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

UNIVERSITY OF CALIFORNIA, SAN FRANCISCO
KALMANOVITZ LIBRARY, SUITE 366
530 PARNASSUS AVENUE
SAN FRANCISCO, CALIFORNIA

UNIVERSITY OF CALIFORNIA, LOS ANGELES
FIELDING SCHOOL OF PUBLIC HEALTH
COEH LIBRARY, CHS ROOM 46-060
LOS ANGELES, CA 90095

FRIDAY, MARCH 2, 2018

9:34 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.(via teleconference)

Paul D. Blanc, M.D.(via teleconference)

Alan R. Buckpitt, Ph.D.

Stanton A. Glantz, Ph.D.(via teleconference)

S. Katharine Hammond, Ph.D.

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

Beate R. Ritz, M.D., Ph.D.(via teleconference)

REPRESENTING THE AIR RESOURCES BOARD:

Mr. Jim Behrmann, Panel Liaison

REPRESENTING THE OFFICE OF ENVIRONMENTAL HEALTH HAZARD ASSESSMENT:

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

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

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. I wanted to call the meeting to order and welcome everybody to this meeting of the Scientific Review Panel on Toxic Air Contaminants. And we have -- on our Panel in person, we have -- there are five of us. And I believe there will be four people on the phone. So I'd like to ask the five panelists who are here to introduce themselves and start with Dr. Hammond.

PANEL MEMBER HAMMOND: I'm Katharine Hammond from UC Berkeley, a professor in Environmental Health Sciences at the School of Public Health, and Associate Dean for Academic Affairs.

PANEL MEMBER ANASTASIO: Cort Anastasio, UC Davis.

PANEL MEMBER BUCKPITT: Alan Buckpitt, UC Davis.

PANEL MEMBER LANDOLPH: Hi. Joe Landolph, Associate Professor of molecular microbiology, immunology, and a member of the Cancer Center at the University of Southern California.

CHAIRPERSON KLEINMAN: Mike Kleinman. I'm chairing the meeting, and I'm from UC Irvine.

And on the phone we have?

PANEL MEMBER GLANTZ: Stan Glantz.

CHAIRPERSON KLEINMAN: Paul and Stan, are you

there?

PANEL MEMBER GLANTZ: Well, Paul isn't -- Paul isn't here yet, but I am.

CHAIRPERSON KLEINMAN: Okay. And we have Stan. And Beate?

Okay. The UCLA contingent, I guess, will sign on as they get available.

But while we're waiting for them to sign on, we're going to -- I think we can start with some of the -- yeah, the beginnings of the meeting. But I just wanted to mention that Dr. Ritz has agreed to serve on the Panel for another term. And that's all been approved, so we're very happy that she will be joining us for the next several years, hopefully.

Okay. A few administrative items for the people who are here. Restrooms and drinking fountains are outside the room to the left. If a fire alarm rings, go down the stairs, proceed out of the building.

Because our court stenographer had another date, we are recording this session, and the stenographer will transcribe from the recording. So it's really important that everybody use their microphones, and try to speak clearly, because he has a hard enough time doing it from live, so...

I guess what would be good, because we don't have

the full Panel on yet, there are some -- there was some discussion by email as to the order in which we would discuss things. And we were initially going to talk about, you know, some of the charge questions. We have -- we described -- we discussed charge questions one and two in great detail at the last meeting.

PANEL MEMBER GLANTZ: Paul -- Paul -- Paul Blanc is now here.

CHAIRPERSON KLEINMAN: Great. Welcome, Paul.

PANEL MEMBER GLANTZ: So does that mean we now have everybody?

CHAIRPERSON KLEINMAN: We are still missing UCLA.

PANEL MEMBER GLANTZ: Okay. Well, I would just suggest we get going on the main --

PANEL MEMBER BLANC: Do we have a quorum?

PANEL MEMBER GLANTZ: We have a quorum, right?

CHAIRPERSON KLEINMAN: Yes.

PANEL MEMBER GLANTZ: Okay. Well, I think we should --

CHAIRPERSON KLEINMAN: And we're able to now proceed. But since one of the charge questions really --

(Inaudible voice.)

CHAIRPERSON KLEINMAN: Instant feedback.

(Laughter.)

CHAIRPERSON KLEINMAN: I guess the recording

works. Okay.

Since one of the charge questions deals with epidemiology, and Beate is one of the most qualified people on the Panel to be involved in that discussion, I think what we ought to do is start out with the DPR response to all the comments that we were providing at the last meeting, and I understand you have a presentation on what -- you know, how the -- those comments are being addressed.

DPR ASSISTANT DIRECTOR VERDER-CARLOS: Okay. So we were -- we were going to present that after the charge questions, but you would like for us to do that now -- or discuss at least what we understood from the last meeting?

CHAIRPERSON KLEINMAN: I think that would be helpful, because I really would like Beate and Jesús to be on line when we start going into the other charge questions.

DPR ASSISTANT DIRECTOR VERDER-CARLOS: So Shelley will be presenting what we were -- what we understood from what we were going to revise in the document when it comes back to the --

CHAIRPERSON KLEINMAN: Right.

DPR ASSISTANT DIRECTOR VERDER-CARLOS: -- to the Panel.

