase cardiovascular disease. So one of the things -- and that has been well shown, it's been shown in a national paper of many years ago.

So I did some of those sessions. So if that is the case, could it be that in addition to these neurodevelopmental inhalation and dermal effects and that you mention in the document, could there be other effects then, and that perhaps are not through the cholinesterase activity inhibition that through the increased oxidation

or through the inhibition of the paraoxonase 1 activity? And it turns out that there are reports. So there are reports on the cardiovascular effects and there are epidemiological studies where it shows that there is in an association of pesticide use with myocardial infarction. And in one study that was published in 2010 -- and I can send you the references, because those were not mentioned in this presentation.

Although there was no overall association with the use of the 27 pesticides that were included in that document, it's in that study. It's a study that include over 22,000 women farmers or spouses of the farmers.

Six pesticides were associated with myocardial infarction. Out of the six pesticides, this is one of those. The alteration was like a 2.1. So it was not insigni -- they couldn't really conclude at the end because they said that they didn't really have the power to specifically determine like a risk and attributable to the specific pesticides, but that it was highly, highly suggestive.

So that goes together with other papers where they have shown effects on lipids. So just one single dose or -- of this compound can increase, and the lipids can increase cholesterol or triglycerides. I didn't have access to the papers, so I couldn't really say what is

specifically. They can be also increases in the glucose. And there are papers that look -- that talk an association with diabetes, either that it increases the risk of the diabetes or that the diabetes could be increasing the propensity of development -- developing in effects.

And there is paper from Beate in our Panel where it shows associations with Parkinson's disease. And I think that she will be discussing that in -- with more details.

So I guess I might -- you know, my recommendation is just to try to broaden, you know, the consideration for all the different factors of growth in the pathogenic mechanisms, to broaden also and include like the other potential effects in addition to the neurodevelopmental.

And I don't know if that will play a role or a factor in your considerations of the uncertainty factors. Because if there are other effects and other mechanisms that we can really account for, that may be the amount of the events is not enough like to take them into consideration to regulate based on those. But it does add uncertainty, you know. It does add uncertainty and it adds -- well, it could actually be that this is more toxic than what we think it is because we're just not considering the full spectrum with effects that could reduce. So that will justify maybe keeping a large

uncertainty factor.

And the last -- the very last comment will be that it seems that there are some individuals that will be more susceptible than others. And you mentioned some in the document, and it has to do with individuals with different polymorphisms for different genes, and very specifically the paraoxonase 1. And so individuals with the polymorphism or the genotype vary and that confuse the lesser activity, so may have an increased susceptibility to develop various of these effects.

DR. DuTEAUX: Thank you very much for those comments.

And for the sake of brevity, the 278-page document, we did try to narrow the focus on the acetylcholinesterase. However, we have edited our documents. And in a previous version -- or previous draft - it was internal only - we did have a large discussion of AOP. And if you have a few minutes before you leave, I would like to invite Dr. Marilyn Silva up here to talk a little bit about those pathways that she's been looking at, including an endocannabinoid. Now, this was specific to developmental neurotoxicity. However, it gives a window into the complexity of this chemical and how the biological systems are interacting.

DR. DuTEAUX: Did you want to bring up slides or

do you just want to talk?

DR. SILVA: Well, I have the AOP.

DR. DuTEAUX: Oh, okay.

DR. SILVA: My name is Marilyn Silva, and I'm in the Human Health Assessment Branch with Shelley DuTeaux.

And so I think the most important -- let's see. Let me get this a little bigger here.

DR. DuTEAUX: The slide show button.

PANEL MEMBER GLANTZ: Hit the little screen.

DR. SILVA: Okay. What -- because I don't have much time and this is very complex, I would take a look at this box down here where you have your key events going on. And before -- and if we go through this really quickly.

First you have - and most important - you have a disruption of the endocannabinoid system by chlorpyrifos. And then this leads to the various other key events, which ultimately ends with reduced connectively and functionality of neural networks. And so there you're going to have your neurodevelopmental effects.

We focus on the diagram on the left. And you'll see chlorpyrifos would act at the CB-1 on the far left and ultimately inhibit the enzyme MAGL that breaks down the endocannabinoids. So the endocannabinoid buildup in the synaptic area will inhibit the release of

neurotransmitters; and therefore you have inhibited function. So we're talking about the GABA system, acetylcholinesterase, NMDA, the glutaminergic system, dopamine active transporter, and serotonin. So you're going to have an inhibition. I mean in a nutshell, you're going to have inhibition of release of these neurotransmitters, which are going to have a long-term effect on -- downstream with your neural progenitor cells, your neural networks, and ultimately neurodevelopmental or neurological effects.

DR. DuTEAUX: Thank you for that, Marilyn.

And also we have found, just in discussions of other papers, that they have mentioned potential metabolic mechanisms, including neuropathology target esterase, monoacylglycerol lipase, fatty acid aminohydrolase, and then other non-metabolic mechanisms, including, as you mentioned, oxidative stress, disruption of neurogenesis, cytotoxicity, disruption in cell signaling, altered nuclear transcription factors, altered neurogenal cell interactions.

And then you have the environmental factors, which we tend to not include, although weight of evidence would make us want to look at those, including whether there's combined chemical exposures, the health status of the mother or the individual, infectious disease, heavy

metal exposures, and social determinants of health. So we're looking at an incredibly complex system not only in neurosynaptic junctions and in the brain, but also in the environmental milieu that a person is in.

Because we are a regulatory agency and we have to come up with a regulatory target number, we can only for a risk assessment look at a single chemical at a time. That's the system that we operate within. So unfortunately we can't look at multiple OPs or the interaction of OPs and carbamates or any of those.

So if we look specifically at chlorpyrifos though, the world is just opening up in the potential pathways. And the AOP has definitely not been completely elucidated. This is from a draft publication that will be going --

DR. SILVA: Has been accepted.

DR. DuTEAUX: That's been accepted.

But you're points about multiple mechanisms and not -- and known unknowns and unknown unknowns is right on point.

And did the selection of an endpoint that we did and the addition of the uncertainty factors to that, does that allow for enough protection for whatever might be happening with this compound, at whatever levels is the target tissue dose?

DR. KOSHLUKOVA: Well, chlorpyrifos oxone inhibits esterases. And we know the esterases are about 11 percent of the total genome in humans. So with that, we would be expecting many pathways affected.

CHAIRPERSON KLEINMAN: And in addition, the inhibition of the cholinesterase in the brain's going to lead to a buildup of acetylcholine, hyperstimulation of the entire cholinergic nervous system and all that, which then can lead to, you know, tissue damage and a number of other things.

So I mean there's a real link to, you know, the inhibition of the cholinesterase as well as all these other mechanisms. And I think it would be very helpful, you know, just leading with where I would be going in our discussion, to improve the document by actually putting some of this stuff in the front end, so that there's a real rationale for why are we looking at, you know, cholinesterase inhibition and how does that link to the developmental nervous changes and nervous system changes. And I think that would help too.

But, anyway, I think this would be a good time for us to take a --

PANEL MEMBER GLANTZ: Does Jesús have anything else he wanted to say before you run off?

You don't have to.

PANEL MEMBER ARAUJO: No, no. I guess -- I understand, you know, the decisions that you made in -- okay. So you're choosing on the neurodevelopmental effects and you're choosing on the cholinesterase inhibition to make your decisions, right, and using the modeling and all the data derived from that. But that doesn't impede at least, you know, in the -- perhaps in the background or in the introduction, mention all the other potential -- I'm not talking about interactions so for the chlorpyrifos with many other compounds. I'm just talking about chlorpyrifos and the way how it acts, it induces all these effects, and the variety of effects that it can induce. And if one of the things that we're talking about, uncertainty, how much uncertainty to say that we will be regulated based on a mechanism that we know that even if nonexistent, the chlorpyrifos could induce some effects. That is a lot of uncertainty.

So I think that rather than just consider like a narrowing or decreasing the uncertainty, the question is that should we increasing the uncertainty factor even more. Because I think that we're not including other things that could be potentially as important or even more important. Maybe because they just haven't been studied enough or maybe because they're not as important as we -- as the -- we just don't know, right?

But this point I already made it. And so I -- if you decide to include it, so I can provide some of the references in some of these searches.

DR. DuTEAUX: Yeah, we'd very much appreciate that. Thank you.

PANEL MEMBER HAMMOND: I just want to express gratitude for those comments, because -- I mean this is stunning, this is really interesting. But this is still all that one pathway. And Jesús is also talking about totally different pathways, right? And so I don't want to lose that point of his. But I think this is great that -- this points out all these other things that we didn't -- that you didn't do. But -- right, right.