CHAIRPERSON KLEINMAN: Now is that okay with the

rest of the panel that we go that way?

Yeah. Okay.

(Thereupon an overhead presentation was presented as follows.)

DR. DuTEAUX: So good morning, everyone. We just want to remind folks who are going to be presenting today, for the record. My name is Shelley DuTeaux. I am the Chief of Human Health Assessment Branch in the Department of Pesticide Regulation. And joining me are Dr. Terrell Barry, who's the lead exposure assessor; Dr. Svetlana Koshlukova, the senior toxicologist in the Risk Assessment Section; Dr. Erik Kwok the senior toxicologist from the Exposure Assessment Section; and Dr. Marylou Verder-Carlos, who's one of the Assistant Directors of the Department of Pesticide Regulation.

So we were going to cover several things today. We don't have the slides for many things other than the charge questions, but I did want to start with an opening statement. And that is just to remind those of us here that the Panel -- by law, the Panel shall review quote, "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". This is from the Food and Agricultural Code, section 1402(b) through (c).

And if the Scientific Review Panel determines quote, "The health effects report is seriously deficient, it returns the report then to the DPR Director who shall revise it and resubmit it within 30 days of receiving SRP's determination of deficiency, and prior to developing control measures or other regulations". Just a reminder of what the charge is to those of us here.

And just a comment about the risk assessment and the database, including all of the studies that we analyzed for this particular assessment. DPR's risk assessments use all available scientific information to define the hazard and to make certain that the critical studies in the assessment are biologically relevant, and scientifically sound.

So as our understanding of some of the comments, especially those that came at the end of the January --

PANEL MEMBER GLANTZ: Excuse me. Excuse me, Paul Blanc wants to ask a question.

PANEL MEMBER BLANC: Hi. Can you hear me?

DR. DuTEAUX: Yes.

CHAIRPERSON KLEINMAN: Yes.

PANEL MEMBER BLANC: Good. So just to clarify on what you -- so clearly laid out in terms of the legal requirements, those legal requirements don't include or specify responding to a series of charge questions from

the agency.

DPR ASSISTANT DIRECTOR VERDER-CARLOS: Dr. Blanc, can you speak up to your microphone, because I can't hear you.

PANEL MEMBER BLANC: Yeah. Okay. So the charge question -- just for the record, the legal requirements that were just laid out don't specifically require that the SRP respond to a series of charge questions. That's the structure of our approach to a document. It doesn't Preclude us from doing it, but it certainly doesn't require it, just if I understand correctly what was just stated.

DPR ASSISTANT DIRECTOR VERDER-CARLOS: That's correct. The approach that we -- that we did and we did check with Dr. Kleinman about this is so that we can get the opinions and -- the scientific opinions of the Panel on specific areas that we thought we could really get your help on. But it doesn't -- you're right, the legal requirement is not to respond to the charge questions but to kind of have a discussion on the things that we need advice on.

PANEL MEMBER GLANTZ: Well, actually -- this is Stan. You know, that's not quite accurate either. And, you know, I thought the charge questions were helpful actually in terms of focusing the discussion. But the

Panel's job is to provide an independent peer review of the report and determine whether it's seriously deficient or not. We're not an advisory committee to DPR, where we give you advice and then you decide what to do. I mean, we -- you guys have to produce a report that we'll approve. So that -- you know, that's different.

You know, I've been on lots of advisory committees, where, you know, you give advice, and then the agency does what it will, but you know in the end, the end result of this whole process is that we're going to write a set of findings that say we find this -- the wording in the law is kind of bizarre. It's not seriously deficient. But for -- what that means in practical terms is that we approve the report, and say we think that it's scientifically accurate.

So that -- you know, that is our job. Now, again, I -- I have to say when I first saw the charge questions, you know, a couple months ago, I reacted a little bit about like we're not here just to answer your questions, but I -- I -- as I went through the public comments and the report, I actually found them very helpful in, you know, thinking about the issue.

But our -- again, we're -- in the end, what we're going to have to vote on is the -- whether or not the report is scientifically acceptable.

So, you know, the things that we're saying to DPR, like the discussion we had last time about changing the endpoint to neurotoxicity, I mean, that's not advice. You know, I think the tenor of the discussion last time is that the report is not going to get approved if you don't do that in a reasonable way.

CHAIRPERSON KLEINMAN: Stan, this is Mike. My take on the charge questions was that I agree they helped focus the discussion. They also indicate some areas of concern that DPR has within the report. And they specifically are asking about the scientific basis for those particular topics covered in the charge questions. So they were sort of separating out individual areas that are important, and could eventually be areas that they will be challenged on.

So our job is not necessarily to -- is to evaluate how they did with regard to some of those topic areas as opposed to telling them how to rewrite the report. I agree, our job is not --

PANEL MEMBER GLANTZ: Well, no, no, that -- no, I'm sorry and this is why having been on this Panel forever -- no, we are in a position and we can tell them to rewrite the report or we won't approve it. You know, our job and, you know, we've had plenty of reports that have come through this Committee, where the Committee made

very strenuous, you know, recommendations to the agency, which were then followed. And, you know, we're not reco -- you know, in the end, I mean, we can discuss these things.

And again, I thought the charge questions were very helpful. But in the end, we're going to have to vote that the report is scientifically accurate and appropriate. And, you know, if there are things that we're raising, like this issue about the endpoints, and DPR doesn't fix that stuff to the Panel's satisfaction, then I don't see how we could approve the report.

So we're not -- you know, we're not just here to help them out. The end -- in the end, we have to vote that this report is not seriously deficient, which means that it's acceptable, and to -- to form the basis of future regulations.

So, you know, I think if the Committee -- if there are issues where the Committee is unhappy with the report, DPR has to fix them. You know, there -- it's not like we're given them some advice. We don't vote for something, if it isn't fixed. You know, and we've had some very -- you know, in the lead report a long time ago, there -- you know, some of that got quite hot, because back when Pete Wilson was Governor, they tried to sneak through a report saying lead wasn't as bad as it was.

So I just think it's really important people understand that. I mean, I don't know if ARB has a lawyer there, like that at a lot of the meetings they used to, but I mean that could get clarified. But no, we're -- we -- in the end, we have to vote the report as not seriously deficient. And if DPR has done things that we think need to be done, then I don't see how we can vote that the report is not seriously deficient.

I'm sorry to give a long speech, but I think that's a really important distinction.

CHAIRPERSON KLEINMAN: Well, I think speaking for myself, I agree with a lot of what you said. The things -- you know, we can, you know, look at the report as a whole and just say there are scientific deficiencies, go fix them. I think the charge questions give us the opportunity to have findings that are very specific areas that we feel are more deficient than others, for example, that they need to --

PANEL MEMBER GLANTZ: So in the end, we do not -- we do not issue findings about deficiencies in the report. In the end, we have to approve the report. And the findings that are issued are -- it's essentially an executive summary of the executive summary of the final report. You know, so, you know, we don't come back to DPR with a report saying like, well, we think this part of it

is okay, and we think there problems with that. In the end, we've got to vote to approve the report as the document sits in front of us, and that -- the findings thing that SRP -- I mean, from the strictly legal point of view, SRP doesn't even have to issue findings.

All we have to do is issue a one or two sentence letter that says we find that this report is not seriously deficient, and we also have to make an assessment of whether or not there's a threshold for effect. Those are the two things that are written into the law.

Now, over the years, the tradition developed of the SRP also making findings, which are a summary of what the SRP thinks are the key points in the report, and -- but that's not legally required. The two things that are legally required is a finding that the report is not seriously deficient. And we have to -- the law requires that we address whether or not we think there's a threshold.

So it's not -- we're -- our report back to DPR is not a, well, this is good and that's not. Our -- we have to say this report is acceptable period, you know. And if we want to issue findings that are written around the way the charge questions are written, you know, that might make a lot of sense, and maybe we'll do that. But one of the findings cannot be, well, DPR didn't handle this issue

properly. If DPR has hasn't handled it properly, then we don't approve the report.

CHAIRPERSON KLEINMAN: Well, Kathy had some -- oh, okay.

I have the actual code. And so just to read it out verbatim. "The Panel shall review as a appropriate 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 then the Panel -- the Panel shall submit its written findings to the Director within 45 days after receiving the report, but it may petition the Director for an extension of the deadline".

So yes, we are -- we do review, as appropriate, the scientific data, the procedures, the methods, and the conclusions and the assessments. So those are all within our bailiwick, and part of the statutory basis for this.

So then it goes on, "If the Panel determines that the health effects report is seriously deficient, the report will be returned to the Director, who shall revise and resubmit the report. So --

PANEL MEMBER GLANTZ: Well, again, not to -- not to beat a dead horse, but the last part is the important point. And that is -- I mean, I've never in all of many years I've been on here, the -- you know, we've never

approved a report in the end that anybody thought there was any problems remaining, you know, because it's -- as you said, if the report -- if the Panel determines that the report is seriously deficient, the report goes back to the Director to come back with a fixed report, and the word is "shall". The Director "shall" revise and resubmit the report, not the Director "may" do it.

And I can just tell you, I mean, it's very -- the way the practices have evolved on the Panel, we have -- you know, I remember way back in the beginning, we used to take a vote the reports were seriously deficient, and send them back.

But the practice -- that kind of fell by the wayside, and there was just an understanding that if we didn't approve the report, it was seriously deficient. And they came back and fixed it, you know, based on the Panel's input. But again, the word there is "shall", you know. And so I think that's really important here, because there were some, you know, fairly major changes that the Panel came up with at the end of the discussion last time, and those need to be made in the report, unless the Panel changes its mind and decides that we were wrong before.

CHAIRPERSON KLEINMAN: No, I don't think that's the issue, I think the issue is that those were only the

first -- you know, addressing things that were summarized in the first two charge questions, and --

PANEL MEMBER GLANTZ: Right, but I think --

CHAIRPERSON KLEINMAN: -- and there were the others.