Well, I -- right. But it's all coming through -- I -- I understand that. It's initiating all from the cholinesterase.

PANEL MEMBER BLANC: No, it's not. That's the whole point.

PANEL MEMBER HAMMOND: Okay. I'm sorry. Then I did -- I misunderstood that. I thought that was first --

PANEL MEMBER BLANC: No, no, this is...

PANEL MEMBER ARAUJO: It's in relation to the neuro --

PANEL MEMBER BLANC: It's related to the end -- the clinical endpoint, if you will, is neurodevelopmental

toxicity. But this is underscoring that that can be independent of the acetylcholinesterase inhibition, and that's the biological plausibility of seeing effects at levels which we have reason to believe there is no acetylcholinesterase inhibition.

PANEL MEMBER HAMMOND: And so Jesús has given us other pathways as --

PANEL MEMBER BLANC: Other endpoints.

PANEL MEMBER HAMMOND: And other endpoints. Both, right.

PANEL MEMBER BLANC: I think the oxidative stress is here.

DR. DuTREAUX: Yes.

PANEL MEMBER HAMMOND: I missed it then. I supposed it was hard to take in.

DR. DuTEAUX: But, Dr. Hammond, your point is well made, that if it's cardiotoxic or lipogenic, there are -- outside of these enzymatic pathways and signal transcriptase pathways, that there could be other phenogenic, phenotypic expressions of toxicity that we can definitely look at. And as I mentioned early -- earlier this morning, I did look briefly at spermatogenesis, which is not developmental, and it's repro so it's different. And the effect was 35 milligrams per kilogram per day for spermatogenic effects, which is well above the effect for

acetylcholinesterase. So looking at that one aside, but what are the sensitivities of the other endpoints? And I think it would behoove us to look at those.

PANEL MEMBER ARAUJO: Yeah. Well, I wasn't impressed in the document as well as in your response now.

You know, on the many different receptors that are -- can interact with the chlorpyrifos. So you talk about FXR, you talk about an LXR, you talk about a lot of, you know, nuclear receptors. And I'm saying, wow, all these receptors are very much involved in carbohydrate metabolism, lipid metabolism, you know, a lot of systemic metabolism. Why we don't have much of many -- you know, more evidence of it.

And that's why I decided doing the searches. And I found some references with animal work and some references with you. But I have to say just that they're few. There are a few. The bulk of the evidence goes into the neurodevelopmental.

Could it be just, and again, that just haven't -- they haven't looked at it? So, for example, you know, you -- you cannot -- you cannot see what you don't even look for -- for it. You know, you have to have some sort of like an educated mind, right, and to discover or, you know --

DR. DuTEAUX: And if we had five more years to

work on this document, it would be wonderful. We could always retire knowing that this one is the --

PANEL MEMBER ARAUJO: But you can certainly take into account at least what we know and what has been published. So even though the bulk of the evidence is on the neurodevelopmental effects and on the cholinesterase activity, the few pieces of evidence that are saying that there is a whole lot of other mechanism effects that haven't really been studied enough, could they at least be mentioned and could be taken into consideration perhaps at least to substantiate in the large uncertainty factor that we are considering.

DR. DuTEAUX: Thank you.

CHAIRPERSON KLEINMAN: All right. I think this is a good time to stop. We'll have a 45-minute recess, and reconvene at 2:15.

(Off record: 1:32 p.m.)

(Thereupon a recess was taken.)

(On record: 2:23 p.m.)

CHAIRPERSON KLEINMAN: Good afternoon. I'd like to call this meeting back to order and continue with our discussions.

So if everybody can get their seats.

The next item on the agenda we're going to have a response that's been prepared by DPR regarding the

findings that OEHHA presented earlier.

And then we'll move on to discussing the charge questions.

So, Dr. DuTeaux.

DR. DuTEAUX: Well, I apologize. I did not realize that we were expected to give a formal response to OEHHA's findings. We have a document that everyone released. But we didn't -- that we released to the panel. But we didn't make a slide presentation particularly about our responses.

CHAIRPERSON KLEINMAN: Well, what I think would be helpful is, you know, there have been a couple of issues raised --

DR. DuTEAUX: Sure.

CHAIRPERSON KLEINMAN: And I think to give us just a feeling -- nothing -- you know, how you intend to deal with that just as an overview. I know you've written up a very detailed discussion of it. But sort of the high view of it.

DR. DuTEAUX: Okay. Well I -- two points kind of bubbled up to the surface in the conversation at the end of the morning, one of which was on the differences on breaking down the uncertainty factors between OEHHA and DPR. So I think if we could start there, that would be a really good place to start; and then we can also clarify

where that extra 10 comes in as a toxic air contaminant. So let's start there and then we can move on from that.

So I'll turn it over to Svetlana Koshlukova.

So the table we're showing on this slide right here is -- Svetlana, if you can do slide show. And that gets rid of all the stuff around.

Next to 71, exactly.

This was actually a table -- Table 4 that we pulled from DPR's response to OEHHA comments which was released in August 2017 just ahead of our PREC meeting.

So we don't want to speak for OEHHA, of course. We pulled the explanation of -- there are parts of their uncertainty factors from their comments to us, but we certainly don't want to speak to that. What we can do, if Lori or David are willing to, is to come up and they can speak on their numbers, we can speak on our numbers.

But if we start, I'll have Dr. Koshlukova start on speaking to our numbers.

DR. KOSHLUKOVA: So just show --

PANEL MEMBER GLANTZ: So I think that's a good idea to have OEHHA talk to. And what I would prefer, since -- or go back to your slide, because your slide and OEHHA's slide are the same in terms of the numbers.

Maybe to go through these one at a time and get -- hear it from you and hear it from them about each

one, and then have some discussion. Because I do think -- I do think that this is -- this is like one of the -- this is probably the biggest single issue in the report, is what these numbers ought to be.

And the other thing -- by the way, I will use my prerogative as the longest serving member of the Committee, who has been on it forever. You know, this process of discussion, you know, rather than having to worry about a lot of formal documents back and forth, is the way we've done these in the past. And then you get to go -- you get a transcript and get to try to figure out what everybody said after the fact.

(Laughter.)

PANEL MEMBER GLANTZ: But, no, I think -- I think this is like one of the two or three key issues. Okay.

DR. DuTEAUX: And I guess let me ask Lori and David before you talk to your numbers -- and maybe we can start with interspecies and then intraspecies.

Would you like to have Randy come up and explain the 10x for the TAC? He's willing to do that if -- that's okay?

Okay. Good. I'm going to turn the floor over to Randy Segawa then.

DR. KOSHLUKOVA: From the PREC presentation, that -- would you like that one?

DPR SPECIAL ADVISOR SEGAWA: No, that's all right.

PANEL MEMBER GLANTZ: I didn't mean to cut Svetlana off.

DR. KOSHLUKOVA: Oh, that's --

DR. DuTEAUX: That's okay.

DPR SPECIAL ADVISOR SEGAWA: Yeah, so part of this discussion this morning was this extra tenfold, quote, uncertainty factor for toxic air contaminants, which adjusted OEHHA's recommended total uncertainty factors from 1,000 to 10,000. That extra, quote, uncertainty factor's really not an uncertainty factor. It's not based on science at all. It's the legal criteria that DPR has for listing as a toxic air contaminant.

So whatever total uncertainty factor you end up deciding, whether it's 100 or 1,000 or something else, then under the State law for listing as a TAC we add in an extra tenfold factor. And so if the margins of exposures exceed cede that extra tenfold, then we list it as a TAC.

Again, it's entirely based on legal requirements. There's no science behind it. And so it really shouldn't be viewed as an uncertainty factor. Okay?

PANEL MEMBER GLANTZ: So just to finish clarifying that. But -- and also from the Chair. But what we should come up with as our recommendation to you

is what we think -- we should kind of forget about that legal thing and we should just tell you what we think the number ought to be, and then can you go fight with the lawyers about that.

DPR SPECIAL ADVISOR SEGAWA: That's exactly correct.

PANEL MEMBER GLANTZ: Okay. Great.

DR. KOSHLUKOVA: So this document that you see on the screen is our response to OEHHA's comments that Shelley mentioned. It was published on the DPR website on August the 15th.

And so these are our responses to their comments to the 2015 RCD. This was before the bulk of the 2017 published -- papers were published on developmental neurotoxicity.

So if you go to page 8, we have this table that we composed comparing the uncertainty factors used by DPR and OEHHA and recommended by OEHHA. These uncertainty factors are for cholinesterase inhibition as an endpoint, and based on point of departures estimated with PBPK-PD model.

Our reasoning is to the left in the blue highlighted section. For the interspecies, we are using uncertainty factor of 1 based on the fact that those are human equivalent doses derived from a PBPK-PD model. This

is a human model, and the outputs, the PoDs are for humans.