PANEL MEMBER GLANTZ: I think the point -- no, but the point, and then I'll stop ranting and raving about this, but this is the first TAC determination that's come up in a while. And, I mean, again, I have no problem. I mean, I thought we talked about more than first two charge questions last time. But I think the important point that people need to take away with is in the end the charge questions may be useful for helping to organize the discussion, but the role that the Panel plays in the end, and what DPR has to do in revising this report is make the changes that the Panel's recommending or talk the Panel out of them. You know, it --

CHAIRPERSON KLEINMAN: Well, I agree, but we need to --

PANEL MEMBER GLANTZ: Okay. Well, then I'll --

CHAIRPERSON KLEINMAN: -- be very specific on the points.

Kathy, had something she wanted to say.

PANEL MEMBER HAMMOND: Briefly, I do agree with the major point that Paul and Stan have made, that we are

not a science advisory panel, we're a science review panel. And so it's right there in the name, as well as in the legislation.

I -- and I don't really -- I don't necessarily feel that that's been misunderstood, but it's there for clarity.

And then I think the -- there are questions that were given to us, and whether they're charge -- maybe we shouldn't call them charge questions, but questions on which you would like to make sure that we address and provide advice. And that is total -- you know, I'm fine with that.

And so maybe -- so the charge question might not be the right word, but I think the questions are good questions that should be discussed together, so that we can be reviewing.

PANEL MEMBER GLANTZ: Well, I just want to -- I have to beat the dead horse one more time.

(Laughter.)

PANEL MEMBER GLANTZ: The way I think -- because I think this sort of linguistic thing is important here. What I see in the -- in these questions are issues that DPR identified, which are particularly worthy of discussion. And that's how I viewed them. And again, I think they were very helpful. But, you know, in the end,

what we have to do is approve a report where we think the whole report is acceptable, and -- which may or may not involve things in those questions, so -- but I think we should just get going on working on the report and seeing how DPR is responded to the issues that were raised at the last meeting, I mean, that's what I would like to do.

PANEL MEMBER HAMMOND: Did we want to -- a question would be, do we want to see how they've responded to the questions in the last meeting, or continue the questions that have been brought up for discussion and continuing the first round.

CHAIRPERSON KLEINMAN: Well, we were in the process of --

PANEL MEMBER HAMMOND: Right.

CHAIRPERSON KLEINMAN: -- going -- you know, letting them respond to the last two, so...

DPR ASSISTANT DIRECTOR VERDER-CARLOS: I heard a beep, so I think I someone --

CHAIRPERSON KLEINMAN: Beate?

PANEL MEMBER RITZ: Yes, I'm on.

CHAIRPERSON KLEINMAN: Wonderful. I announced that you accepted another term on the Panel by the way.

PANEL MEMBER RITZ: Yes. Thank you.

CHAIRPERSON KLEINMAN: Thank you very much.

Okay. So we are -- I don't know how much of the

discussion you heard, but we are going to have the response to our previous suggestions and talk about those first, and then we'll move on to the -- you know, discussing the rest of the report.

PANEL MEMBER RITZ: Yeah. I've been on for 20 minutes.

CHAIRPERSON KLEINMAN: Okay. So let us continue.

DR. DuTEAUX: So this is Shelley DuTeaux again. So following the January 23rd meeting, although we're just going by the transcript, and haven't received anything formally from the Panel, these are what we took from that meeting, and issues that we started working on prior to that meeting, as well as what we will continue to work on in the revised or final TAC evaluation document for chlorpyrifos.

Those include the following:

One is to present both acetylcholinesterase inhibition and developmental neurotoxicity reference concentrations in the risk appraisal section of the TAC evaluation document. And this largely follows what Professor Landolph suggested at the very end of the meeting.

The reference concentration for acetylcholinesterase inhibition is 28.5 micrograms per meter cubed. And the reference concentration for

developmental neurotoxicity based on our current assessment of the new data is 3.3 micrograms per meter cubed. So they're approximately an order of magnitude different from each other. And we will be writing the document to not only show MOEs and points of departure for both endpoints, but a discussion of the weight of evidence, and the database support for both endpoints in the risk appraisal section as Dr. Landolph had suggested.

The next --

PANEL MEMBER BLANC: Okay. So, I'm sorry -- Paul Blanc here -- what else are you intending to say at this meeting about that -- about those points?

Hello?

DR. DuTEAUX: Well, at this point, I was going to go through a summary of what we took from the January 23rd meeting for changes to incorporate into the TAC evaluation document. We can certainly discuss the developmental neurotoxicity and acetylcholinesterase points of departure after I go through that, or if you'd like to talk about that more now.

PANEL MEMBER BLANC: Well, isn't that -- isn't that the elephant in the room? I think you have to start with that, and I think you have to make it clear to us. Obviously, your report can't equally weight two possible TACs. So you have to say which TAC you're going with,

which approach you're recommending, and then presenting a secondary line of information just for contextual purposes.

And I think the thrust of the discussion at the last meeting is that the Panel would be receptive to a TAC that was based on a neurodevelopment -- neurodevelopmental toxicity, and we are certainly open to a contextualized presentation of what a TAC might have looked like had it been based on acetylcholinesterase, but we are not looking -- speaking for myself, but I think this was the consensus, we are not looking for a document that presents equally two TACs and leaves open the question as to which one the Air Resources Board could choose to use.