For the interspecies factors, this is the inter -- the variation between insensitivity within humans. We retained a default of 10. At that time, the model -- the model that U.S. EPA used, it was developed by Dow, established a so-called data-derived uncertainty factors of 4 for chlorpyrifos and 5 for oxon, which would indicate that people can vary the sensitivity to cholinesterase inhibition in humans is fourfold for chlorpyrifos and fivefold for chlorpyrifos oxon.

However, we had concerns about the DDEFs, the data-derived extrapolation factors, mostly because we did not -- EPA at that time - we adopted their endpoints - did not utilize the pregnancy compartment of the model. So that life stage was excluded. And at that time, we had some concerns regarding the metabolic parameters and their variability.

And the final uncertainty factor is a 10 for neurodevelopmental toxicity. This is to account for the fact that we're using endpoint for cholinesterase inhibition. And we are aware of potential neurodevelopmental effects. As such, we involved the uncertainty factor of 10 for this potential -- for this neurodevelopmental toxicity that may occur in doses lower

than cholinesterase inhibition.

We did not have a lot of evidence where the neurodevelopmental effect may occur at doses. At that time, we had one evidence from zebrafish studies. It was not a ToxCast or high throughput toxicity study. It was a normal test where they measured cholinesterase in zebrafish and also behavioral effects and malformations, and they found that those neurodevelopmental, neurobehavioral effects occurred about tenfold lower concentrations than cholinesterase inhibition.

So that was the reasoning for our uncertainty factors.

Okay. So then since then we...

PANEL MEMBER BLANC: So in your tables of -- in the document here, in your parent document where you had tables about neurodevelopmental toxicity, the tables at least seem to be limited to rodent studies. So the zebrafish data aren't included there. Are they included somewhere else that's just hard to see where they are?

DR. KOSHLUKOVA: They are. They are in the RCD. Yes, they are included in the RCD.

DR. DuTEAUX: It's in the ToxCast section.

DR. KOSHLUKOVA: It's in the ToxCast section.

PANEL MEMBER BLANC: Okay. I -- no, I understand. So that's probably why I missed it. But

it -- one goes through the document and sees this section on neurodevelopmental toxicity, and it's the -- all the, you know, rodents and there's nothing about zebrafish there at all. You may want to give a shout out to you're going to -- there's also a zebrafish data which is covered in a different section.

DR. KOSHLUKOVA: Right. And we will ask Marilyn to present a little later. We have prepared a table where we compare the developmental neurotoxicity studies, the newly published ones, as well as zebrafish on the next slide.

PANEL MEMBER BLANC: So let me just go back to the topic of the endpoint. Maybe we're too far down the road. Maybe we need to establish something else a bit more basic first.

What do you propose as the endpoint for toxicity in your standard setting?

DR. DuTEAUX: Specific to chlorpyrifos?

PANEL MEMBER BLANC: Yes.

DR. DuTEAUX: So our assessment to date shows that the database for acetylcholinesterase inhibition --

PANEL MEMBER BLANC: I didn't ask what the database was better for. What do you think is the key toxic endpoint for chlorpyrifos? Not what can we model with acetylcholinesterase. What do you think is the

target organ and target effect that is the public health concern here -- the greatest public health concern? That's I think what we need to decide first, because then everything else is just tactical. But strategically what...

DR. DuTEAUX: So you're asking a question of a regulatory agency that is difficult to answer. Because if we're protecting public health as we are, we have to reflect our entire mission. And so what we have to do with establishing a regulatory target is have something that's scientifically justifiable and also defensible in court and defensible with the legislature.

PANEL MEMBER BLANC: Right.

DR. DuTEAUX: So we're not simply coming to this body to come up with a guidance level. We're actually going to be making regulation following this.

And the weight of evidence that goes for that may have a different factor that we have to consider. So I cannot answer that question without talking about database certainties and database -- just the volume and certainty of a database.

PANEL MEMBER GLANTZ: Yeah, I really -- I really think it's a little bit of an unfair question to ask them. I mean, I -- they've come forward with their report. And I think it's our job to say what we think they should do.

I mean if you read it -- I mean at the very -- as I recall, the very last thing is we're using this red blood cell acetylcholinesterase, but we're -- we recognize that the neurodevelopmental toxicity is important and we're thinking about it. And I think the question -- the thing -- and I agree with you, this is the fundamental question. And I mean, just to speak for myself having, you know, read all of this, listened -- you know, talked to them a week or so ago, read the public comments, listened to the discussion this morning, I mean I think that the developmental neurotoxicity is the more appropriate endpoint, and that -- that you could develop a defensible document and a defensible position with. I think that you have -- I mean I think the document is actually pretty well put together. I could follow it, which is like amazing --

(Laughter.)

PANEL MEMBER GLANTZ: -- because this is -- a lot of this is not what I do all the time. And I think it's really a matter of judgment and emphasis. And I think that you have in the document, you know, the information that you pretty much need to make the case for developmental neurotoxicity being the appropriate endpoint from a regulatory point of view. I mean that's -- I'd be interested in hearing what other people say.

Now, the -- just one more second. The next question after that is then, how do you then convert that to a number that you can use for regulation?

PANEL MEMBER BLANC: That's what I was trying to ask.

PANEL MEMBER GLANTZ: And that brings us back to this.

PANEL MEMBER BLANC: Thanks for --

PANEL MEMBER GLANTZ: Huh?

PANEL MEMBER BLANC: Thanks for restating it, because that's really what I was trying to ask.

PANEL MEMBER GLANTZ: No. But the thing that was different, I think just -- then I'll -- because I was quiet this morning.

(Laughter.)

PANEL MEMBER GLANTZ: And my head almost exploded. But everybody else was asking all my questions.

But I think -- I don't think it's fair for us to ask them at this point what they think, you know, should be done. I think it is now our responsibility to say to them what we think they should do. Do you see the difference?

And I think -- they've put forward what they think in this report. I think its a well written document. And I think it's -- I think it's been very fair

in presenting the data on all of these issues. I think they were very responsive to the public comments, you know, within the point of view that they ended up with. And I think the question we have to ask is, do we agree with the primary conclusion they drew; or do we want to recommend they take the alternative pathway, which is outlined in the report pretty clearly I think.

So that's -- so I'll be quiet now for five seconds.

PANEL MEMBER HAMMOND: I'll try to make this quick.

And to answer that question -- and I agree. I think that this is the -- these are the two primary questions that we've been talking about.

I think -- I understand what you're saying about needing the strong database. I think you have shown using an outcome that you don't think is the prime outcome if you really had your choice -- well, at least, this -- let me say, I think - all right - from --

PANEL MEMBER GLANTZ: But we need to speak for us now.

PANEL MEMBER HAMMOND: Yeah, okay. So for myself, the red blood cell acetylcholinesterase inhibitor -- I want to get that all.

PANEL MEMBER GLANTZ: Cholinesterase.

PANEL MEMBER HAMMOND: -- cholinesterase inhibitor as an outcome is less important I think than the neurotox -- the neurotox developmental outcome. But there's a stronger database.

But what I see is you've got -- you can take the first outcome, and you can do all your uncertainty factors and your numbers and work that out. And we have enough data to say that we're seeing these neurodevelopmental effects happening at lower concentrations.

And so I think you make your strong case for outcome 1, and you -- and what the level would be to protect from that. And then you know for sure that outcome 2 has got -- there's no uncertainty factor; we can talk about what that should be. But you've got an uncertainty factor, and you can start saying where can you work from there. But it's sure as heck going to have to be something way below the -- a first one because you already see that effect.

So I think there's enough data, and that's how you would support it, you know, if you do -- you prove A really well and then you say B is less and then you work on how much less.

PANEL MEMBER GLANTZ: And just to -- again, because I was so quiet this morning.

I think -- and I don't think this is going to

require a huge amount of rewriting of the report; because I think you have a huge amount of information on just this point in there, and it's very well presented. I think the stuff that you presented right before lunch, without getting into a whole, you know, writing another hundred pages, I do think that strengthens the case quite a lot, because it points to the -- to the biological pathways that kind of connect all these things together. So I definitely think that's -- and I thought you presented it pretty clearly too. I think that's worth adding.

But I think the way -- again, the way that Kathy framed it is I think what the path forward is, if the committee ends up agreeing that neurotoxicity should be the endpoint, you know. So...