DPR ASSISTANT DIRECTOR VERDER-CARLOS: So, Dr. Blanc, are you -- just for clarification, are you then asking to discuss those two points now or -- because our understanding from the transcript of the meeting last time is that we were going to present the cholinesterase endpoint, and then put all the scientific discussions on that, and then also put the neurodevelopmental endpoint, and have a discussion on the robustness of the data that presents that. So -- and, Dr. Landolph, I don't know if you could chime in, but that was what our understanding was from the last meeting.

PANEL MEMBER LANDOLPH: Yeah. This is Joe

Landolph. Yeah, Paul. What Marylou Carlos-Verder just said -- Dr. Carlos-Verder just said I think was what I had mentioned last time, because we mentioned that the robustness of the acetylcholinesterase inhibition is very strong. There's not much question about that as an established toxicological endpoint.

The neurodevelopmental material is newer, some of the database is not that robust, and it's an emerging endpoint, so I think it would be prudent to list both things, and then --

PANEL MEMBER BLANC: I -- I would --

PANEL MEMBER LANDOLPH: Wait just a second, please -- and then make a decision as to whether -- which one you choose and why. I mean, I can see two ways of going. One is you go with the acetylcholinesterase. But as I mentioned -- as I am going to mention later on, in this document from DPR about cases reported on incidence of disease and -- to humans, it's clear that some of these, even for acetylcholinesterase, they're not strong enough. I think they should be strengthened, the endpoints.

And -- but then I think you're obligated, because of the emerging science, as Jesús discussed extensively last time, to still give credence to the neurobehavioral development, and assess the robustness of the database for

the DPR, and then make a decision which -- you know, the one they're going to go with and why for now.

PANEL MEMBER BLANC: Well, if that's the case -- yes, I mean, you've -- at the very last you made clear it can only be one of them that's the TAC. So let's -- we should be clear about that.

PANEL MEMBER GLANTZ: The reference level.

PANEL MEMBER BLANC: The reference level. I'm sorry for my sloppiness.

The reference level can only b one of the two approaches. It can't be both. One could be presented as context, but one has to be what is chosen. So if it's still not clear to DPR which way to go, and they would like to get an assessment from the Scientific Review Panel which is the more valid approach, then I would say all of our time should be spent on that, starting -- I don't care if you start with -- which one you start with -- although my slight preference would be for starting with the neurodevelopmental toxicity approach. Those should both be outlined in exquisite detail today and get feedback from the Panel, because that's going to drive the heart of this report, which will have to be written one way or the other.

DPR ASSISTANT DIRECTOR VERDER-CARLOS: So you're -- so Dr. Blanc, you're asking for us to -- so back

to the point of toxic air contaminant, the -- and I think we've discussed this before, is the -- the science, to back up, if we are going to list it as a toxic air contaminant is what's being reviewed. So right now you want us to discuss the neurodevelopmental endpoint. And so what -- the slides that we did last time had the different tables and all that. So is that what you want the approach to be right now or -- did you want more robust discussion on that endpoint or the --

PANEL MEMBER GLANTZ: Well, no I -- this is Stan. I think -- I think that there was a pretty good discussion of the two endpoints last time. I don't think we need to repeat that. But, you know, what I thought we left the room with was a pretty strong feeling that the reference level or point of departure, whatever it's called, by DPR should be based on the neurodevelopmental endpoint, realizing that there's a more robust database on the acetylcholinesterase inhibition.

And, you know, there are a couple of different ways you could relate those. One would be if you were capable of coming up with a dose response based on the neurodevelopmental toxicity just doing it directly. If there's not enough evidence to do that, it may be that doing the acetylcholinesterase to get the safe of the dose respond, and then including an uncertainty factor to

account for the different biological endpoint.

I mean, that would be my bias of the way to do it, because what my -- my sense at the end of the discussion last time was that we had lots of data that could be used to get a dose response, and the acetylcholinesterase, but not the neurodevelopmental toxicity, but there was more than enough neurodevelopmental toxicity evidence to conclude that that was the appropriate endpoint, but probably not enough evidence to define a dose response relationship.

And the way to bridge that gap could very well be to use an uncertainty factor, which, based on just what you said in your introductory comments, sounds like it would be 10, but we'd have to judge, you know, whether or we like the way you came up with that number of three.

So I don't think we need to rehash the whole suggestion from last time.

PANEL MEMBER BLANC: Yeah, I think -- Paul Blanc here. I would say that also is consistent with what the impression was that I took away, bearing in mind that I wasn't there for the last 15 minutes or 20 minutes of your discussion, and the open-ended questions that remained were a reaffirmation of the commitment of DPR to use as its primary endpoint neurodevelopmental toxicity. I think we need to hear that today.

And then we need to hear what -- what happened with -- when you went back to the data, what methods did you apply to derive the -- the values that you did? Was it, in fact, a lowest effect level approach or was there someway of benchmarking. And within the neurodevelopmental, that seemed to be the big question. I think that for the parallel contextual acetylcholinesterase-derived endpoint, I believe there was a question as to, in fact, what were your uncertainty factors going to be? And depending on those uncertainty factors, what was the contextualized endpoint you reached, and how did that compare with the interim federal EPA endpoint for acetylcholinesterase as a sort of third leg of the stool?