PANEL MEMBER RITZ: Well, I'm actually really stunned to think that what I heard - and I might be completely wrong - is that you're basing all this on the acetylcholinesterase inhibition, more or less, even though you're presenting all this modern data: the ToxCast, the assays. And all of these assays are pointing all in the same direction, right - receptors, pathways. And this is -- this is not that modern anymore. I mean this has now been accumulating over a decade. That's probably why you were able to put this in here. But it seems like you're ignoring the huge database, that was created with

these assays, that all tell you something or parts of that big story that probably leads to neurodevelopment, neurodegeneration, something brain related.

So I didn't really see how that was brought into your overall ruling. You described it beautifully. And, you know, that's nice and thank you. But how was that brought into the decision making, the rulemaking, or was that all knowledge you put in after you already had decided on these factors? It's not clear.

DR. DuTEAUX: Okay. So just to clarify, I think.

We chose an endpoint, which is acetylcholinesterase inhibition, for this document. And then we justified what the uncertainty factors were to get to our reference concentration for an inhalation toxic air contaminant. And I believe - if it wasn't clear in our risk appraisal section, we can certainly go back and make it more clear - that to underpin a tenfold uncertainty factor for neurodevelopment, that is underpinned by the -- the AOP that we -- is still in formation at this point, also by the zebrafish data, and also for the epidemiology data. All of that goes into basing a 10x neurodevelopmental uncertainty factor, where we are right now.

The additional animal data and any additional epidemiology data that comes in could certainly strengthen

that number or change that number. So hopefully we didn't discount it. Hopefully it was just a matter of not being as explicit as we should have been in the explanation.

PANEL MEMBER RITZ: So that sounds to me like you have three lines of evidence - epidemiology, the animal data at very low doses, and the ToxCast assays - and all of them -- all three of them give you a factor of 10. I'm wondering how that number is justified?

DR. KOSHLUKOVA: Well, so our first risk assessment came 2015. So you understand this was two years ago.

So this is the -- this table that you see is responding to comments to our 2015 risk assessment. Since then, we have made two more drafts, and new information came. So in this particular case, at that time the only information that we had regarding to how much lower neurodevelopmental effect might occur, or from the zebrafish studies.

We have experts in ToxCast. We have an award-winning group here, we here in DPR. And so we did explore ToxCast.

We have a lot of pathways by -- at that point, we were unable to quantify how these pathways, individual pathways would produce in vivo human equivalent doses.

But that was at that time.

Now, recently this year, since 2015 there were two posted presentations from Dr. Carr's lab, and then several papers were published, most of them this year.

All of the effects that we see on neurodevelopmental toxicity, they're in three domains - cognitive effects, behavior, and motor activity. All of them occur -- in the four papers occur at 0.1 milligram per kilogram per day. Remember, the threshold for cholinesterase inhibition is 1 milligram per kilogram per day. So we are about a 10 in animal studies.

PANEL MEMBER BLANC: Sorry. So that -- to come back to Kathy Hammond's direction of questioning, and to combine that with Beate's questions, there are -- there are -- seems like there are only two logical ways to go. One way to go is you say that acetylcholinesterase is our surrogate endpoint even though we do not believe that that is the mechanism of toxicity.

DR. KOSHLUKOVA: (Nods head.)

PANEL MEMBER BLANC: But we're still going to use it because we believe our data is more robust. And we believe that at least -- that a dose of 0.1 is the lowest effect level. It's not a NOEL. It's a lowest effect level. Right?

DR. KOSHLUKOVA: There is one.

PANEL MEMBER BLANC: But we're still going -- but

if I understand it correctly, despite all of these correction factors, you're still using the point of departure as 10 percent inhibition. And then after the fact you're doing a series of adjustments for uncertainties. But usually when we're talking about uncertainty factors, it's not like -- actually we're pretty certain this isn't the mechanism of action, but we're going to use this anyway. So that's what's not so attractive about using acetylcholinesterase inhibition as a surrogate measure. But if you are going to use it as a surrogate, you're going to have to assume that the surrogacy occurs at 1 percent inhibition or half a percent inhibition of acetylcholinesterase. That's even assuming that it's a linear effect, because you're seeing something, instead of at 1 milligram, you're seeing at 0.1 milligram.

So I don't think you get there just by throwing in an uncertainty factor of 10.

The other way you could do it - and I'm not so sure I understand why you can't do it this way - is forget about the acetylcholinesterase inhibition, forget about the PK-PD modeling. Take the animal data that you have for neurotoxicity, and either try to estimate a benchmark effect or a LOEL and divide it by 10 and use that and do all your risk calculations with that value, or at least

compare them side by side and see what they look like.

PANEL MEMBER RITZ: Under that paradigm you need a 10 for interspecies extrapolation.

PANEL MEMBER BLANC: Yeah, so we'd use that 10 for interspecies because you'd be using animal data. You'd have to --

DR. DuTEAUX: Right. And I think that the 10 for developmental neurotox would then --

PANEL MEMBER BLANC: Go away.

DR. DuTEAUX: -- reduce to 1. So --

PANEL MEMBER BLANC: Yeah.

DR. DuTEAUX: -- it would be the same number.

PANEL MEMBER BLANC: I understand. I understand that. But --

DR. DuTEAUX: The same total. I'm sorry.

PANEL MEMBER BLANC: Right. But since you'd be doing a LOEL I guess at 0.1, it's actually going to be 0.01, right? So you're going to get 10 more that way.

So my guess is -- so my guess is you'll come out, you know, sixty-fold lower or something - I don't know - than where you are now. Something like that. But at least it will be -- it will be a bit more logical than saying we know that this isn't the mechanism we care about, but this is -- you know, this is what we have a good data for, you know, doing our calculations. But

that's kind of putting the cart before the horse a little bit, I think.

It would be better to do the cruder, you know, NOEL way. But you might even be able to have a model for, you know -- what word do I want where you do the doses and you -- a benchmark or a ben -- yeah, thing that will work. I don't know if the data are robust enough, but I would at least try to go down that path. And then you're not forced to put yourself in this double bind that you're otherwise in, it seems the me.

CHAIRPERSON KLEINMAN: And I think it's important to keep in mind that the inhibition of the enzyme is part of a mechanism and could be a toxic outcome, just the fact that other things are happening even at lower levels.

PANEL MEMBER BLANC: Yeah, the target organ toxicity -- I mean target health effects.

CHAIRPERSON KLEINMAN: Yeah. But to amend what you were just saying, I would not say that it's not the mechanism -- not a mechanism -- I would say it's not the only mechanism.

PANEL MEMBER BLANC: Well, it doesn't appear to be the mechanism for neurodevelopmental toxicity since it's occurring at levels below which we would have anticipated there be any and in which there doesn't appear to be any acetylcholinesterase inhibition.

And I thought, you know, your figure, which tended to indicate that if you had to -- someone put a gun to your head and choose the mechanism, you would say it was the cannabinoid mechanism. That was kind of what I took away from that figure, even though that there's some other possible explanations.

But, anyway, we've put --

DR. KOSHLUKOVA: Not necessarily. This is the one that we have more information how chlorpyrifos works. It just -- the data is there. There is quite a bit of information on serotonin -- hitting the serotonin system, oxidative stress.

But this one is the one that we can make the adverse outcome pathway as a first try.

PANEL MEMBER BLANC: Yeah. Anyway, that -- wouldn't that make your life easier, not harder?

(Laughter.)

DR. DuTEAUX: It still would require an extensive rewrite of the document.

That aside, we would be interested in seeing what this Panel's recommendation and findings are to us.

PANEL MEMBER BLANC: Well, that would be mine.

And why don't you speak next.

PANEL MEMBER RITZ: Well, I'm an epidemiologist. I just want to see all the human data acknowledged. And I

think we already heard from my colleague that there might be other data out there, which -- because, you know, we live longer, we have different -- we have a neural network that is slightly different from all these animals. And there might be more chronic effects than we really can imagine. So we should at least point to them even so we can't use them for regulations yet. But they should be acknowledged and taken into account, especially if then ToxCast shows more and more of these pathways coming up.

DR. KOSHLUKOVA: It all comes to the uncertainty. Which endpoint selection would lower the uncertainty? Is it the well doc'd cholinesterase inhibition that we know and then just add additional uncertainty factors to account for neurodevelopmental effects? Or use neurodevelopmental endpoint, which comes with uncertainty because the database is not rich and they're not solid endpoints at this time?

So we prepared this table per Dr. Glantz' request. So I can walk you through it a little bit. It's complicated and I'll try to narrow down to the topic of the conversation right now, and then I'll get some help.

So basically it has four panels. The first one is the uncertainty factors, the routes and duration, and then various exposure scenarios as well as the sensitive population that we evaluated.

So it starts with -- the second panel is in pinkish, and that's our current document, 2017 -- 2017 December.

It shows -- the first column shows PBPK PoD-derive -- or PD-derived point of departures. Those are based on 10 percent acetylcholinesterase inhibition using the model.