Because initially it seemed as if the neurodevelopmental based outcome, taking into account lowest observed effect level and the appropriate uncertainty factors came out within an order of magnitude of the EPA -- federal EPA endpoint, but was considerably lower than your original acetylcholinesterase.

And let me just reiterate something that I said, and I think was echoed by others at the last meeting, it doesn't matter how robust your date are if the endpoint is not the correct endpoint to use.

PANEL MEMBER LANDOLPH: Yeah. Paul, this is Joe.

I think robustness is very important, because it allows you to make a decision on whether, you know, that endpoint is credible. So the newer data on the neurotoxicology neurobehavioral endpoints, et cetera, I think that's very interesting stuff. But I think the database is clearly more sparse.

So that's why I had wanted to see both endpoints discussed, and the rational, and the data presented as to why you picked one over the other, so that DPR could just this when it went forward for regulation.

PANEL MEMBER BLANC: So I think let's go back to Stan's point is if the Committee doesn't find it appropriate, it won't go forward.

DPR ASSISTANT DIRECTOR VERDER-CARLOS: Okay. So then what we -- what DPR is tasked with is to -- to discuss all this and revise the document. And then when it goes to you, then that's when you can -- that's when you say if it's scientifically deficient or not based on this discussion.

So we will then change the document based on what Shelley had already said here, and then go through the list of the things we are going to be revising based on our discussion for -- in January 23rd. So we'll -- we'll make sure to revise that, and then you'll receive the document. And then you can make a decision if that is

acceptable or not.

PANEL MEMBER GLANTZ: Yeah, but I think -- I think -- no, think any that's fine, but I think what I'm -- I mean, I thought at the last meeting we were moving toward a consensus on these points. And so I -- what I'm hoping will come out of the discussion today will -- you know, hear what DPR thinks about, you know, the issues that came up before, and further refine a consensus, so that you can go back and, you know, actually revise the document in a way that when it comes back to the Panel everybody will just vote yes, you know, without a lot of additional discussion.

So I think it's a matter of kind of getting down to the -- to the details, you know, on -- you know, I mean, I think it's fine that you guys didn't bring a document back. I mean --

PANEL MEMBER BLANC: Right, right. Absolutely.

PANEL MEMBER GLANTZ: -- that would be a waste of time. But I think what we were trying to get to is a focused enough set of direction, so that when you do bring the document back, everyone will just read it and say isn't this dandy?

PANEL MEMBER BLANC: Yeah, I mean, I think our cup is half full, not half empty. But I just want to hear the details behind the brief presentation that was -- the

brief comments that were made. Here's how we got to this value for neurodevelopmental. And by the way, here is the acetylcholinesterase version, and how has that changed or not changed from the presentation that we had at our last meeting?

And I outlined for you the ways in which I think you got to the numbers. I think the acetylcholinesterase based value has a higher uncertainty factor than the last time around based on the discussion, and -- but otherwise, it probably uses the same approach more or less, I think, but I need to hear that.

And I'm not really clear at all, you know, without hearing more, and would like to hear more, how did you get to the value you got to with neurodevelopmental? So is there someone --

DPR ASSISTANT DIRECTOR VERDER-CARLOS: Yes. So --

PANEL MEMBER BLANC: -- from DPR that's prepared to present those details? And that's what I'd start with.

DPR ASSISTANT DIRECTOR VERDER-CARLOS: Okay. So we'll just go that way, because Svetlana does have a table to talk about exactly to Dr. Blanc's point, and then we will continue the list after that discussion.

PANEL MEMBER GLANTZ: Paul said great. I had to unmute the phone though.

DR. KOSHLUKOVA: This is Svetlana Koshlukova.

So I'm going to walk you through the table again. We revised the number for the inhalation POD for coming from the developmental neurotoxicity study, and I will explain. The first column is -- shows the point of departures, as well as the reference concentrations and reference doses that are derived based on acetylcholinesterase inhibition as an endpoint.

We adopted these values from the 2014 U.S. EPA risk assessment, and based on -- except for the steady state inhalation point of departure, which we derived recently here at DPR.

So this number -- 2850 micrograms per cubic meter is DPR number. This is based on 21-day dosing, and predicted by the model. And the reference concentration is 28.5 microgram per cubic meter. This number is derived as dividing the point of departure by a total uncertainty factor of 100. This incorporates a uncertainty factor for interspecies sensitivity between human and animals as 1. The model is a -- derives human equivalent concentrations, and, as such, the default uncertainty factor of 10 can be reduced to 1.

The -- a default number factor of 10 for intraspecies variability was used, and additional one of 10 is to account for the potential developmental

neurotoxic effects which -- which are -- which the cholinesterase based endpoint does not -- may not protect for. As such, the number we derived for children 1-2 years age is 28.5 micrograms per cubic meter.

We probably don't need to go through the other route.

So this was -- this is -- the majority of our risk assessment was based on cholinesterase inhibition. The two of the drafts that we had put together since then starting from 2015, two reports came. They were platform presentations at the -- at the scientific meeting, which indicated developmental neurotoxic effect in animals may be occurring at doses where cholinesterase inhibition is not observed, at least not bring cholinesterase inhibition

Since then, 2017, four more papers came in animals by various groups. All of them are in rats, except one that was conducted in mice. In the studies, the treatment -- the treatment periods were different. They were starting during the gestation, early or late, during the postnatal development or combination of gestational and postnatal treatment. There was one paper in mice, which used only one single dose during postnatal day 10. We will show the table too.