And we expressed everything as microgram per kilogram per day. So it's a little confusing about the -- the units, so remember, it's microgram, not milligram. So...

For the second part is the reference dose or reference concentration, which we calculated as the critical endpoint divided by the uncertainty factor. In this case for the model that we used for the endpoint, our total uncertainty factor is 10, based on 1 for interspecies sensitivity, 10 for intra, and 10 for developmental neurotoxicity.

So if you'll look at children only for acute auto, the reference dose would be 5.81 micrograms per kilogram per day. We go down -- this is for acute.

Then we go down the road. And for children the steady state -- this is short terms of chronic. This is a steady state or equivalent to subchronic. Repeated dose treatment would produce a dose of 0.99 for 10 percent

cholinesterase inhibition. This would be the reference dose. And I think higher than this would be acceptable.

And then we have the same for dermal.

And then the same for inhalation.

The one that's important is 28.5. That's the reference concentration, which for now is used as a target concentration.

The panel in green is the published developmental neurotoxicity studies in animals. The point of departure, there are four or five studies. They all come with a NOEL of 0.01 milligram per kilogram per day, which would be 10 microgram per kilogram per day.

If you compare -- now, those studies are done through different exposure regimen. So it's -- one of the studies is a single dose, acute; and then the rest are repeated treatment, either during gestation, during postnatal period, or combination gestation and postnatal.

So most of -- it's all oral. That's a very important point. We only have oral data oral studies.

So again, they -- the new developmental point of departure will be applicable for both acute and short-term duration; and perhaps even longer because at least in one of the studies treatment is, one, during the postnatal period and then the pups are assessed when they become adults.

So then we compare -- if you look at the steady-state cholinesterase inhibition based reference dose compared to the one that would be coming from the published developmental neurotoxicity studies, the difference is tenfold. That's where we come here.

If we compare this reference dose to the acute number for cholinesterase inhibition, the difference is 58-fold.

Then we continue on to dermal and inhalation. We do not have route-specific data for neurodevelopmental. Therefore we have to do some conversions using default assumptions of what the -- yeah, breathing rate is, and body weight for -- for children; and then in the case of the dermal, we would need to have some idea of the dermal absorption in animals. So using 3 percent dermal absorption in the rat, which is the published value in one of the U.S. EPA's documents, 2011, the last document that's used animal data for point of departures, we calculated a dermal PoD based on the developmental neurotoxicity study of 3.3 micrograms per kilogram per day. And this going to be 403-fold lower than the corresponding one from cholinesterase inhibition.

But, again, this is based on route-to-route extrapolation.

And for inhalation the important number that we

have -- this is the current one based on cholinesterase inhibition. And if we use default breathing rate of 0.33 cubic meters per hour and body weight of children 11, then we come up with this number. And it's going to be a thousandfold lower.

And then the third column is -- that's Dr. Glantz' request, to also include the U.S. EPA risk assessments using epidemiologist study. So we selected the November one because the previous one -- the previous one in April did not really establish PoDs. It was based on internal -- in blood concentration, the cord -- the concentration of chlorpyrifos in the cord blood. And so this one had the reverse dosimetry established reference point of departure.

So U.S. EPA risk assessment did not deal with acute toxicity, so everything was done on the steady-state base.

These are the numbers, and this is how the difference would be compared to our current document.

PANEL MEMBER BLANC: Very helpful.

It's also quite reassuring actually to see that this middle pathway gets you a bit closer to the EPA estimates but without having to jump through all the hoops of their complicated model that was hard to decipher based on what you've said.

DR. DuTEAUX: And it hasn't been vetted yet. It hasn't gone out to scientific review as yet.

PANEL MEMBER BLANC: Their model.

PANEL MEMBER RITZ: A question for clarification.

So all of these models steady state assume you're only exposed to that one route, right?

DR. KWOK: Yeah, that's correct. Because that's how we model it based on -- it's a route-specific PoD.

DR. DuTEAUX: And for being a TAC, although I know in the past when pesticides have come in front of the SRP, the panel has considered either aggregate exposures or different routes of exposure other than inhalation. But we are looking at toxic air contaminant; the route of exposure that we should be concerned about for this particular case should be inhalation.

PANEL MEMBER HAMMOND: Well, just to that point. I think -- but we're also interested -- the reason the others are important is if the inhalation adds to a burden and takes it over the magic line.

DR. DuTEAUX: Absolutely. And --

PANEL MEMBER HAMMOND: So that's why you have to look at all those.

DR. DuTEAUX: Absolutely.

PANEL MEMBER HAMMOND: And you did.

DR. DuTEAUX: And I think -- and maybe Erik or

Svetlana can add to this. But the reason why a steady-state exposure that we've modeled in our risk assessment is so important is twofold: One is that it's -- it's a departure from what DPR has done in previous risk assessments, in that we are setting up a population that's already at risk. We're looking at a population that has been exposed, according to the EPA model in 2014, for one hour a day for 21 consecutive days.

And as that decreases the amount of cholinesterase available, the baseline inhibition kind of bottoms out or it reaches that 10 percent steady state. And then we look at what happens to that population with that decrement when they get another hit.

So we're not looking at a healthy population. We're looking at a population that's already affected.

PANEL MEMBER HAMMOND: So to me that's a new point that I didn't realize, that that effect is long lasting. I was assu -- I didn't know how long the inhibition lasted. So that -- that is a subchronic or chronic effect?

Okay. And I was thinking it was like a day or two.

DR. DuTEAUX: Subchronic. Right.

And I know that you've seen many charts in your lifetime about occupational exposure. And that's why, you

know, we talk about people having headaches over the weekend and then they come back to work on Monday and they feel great.

With carbamates that's definitely the case with cholinesterase inhibition, where they get a hit and then they rebound. But this is a successive decrease in the ability of the body to handle the insult. And it goes and goes and goes and goes until it bottoms out.

PANEL MEMBER HAMMOND: So then -- but I had another -- I started out with another question. And that was in the green set of columns. You have -- for the female, is that "not applicable" - I'm not sure - NA, or "not available"? But I thought -- this is the animal studies, and I thought the animal studies included exposing the mother when she was pregnant and the gestational exposure. So I -- and I think that's one of the exposures we worry about.

So I wasn't -- I mean this is a wonderful table. I mean this is great, so -- let me be really clear. So I'm going to pick on the little things.

DR. KOSHLUKOVA: I have to -- I want to make two points.

The animal studies are few of them. And usually -- so those are published studies. Those are not registrant submitted studies. So for those that are under

FIFRA requirements, there are all kinds of examinations that are done on the moms. Published studies do not follow FIFRA guidelines. Therefore, at least the one that I'm familiar with, the most -- the 2017 study by Silva, et al., mothers were treated late gestation, and then all of the evaluations are done on the pups.

PANEL MEMBER HAMMOND: I understand the evaluation's being done on the pups. But I was thinking that the exposure would be in utero.

DR. KOSHLUKOVA: Yes.

PANEL MEMBER HAMMOND: And I think that that's one of the exposures that we're concerned about as a society, so --

DR. KOSHLUKOVA: But the effect is a behavior of the pups, so --

PANEL MEMBER HAMMOND: Yes.

DR. KOSHLUKOVA: -- that's the --

PANEL MEMBER HAMMOND: Oh, so when -- so you're talking about where the effect was evaluated, not when the exposure occurred?

DR. DuTEAUX: Right. They didn't do a gross morphology or anything in the females. Although there was the one study -- who did the adults with the subcue.

DR. KOSHLUKOVA: Muller.

DR. DuTEAUX: Muller did a study on adults --

male rats subcue, and there were effects in that species. But it's really hard to take a subcue, you know, dose -- subcutaneous, an injection under the skin and make it relevant to a human exposure out in the real world.

PANEL MEMBER HAMMOND: Yeah. No, I -- that's fine. No, I just wanted to be accurate with the little shortcut words that --

PANEL MEMBER BLANC: But there's a point in Kathy's question, which is this: The fetus is exposed, from the air, going through the mother - right - for the respiratory?

DR. KOSHLUKOVA: The mom is gavaged or treated --

PANEL MEMBER BLANC: No, no. But assuming that mother is not gavaged but mother is outside next to the golf course and is inhaling in her last trimester, right? And in your adjustments of course you use the breathing rates of 1- or 2-year olds in this class. Right?

But how -- this -- I don't know the answer to this question. But how are you going to take into account that what really matters is that the breathing dynamics of a woman in her last trimester, which is when this -- this in utero exposure occurs, that may be the most important exposure in terms of safety?

PANEL MEMBER HAMMOND: I mean, I guess the thing is that this -- the table, as I said -- I was thinking of

it as at the exposure level. You could make this table the -- where you say which was exposed. The mother -- the female who's 13 to 49.