These studies evaluated various endpoints, and actually they can be summed into three groups, behavior,

cognition, and motor activity. And those were altered at doses that were generally lower than 0.5 milligram per kilogram per day to 0.1 milligram per kilogram per day.

Many of these studies -- pretty much none of these studies measured cholinesterase inhibition concurrently.

So the assumption that the neurodevelopmental effect that have been -- that occurred in these studies are below doses inhibiting cholinesterase is basing on the general threshold that we know for animals for red blood cell cholinesterase inhibition of 1 milligram per kilogram per day.

I will repeat one of the studies measured brain cholinesterase at the same time as neurodevelopmental effects were observed, and it was not inhibited.

So of all these available new data -- new studies, all of them, except for one, dosed animals in a way that the lowest bested dose was the LOEL. One provided a NOEL. So these were dietary or gavage treatment. There was no inhalation or dermal study.

So the point of departure from the collective developmental neurotoxicity studies point to a 10 microgram per kilogram per day. This is an oral NOEL. So then we're going to focus on the uncertainty factors. Because this is an animal database, we're using the

default of 10 to account for interspecies sensitivities, and then the default of 10 for intraspecies variability, and 1 for developmental neurotoxicity because the endpoint is based on developmental effects.

And as such, the reference dose will be 0.1 micrograms per kilogram per day. Because we do not have inhalation study, we are using a typical route-to-route extrapolation to calculate a inhalation point of departure and from then a reference concentration.

So for the route-to-route extrapolation here in the legend, the assumptions are used. So the way it was calculated is we multiplied the number by breathing rate divided by body weight. And so those are the assumptions used for the breathing rate and body weight of children.

This number, 333, is different from the table that we showed you before. We had -- in our formula, there was a mistake. Instead of dividing by body weight, we multiplied. So it's now corrected.

So basically, the number -- the inhalation number from the developmental neurotoxicity studies is roughly 10-fold lower than the POD -- the point of departure -- inhalation point of departure based on cholinesterase inhibition.

So I would like to point something else. The developmental neurotoxicity database that we have now

points that the developmental neurotoxic effects occur at about 10-fold distance compared to cholinesterase inhibition.

We would have had the same reference concentration had we not used a model that eliminated the interspecies default factor for cholinesterase inhibition.

And the right panel is the 2016 U.S. EPA human health risk assessment where they used biomonitoring data at reverse dosimetry to calculate a point of departure of 1.65 micrograms per kilogram per day. And the uncertainty factor that they used was 1, because they utilized the same model, the kinetic part of the model 10 and -- for intraspecies. And then the FQPA was adjust to 1, but the level was considered LOEL, so LOEL to NOEL extrapolation came with that number.

So just in conclusion, a comparison between the inhibition of cholinesterase and neurodevelopmental effect, it appears that they're spaced by 10-fold.

PANEL MEMBER LANDOLPH: Could I ask you a quick question?

Thank you for the nice exposition. You know, I was reading over this nice report that Dr. DuTeaux mentioned in the last transcript about the disease and illness reports from exposure to chlorpyrifos by accident. And so if we accept this lower neurodevelopmental toxicity

point of departure, then I think this would give the added protection to protect the pesticide sprayers and applicators in the farm workers, would it not? It should give us another factor of 10 by accepting this endpoint. Do you agree with that? I mean I'm in favor of it.

Did I not make myself clear?

Let me see. So, you know, I was concerned in this Department of Pesticide Regulation report, which Dr. DuTeaux discussed in the last meeting, that I thought because of operator incompetence, you know, people doing stuff they are not supposed to do like when they turned at the end of vegetable rows, or whatever, they're supposed to shut the sprayer off, and they were not doing it, so it was affecting children and workers, you know, 100 meters downstream, et cetera.

So I feel that we need more protection. So I was asking you, do you agree that accepting a neurodevelopmental toxicity lower concentration, that this would give that added protection to protect the farmhands, and the field workers, and the sprayers, and applicators from chlorpyrifos toxicity.

DR. DuTEAUX: So I understand your question. And I'm going to answer it in a roundabout way. DPR has purposely separated the risk assessment procedures, and methodologies, and outcomes from the risk management

portion, unlike EPA, which actually has the risk management and risk assessment intimately together -- woven together in their human health risk assessments, we separate the two. So the risk -- that TAC evaluation document that you have in front of you is simply the risk assessment part.

We have a separate risk management decision-making process that is underscored by the scientific findings, but also takes into account another issues.

So it would likely be -- and Dr. Verder-Carlos can correct me, it would likely be on the risk management side, whether they would decide whether it is protective or if an other 10 should be added.

PANEL MEMBER LANDOLPH: Thank you.

DR. DuTEAUX: So, Dr. Kleinman, would you like us to show the summary table of the animal studies, so we -- because I.

PANEL MEMBER BLANC: Hi. Dr. Blanc here. Can I -- before we go there, can I ask a couple clarifications?

DR. DuTEAUX: Absolutely.

CHAIRPERSON KLEINMAN: Sure.