DR. KOSHLUKOVA: I can pull the table --

PANEL MEMBER HAMMOND: But the outcome would be at the top. That is the DNT outcome.

DR. KOSHLUKOVA: Right.

PANEL MEMBER HAMMOND: But which would be on the children.

PANEL MEMBER BLANC: So it might -- I think it might mean that you should consider not -- I know you've only considered here for this quick thing the children. But you might actually for the neurodevelopmental endpoint need to consider the women of childbearing age as well; because even though the endpoint of effect wouldn't be them, it would be their fetus.

DR. KOSHLUKOVA: So are you saying that if there is a behavior alteration -- alteration in behavior, for example, anxieties that is increased in this study, would we consider that level that causes anxiety as --

PANEL MEMBER HAMMOND: Let me try to say this, okay, because I brought it up.

I'm sorry. I'll do this quickly then. I'll try to.

What I'm trying to say is the outcome that we're

interested in is just some neurobehavioral effect at age 1 or 2, right, for the children; but we would actually look at two levels of exposure. And I know that the -- the animals, you said earlier the studies had this. Some animals were exposed only while the mother was pregnant -- I mean the animals, the -- I don't have the right words -- the dam, I guess, and is exposed while she's pregnant but that's it. And then the offspring are not exposed. So it's just an in-utero exposure and no light. Others were exposed only after they were born. And then a third group were exposed for both. And I think those -- that's what I'm interes -- the outcome that you're going to look at would be - I'm just making this up - like the 2-year-old neurobehavioral outcome, that's the one outcome.

But those three different exposure scenarios are really important and have different implications. As Paul says, the inhalation rate is going to be very -- you know, if you're talking about an in-utero exposure, it's the dam or the mother's inhalation. So that I think is the way one would want to look at it.

DR. LIM: Can I make a comment?

Yeah, I totally agree with that because the -- experimentally is the dam then exposed to the chlorpyrifos in the air? So technically when you take that point of departure and convert it, it should apply to the female 13

to 49 years old, which is a child -- woman at a childbearing age, not applying it to the -- for the children, because the idea is that the reference dose would protect the pregnant woman; therefore protects the fetus.

DR. DuTEAUX: And I also wish that we had inhalation exposure data in animals. It's very hard to expose pregnant dams.

So the numbers that you see, the inhalation number that you saw on the table is a route-to-route extrapolation. All of the animals were either exposed by gavage, so the tube down their throat, so an oral exposure, or subcutaneous injection.

Inhalation is a very rare thing for us to find. In fact, we're working with one of Dr. Buckpitt's colleagues at UC Davis on doing one for chloropicrin right now. And the amount of work that goes into creating an inhalation chamber is intense.

So I wish we had more, but -- so as Dr. Koshlukova was mentioning, there's a lot of assumptions underlined in route-to-route extrapolation, from going, okay, if you're giving a bolus amount down a tube, down into someone's stomach or this rat's stomach, what does that translate into airborne exposure?

So I mean if we added the inhalation rates, which

do change, for -- during pregnancy, you know, we could modify that somewhat by what our assumption is for inhalation rates. Instead of 3 liters per minute, maybe it's 3 1/2 liters per minute or whatever it is.

PANEL MEMBER LANDOLPH: Yeah, I really enjoyed reading the document. Took me a while to get through it. It's a very long document, but it's a nice document.

I would second what was said earlier, or third it maybe. I would -- just write in your document, there's two mechanisms for neural data and, you know -- at least two, and one is the classical nerve gas inhibition of acetylcholinesterase; and that one you've got covered very well. It's very defensible scientifically and in court. You won't have any problem with that.

And then just write "Number 2." And number 2, you know, the neurotoxicities, something that probably began to be recognized about seven years ago when I was on a science advisory board of EPA. We put a lot of pressure on them to write a review article on that. And then it began to show something from a review article Bob Sonawane wrote. And now, you know, it's beginning to become more clear, but it's still not very, very clear.

And if you leave that in there, then you can convince them that you're trying to protect the public health. That's defensible. And you're pretty sure that

there is a mechanism that's just not mature enough scientifically that we know what that mechanism or mechanisms are.

And then you take your stab, as was suggested earlier, at what kind of calculations that gives you.

And when I first looked at this and the response Dow was giving it and stuff, I thought, "Yeah, it's going to be a little shaky to defend this. You'll have some difficulty." But you say, "This is what it is, this is what we know, this as far as we can go," and that's it.

But we've tried to be health protective. We're pretty sure there are things like Parkinson's and other neurologic damage that's the tip of the iceberg here with this pesticide and probably with many more that work through this type of mechanism. And I think you're obligated to put that mechanism -- you know, whatever you know about it in there. And do exactly what was said, make your calculation -- your second calculation based on that.

And that way if that gets knocked down in a court battle or something like that, then you still got the other one to fall back on, but you've done your best to substantiate this other one, the newest one because it is more health protective, and that's an honorable thing to do too. So I think I would put them both in and

substantiate them as best as you can.

And draw them -- give them names, you know, that they have different mechanisms.

PANEL MEMBER GLANTZ: I mean I agree with that too.

But I just want to come back -- I don't think this will take totally rewriting this document. I mean I think you pretty much have everything you need. I mean I didn't know a dam thing about this till I started reading it. And my wife every night, "What are you doing?" "I'm reading about this chemical where I can't pronounce the name."

So I really think these are matters of sort of framing and emphasis. I like the way Joe's suggesting it. And I mean you've done the calculations in a week. So that's good.

(Laughter.)

PANEL MEMBER GLANTZ: And I think this is much easier to follow, you know, the green column, than all those gyrations the EPA went through to kind of back calculate things and do handsprings. So I mean I -- I mean, again, having been on this committee forever, I mean I think, you know, seeing things that we've dealt with, and that have gone through and where people -- you know, ARB got sued over them. They won all the lawsuits. So I

think -- you know, our job is to help give you that guidance, and I think you're getting a pretty strong consensus, unless I'm missing something. And I think you've got it pretty much here.

And I don't hear -- the last thing is, I think -- at least in listening to people talk about this, I think the approach that you took -- and by the way, one thing if isn't obvious to anybody, which the DPR told me on the phone, is that these animal studies in the green weren't available when the original document was written. This was new information that -- right, that came available as the document was evolving?

DR. DuTEAUX: Yes.

PANEL MEMBER GLANTZ: And so it's just a matter of now that it's there, making the full use of it.

And the other thing that I found interesting in listening to this is like you have your uncertainty factors up there, and nobody's complaining about them.

I mean maybe I'm missing something. But, you know, I think by using the more direct endpoint, that makes the uncertainty factors less controversial, unless I'm missing something. So I think this is kind of the way you ought to go with this.

DR. DuTEAUX: Well, this is different than what I learned in class 20 years ago from Dr. Hammond; and, that

is, if you have human data, use it.

So now we were using a human-based PBPK-PD model, and now we're saying, "It's not so great. We're going to go back and use the animal data."

PANEL MEMBER GLANTZ: No, I think -- I actually thought --

DR. DuTEAUX: But I just -- I needed to -- I needed to give her shout out about this.

PANEL MEMBER GLANTZ: Well, but the thing is though, I think that the -- I mean and it is a very nice model. And I thought the sensitivity analysis you did in it and all of that was actually quite impressive. But what -- but it's like the facts kind of overcame the model. And now I think the -- the big thing that I see the epidemiology contributing to this is that it shows that these neurodevelopmental effects are very important and occur at lower levels than the red blood cell effects. And you saw that in the zebrafish and you have the animal studies. And so I think that -- I mean the way I read this is that the epidemiology justifies the change in the endpoint. Even though the animal studies that you have aren't as extensive as what you have on the red blood cell outcome, they do give you enough to estimate a dose-response. And you're selecting them because of the human epi. That's how I read this.

PANEL MEMBER RITZ: Can I make a comment.

I teach occupational epi and environmental epi, and I know where you're coming from. We are all coming from worker cohorts where there's high dose exposure in humans that we can characterize pretty well.

To characterize pesticide exposure life-long even in farmers is extremely hard. And to characterize anything in children is also very hard. And here we had an opportunity to take blood samples at one point in time and urine at one point in time but then extrapolate out the neurodevelopment. That is not the greatest data. But even so it's really not the greatest data, it shows something, but it may not be good enough to justify everything that you want for regulation. But it points you in the right direction. Right?

And of course we need more data from the humans. But then the animal study comes back in and says, "Hey, we actually can do this now." And that's the beauty of the animal studies, going back to them with the -- you know, with the dosing.

DR. DuTEAUX: And I think that even though there's a paucity of animal data right now, there are some FIFRA studies that we could maybe go back to. And I think maybe either Svetlana or Marilyn can speak to briefly. But there was one FIFRA registrant-submitted study that

was a developmental neurotoxicity study, right? I know that they did not measure chlorpyrifos concurrently with the DNT effects, but -- Hoberman?

DR. SILVA: Yes, it was Hoberman.

DR. DuTEAUX: Hoberman in 19...

And those were the kind of studies that we mentioned at the December meeting where we have a volume of data. There's, you know, a hundred page summary report and then a thousand pages of individual animal data. Those are the kind of data that we would really like to be able to have, get our hands on and do some individual analyses. Like Dr. Blanc was suggesting that we could do our own 95 competence intervals or covariants or whatever we want to look at. But on a published study where we don't have individual data and they're only publishing summary data without supplemental information, it's kind of hard to get to the detail that we normally use as a standard for our level of data precision and accuracy for our risk assessment.

But I'll let Dr. Silva talk to this one registrant-submitted study.

DR. SILVA: The interesting thing about this -- the interesting thing about the -- it's the first line. Now all these effects that I've described here are occurring at the LOEL; and the LOEL for all these is LOEL

for behavior. The Carr and Mohammed studies were all done with 0.5 was the lowest dose tested. And like Dr. Glantz was saying, it's so new that I was presenting a poster at the teratology society meeting and I just happened to run into this poster about chlorpyrifos that was Dr. Carr's. And that's kind of what, you know, sort of got the idea started.

But so 2015A is a poster. And Mohammed, et al., is a poster. But they're all out of the same laboratory. And he used postnatal day 11 to 16 as his time of dosing because he said that was -- corresponded to the human postnatal period of brain development.

But as you can see by these main lines, there's different strains of rat, mouse, all different treatment periods. There's the DNT, the standard GD through -- GD3 -- 6 through lactation day 11. And the Sprague-Dawley rats, the pups treated postnatal day 11 to 16; Wistar rats treated during gestation; and male pups were tested postnatally, Wistar rats. So there's a whole gamut of developmental periods covered.

And it's -- so it's not just in utero treatment that's important, because you're getting a lot of things happening with postnatal exposure as well.

And then the bottom line is treatment in adult males. And you're still getting the same LOEL.

DR. DuTEAUX: And Hoberman is --

DR. SILVA: Yes, Hoberman is the DNT study.

PANEL MEMBER BLANC: Yeah, I don't think the point about gestational exposure was that you shouldn't develop a value for 1- to 2-year olds. It's just that you might need to develop a value for the childbearing age women as well. They're two separate estimates, because -- I think that was really more the point of that.

And then I think that as you write your narrative to justify the tenfold safety factor that is interspecies, I think you need to emphasize that the things that you can look at in a rat are not as subtle as what you can -- could look at in humans, right? I mean that's the main thing, because if it's just -- there's a terms of neurobehavior outcomes that's not -- it's not nearly as subtle.

And then I think for the intraspecies tenfold factor, there are a variety of things that would make you, you know, consider vulnerable subpopulations that would justify that without -- I don't think without much trouble given the endpoint?

DR. SILVA: I think what's interesting about this too is that so many different vehicles were used and different laboratories and different treatment periods but you're still coming up with this number, which is --

PANEL MEMBER HAMMOND: Well, actually I'd be a little careful at -- you're right.

DR. SILVA: No, no --

PANEL MEMBER HAMMOND: But it's -- but the reason the LOEL's coming into the same number is that that's the lowest level that everybody tested.

DR. SILVA: That's right. That's right. But it's --

PANEL MEMBER HAMMOND: You know, if you had the full data set that we could conceive of, it might well be they'd have different numbers where they happened.

DR. SILVA: Yes. And I think, you know, Carr's lab had 0.5, but who knows what it could have been. And there was one study, I think it was Silva, that actually had a NOEL 0.01. And so some of the -- some of these studies did not have a dose-response for those effects. And that's where I think the, you know, effects may be occurring at the level of the endocannabinoid system before the acetylcholinesterase inhibition occurs. And so, you know, you could be having low -- things neurodevelopmentally happening before that.

PANEL MEMBER BLANC: Another argument, by the way, in terms of the interspecies safety factor is that we actually don't -- remarkably don't have any kind of nonhuman primate experimental data. You might want to

allude to that one Dow study of Rhesus monkeys --

DR. SILVA: Oh, Rhesus monkeys.

PANEL MEMBER BLANC: -- which is for six months. That's the only primate study that I saw anybody ever refer to.

DR. SILVA: We're trying to get that. It's actually a -- a medical college -- of a medical college report which was never published. But we're trying to get that.

PANEL MEMBER BLANC: That would be great. Or at least to refer to it as a limita -- you know, a great example of how limited the interspecies are.

PANEL MEMBER LANDOLPH: The other thing is -- I agree with Stan completely. You know, we do this with carcinogens all the time. We look for genotoxicity in animals data and epi data.

And sometimes you don't have any of these or sometimes just one.

And you can sell this second mechanism, but you have to work in your introduction to sell it, that that epidemiology data has become stronger with time, and now it's into specific classes and specific compounds. So you'll have to make that clear, you know, by analogy with carcinogens, that it's real and you can regulate it that way. You don't have to have the animal data. You can do

it based on the epidemiology if it's strong.

PANEL MEMBER GLANTZ: And also -- I'm sorry. The zebrafish data supports it too.

DR. SILVA: I have that too.

PANEL MEMBER ANASTASIO: Can I ask a question about the colorful three-column figure with the original DPR, the DNT DPR, and the U.S. EPA?

So first just a technical question. Point of departure. Sometimes it's a LOEL, sometimes it's a NOEL.

DR. KWOK: According to the U.S. EPA definition, actually the point of departure is the point where the extrapolation occur. So you know that means actually -- the dose you actually divide it in uncertainty factors. So if you have the -- you've got -- the lowest test turns out to be LOEL. The lowest of them the level, then your PoD become the NOEL. And then you -- of course, you divide uncertainty factors to compensate in the absence of a Noel. But most of the time --

PANEL MEMBER ANASTASIO: And it's usually by a factor of 10?

DR. KWOK: -- to the NOEL or the BMD 10. It really depends on how you get it.

PANEL MEMBER ANASTASIO: Okay. So --

DR. KOSHLUKOVA: It's in the table legend in our Executive Summary Table -- Summary Table 1. We define the

point of departure. This is Executive Summary Table 1, and here is the point of departure definition.

PANEL MEMBER ANASTASIO: Well, that sounds like a LOEL.

PANEL MEMBER BLANC: Well, when you don't --

PANEL MEMBER GLANTZ: Microphone.

PANEL MEMBER BLANC: Well, what we've done traditionally is if you only have a LOEL, then you divide it by 10 and start from there with -- and then you start doing all your other things, whatever you want to call it. But that's the starting point.

PANEL MEMBER ANASTASIO: I see. So when you have a point of departure -- can we go back to the very colorful table.

DR. KOSHLUKOVA: So point of departure came fairly recently as a terminology. And it's typically -- at least to my knowledge it started being used after the benchmark dose modeling became more and more use in risk assessment. Before that, it was usually a LOEL-NOEL extrapolation or a NOEL -- NOEL established as a dose in an animal study.

And then so PoD we would see -- we would see for a benchmark dose modeling for PBPK-derived endpoints for -- when it's not modeling we would traditionally refer to a LOEL-NOEL. But PoD would be the equivalent of a

NOEL.

PANEL MEMBER ANASTASIO: Okay. So then I think I understand.

So the point of departure here in green, it's 10 micrograms per kilogram per day. So the LOEL from the animal study was 100 micrograms per kilogram per day, and you're dividing that by 10 to go essentially from the LOEL to the NOEL, which here is the point of departure?

DR. DuTEAUX: Right, exactly.

PANEL MEMBER ANASTASIO: Okay. So I understand that. Thank you.

So getting back to Stan's point about uncertainty factors, you know, Andrew was just saying in the intraspecies uncertainty factor for hot spots, we -- or they consider a factor of 10 for adult variability but then add an additional factor of 3 to go from adult to child.

So I'm wondering then should that 10 for intra instead be 30?

DR. LIM: Wait. You want Andy or you want OEHHA?

You want OEHHA.

I think you want Andy Salmon --

PANEL MEMBER ANASTASIO: Whoever would like to address this point.

DR. LIM: I think you're referring to Andy

Salmon --

PANEL MEMBER ANASTASIO: Yes.

DR. LIM: -- when he gave the presentation.

Yeah, the other Andy.

So we made a table as requested. And it shows the three columns. And, Svetlana, you can show that on the screen.

No, not that one.

Well, I'll go ahead and start talking.

So the first column has the DPR draft TAC, obviously acetylcholinesterase inhibition with the uncertainty factor of 1, 10, 10, with a total of 100. So that you've seen many times.

And then second column has the OEHHA finding, if the RBC acetylcholinesterase is on screen now, is based on -- is the basis for the point of departure where the interspecies was 3, which includes the model uncertainty, and then the intraspecies based on the Hot Spots program is a factor of 10 for pharmacokinetic differences, and then a factor of 3 which is actually the square root of 10 for pharmacodynamics. So that's where the 30 comes from that you're familiar seeing in the Hot Spots program. And the additional uncertainty factor is the one we talked about when you're using RBC as the endpoint with a total 100.

And I had to sort of explain is that instead of -- the 3 is really the square root of 10, so that how come the math comes out to be 1,000.

Earlier you also asked what would we propose the uncertainty factor for DNT would be. I think -- we don't have a firm position right now, I think -- for the interspecies. It would likely be 10 if it's based on an animal study.

We also would like to weight the human studies into the mix before we come up with some definitive answer.

Intraspecies will be probably 30. That's, you know, accounting for pharmacokinetics and pharmacodynamic differences.

And here's where the -- we might need to have additional uncertainty factor, not the FQPA one but to -- for extrapolating from a LOEL to a NOEL or other kind of uncertainty that we might need to take into consideration.

DR. DuTEAUX: These would be recommendation.

DR. LIM: Yes.

DR. RUBIN: Hello. I'm Andy Rubin, and I'm a Risk Assessor with the Human Health Assessment Branch.

First I'd like to say, it's somewhat reassuring: I started in this 20-25 years ago. People used to argue

about what the PoDs were. And then as time went on they began arguing more about what the uncertainty factors were and left the PoDs behind. Now we're arguing about both the PoDs and the uncertainty factors. So its a very talmudic process.

Anyway, I just have a couple of brief remarks about the intrahuman uncertainty factor. Everyone accepts that there is uncertainty regarding the range of sensitivity in human populations. DPR, OEHHA, U.S. EPA, the Scientific Review Panel, we all know that there is uncertainty there.

The widely adopted default is one order of magnitude. In other words, an uncertainty -- a human uncertainty -- intrahuman uncertainty factor of 10. And Dr. Blanc mentioned this this morning that the 10x was at least -- is at least traditionally considered a conservative value.

DPR has traditionally accepted this default value. But in 2008 OEHHA issued a technical support document - it's a wonderful document - that advocated higher intrahuman uncertainty values. It's there -- there are lots of references in there and examples of chemicals and so forth.

So the -- the uncertainty factor for humans is now commonly divided into two parts, as we've mentioned, a

toxicokinetic part and -- hope that's not my phone.

(Laughter.)

DR. RUBIN: Yeah, yeah.

-- a toxicokinetic aspect and a toxicodynamic aspect. Both are assigned a square root of 10. It's sort of a logarithmic half of -- for each of those components.

In the OEHHA 2008 document, which was part of their Hot Spots program, they showed that with respect to the toxicokinetic uncertainty factor, there's just a whole range. I think they looked at 25 chemicals, and 12 or 13 of them had toxicokinetic factors of 3 or less actually, and then five had toxicokinetic factors of 10 or more, and the rest were between 3 and 10.

So there's a whole spectrum. We can throw all these numbers into the air and then grab the one that we feel has the -- you know, that we can support.

They -- OEHHA stated that the reason for adopting higher values for the intrahuman, whether we're talking about toxicokinetic or toxicodynamic, is that there are -- there are special populations that may have -- have greater sensitivity.

So all of these results, the spectrum of chemicals, lower than 3, higher than 10, and so forth, emphasize the difficulty in assigning a default uncertainty factor for intrahuman variation.

In a way it's -- there's tremendous uncertainty in defining the uncertainty.

And I don't know -- there's just no absolutely right answers about these things. We just have to go to what we feel are best supported now today.

DPR decided for chlorpyrifos for the present to stay with a -- with an intrahuman uncertainty factor of 10, feeling that that represented the -- adequately represented the human population, the variants -- the variation in sensitivity in the human population. And obviously there's some disagreement on this. There is some modeling work. I think Svetlana is -- might want to comment on this, that with respect to variation in sensitivity with respect to cholinesterase activity, that supports a 10 or perhaps even less.

So would any of you like to...

DR. DuTEAUX: Bootstrap.

DR. RUBIN: Yeah, this is a study that used modeling and bootstrapping. Lori mentioned it earlier in one form.

DR. DuTEAUX: The one that I sent you. That's -- you know, that's from --

DR. RUBIN: That's it.

DR. DuTEAUX: There you go. The next slide.

DR. RUBIN: I'm deferring to them because they

have better knowledge of this particular study.

DR. KWOK: I think it -- kind of like follow up with what Dr. Ruben just said, that, you know -- this is an example of a cholinesterase inhibition. But, you know, the table show here is pretty much in an even if you measure the range based on the mutual study. And, you know, if you look -- do the bootstrapping, meaning actually you keep doing the resampling, and then get a wider range and, you know, to integrate into the PBPK model, I mean after you consider all the variation. Then you can see that the -- the -- that's how they actually divide their so-called data -- divide the uncertainty factor.

CHAIRPERSON KLEINMAN: Excuse me.

We are going to be losing our quorum in a few minutes, because we're -- we have a plane that's going to be caught.

But I think that we're at a point -- there are still a lot of things to discuss. We're not going to be able to finish everything today.

We're going to have to have at least one more meeting on this topic. And I'd like to invite everybody back as soon as we get the date picked for that.

In the meantime, you know, it would be very useful, since there is new information that you are

considering, if we could get, you know, anything like that distributed to the committee so we can look at it before the next meeting. And then we still -- you know, we've not -- I think we've covered a lot of what was in those charge questions already. And we may be able to, you know, sort of expedite things out at the next session.

Stan.

PANEL MEMBER GLANTZ: Just quickly to -- I do think we made a lot of progress today actually. But I'd just like to -- I don't want to make this an official motion or anything, but just to see -- I mean it seems to me the sense of the Panel is that the risk assessment should be based on developmental neurotoxicity and that the -- you know, with the epi used to justify that, but doing the actual dose-response on the animals.

And so it would be nice -- and I -- again, I keep saying this. I don't think you need a drastic revision of the report. Because I don't want you to go off and spend another year doing it.

But it would be really helpful if it was possible to just get -- and I don't know if it's a matter of doing a track changes on this or just some kind of supplemental memo about like taking the stuff you showed us here and putting it down on paper so we can look at it.

And then it seems to me -- I mean there seem to

me two other sort of outstanding issues. One is to finally reach some kind of consensus about the uncertainty factors. And I think there's been a lot of good discussion of that.

And then the one other issue that we haven't talked about at all is the exposure stuff, which we'll talk about next time. But I think in terms of the biology, unless somebody here disagrees, I think you've heard a pretty strong consensus out of the Panel on where to go with this. Is that...

Okay. I hope that's helpful. And again, it's all based on what you have in here.

PANEL MEMBER LANDOLPH: And Keep the nerve -- the acetylcholinesterase inhibition and that mechanism in.

PANEL MEMBER GLANTZ: Yeah. Oh, yeah. I agree.

PANEL MEMBER LANDOLPH: So you won't have to do that much work.

PANEL MEMBER ANASTASIO: I have just one other thing to add. I think you really do need to consider the vapor exposure. The concentration is much lower at time of application, but it's this huge reservoir sitting in the field that's then volatilizing over probably days to weeks. So I think you need to at least look at what's the potential exposure to the vapor phase given that, you know, most of the stuff that gets applied stays on the

field. And then it's volatilizing.

So, it really should be looked at, how important could that be?

PANEL MEMBER HAMMOND: And quickly I would add, I really would like to see some data on air sampling. That would help to buttress the models.

DR. DuTREAUX: And we can of course.

PANEL MEMBER HAMMOND: But that's for next time, I mean. I understand.

CHAIRPERSON KLEINMAN: All right. At that point I'd like to entertain a motion to adjourn.

Stan.

PANEL MEMBER GLANTZ: Moved.

CHAIRPERSON KLEINMAN: Okay. Seconded?

PANEL MEMBER RITZ: Second.

CHAIRPERSON KLEINMAN: We're adjourned.

(Thereupon the California Air Resources Board, Scientific Review Panel adjourned at 3:49 p.m.)

C E R T I F I C A T E O F R E P O R T E R

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

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

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

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

IN WITNESS WHEREOF, I have hereunto set my hand this 11th day of February, 2018.

JAMES F. PETERS, CSR
Certified Shorthand Reporter
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