PANEL MEMBER BLANC: So from our previous speaker, can you -- you've taken as a point departure 1

milligram, is that correct?

DR. KOSHLUKOVA: No.

PANEL MEMBER BLANC: What have you --

DR. KOSHLUKOVA: One milligram per kilogram per day is the generally accepted threshold for choline -- RBC cholinesterase inhibition.

PANEL MEMBER BLANC: No, I'm talking about for neurodevelopmental, what is your starting point at the top of your column?

DR. KOSHLUKOVA: So the starting point is 0.1 milligram per kilogram per day.

PANEL MEMBER BLANC: And is that based on 1 milligram being a lowest observed effect level?

DR. KOSHLUKOVA: 0.1. 0.1 is the lowest effect level.

PANEL MEMBER BLANC: And then you divide that by 10?

DR. KOSHLUKOVA: By 100?

PANEL MEMBER BLANC: No, but first by 10 for 1 and 10 again, is that right?

DR. KOSHLUKOVA: Yes.

One of the studies -- one of the studies established a NOEL, which is 0.01 milligram per kilogram per day, or 10 microgram per kilogram per day. The other studies finished with the lowest tested dose was the LOEL

of 0.1, or 0.5.

PANEL MEMBER BLANC: So functionally if you took 0.1 or 0.01, it would end up at the same place, is that correct?

DR. KOSHLUKOVA: So the lowest observed effect level in this table is 0.1. And so dividing by 100 will go to 0.01 milligram per kilogram per day, or 10 microgram per kilogram per day.

PANEL MEMBER BLANC: Well, no, if you took 0.01 and divided it by 100, it would be 0.001.

DR. KOSHLUKOVA: That would be the reference dose.

PANEL MEMBER BLANC: Can you go back to your slide with the columns, please?

DR. KOSHLUKOVA: It's on the screen.

PANEL MEMBER BLANC: Oh, it's not on my screen. Sorry.

PANEL MEMBER GLANTZ: No, the control version at their end has to do it.

PANEL MEMBER BLANC: The control person at your end has to put it on the screen for the show, I think.

It's not on. Those of us by telephone on the meeting thing are not seeing that slide now.

PANEL MEMBER GLANTZ: Yeah, we're just seeing the room.

CHAIRPERSON KLEINMAN: Are you on the webcast?
PANEL MEMBER GLANTZ: Yeah, we're on the webcast.
PANEL MEMBER RITZ: Yes.
PANEL MEMBER GLANTZ: But all we see is the room and it says Scientific Review Panel. And before we could see your -- there it is. Thank you -- or no, now why.
CHAIRPERSON KLEINMAN: Okay.
PANEL MEMBER BLANC: Oh, there it is. Thank you. Okay. Thank you. I can see it now.
So you've got -- you've gotten to 0.1 by a 10 interspecies, and that's because you're taking a lowest observed effect level in the animals, is that correct?
DR. KOSHLUKOVA: No. No, no, no. So focus on this column here on this box. The point of departure is 10 microgram per kilogram per day, or that would be 0.01 milligram per kilogram per day. That is the NOEL.
PANEL MEMBER BLANC: Okay. Gotcha.
DR. KOSHLUKOVA: From the NOEL, we derived reference dose by dividing of a total uncertainty factor of 100, and becomes 0.1 microgram per kilogram per day or 0.001 -- 01.
PANEL MEMBER GLANTZ: This Stan, because there -- we maybe didn't hear you? Can you hear me?
PANEL MEMBER BLANC: Can you hear Stan?
DPR ASSISTANT DIRECTOR VERDER-CARLOS: No.

PANEL MEMBER BLANC: Stan come over here.

(Laughter.)

PANEL MEMBER GLANTZ: Okay. So again we may have been a little it confused here at this end and we apologize for not being here. But are you saying that -- because we can't see the flip notes on the table, so are you saying that the numbers in the second green column are in micrograms per day?

DR. KOSHLUKOVA: Here. Look at the first column under oral -- acute oral. It's microgram per kilogram per day. And then we're following children 1-2. So the NOEL, or point of departure, is 10 micrograms per kilogram per day, and dividing by an uncertainty factor of 100 will -- will --

PANEL MEMBER GLANTZ: Okay. Thank you. We were misreading that. Sorry.

So I just had one other question, since I'm close to the phone now. So did that answer your question, Paul, about the unit?

PANEL MEMBER BLANC: Yes. And then there was one other question which has to do with the acetylcholinesterase version, because we --

PANEL MEMBER GLANTZ: Well, let's go do that later.

PANEL MEMBER BLANC: Okay.

PANEL MEMBER GLANTZ: Okay. So the other -- the question I had is if you look at your green column and then you look at the EPA column, you know, there's like a couple of orders of magnitude different. And could you explain why that -- why they're so different?

DR. DuTEAUX: This is Shelley DuTeaux. We took the numbers from the November 16th HHRA, the Human Health Risk Assessment, from U.S. EPA. So we pulled the numbers out. And in our risk characterization document, the TAC evaluation document, that you received in December, it has an explanation both in the introductory portion of the document, as well as in the risk appraisal about our understanding of how EPA came to these numbers.

However, it's our best guess as how they derived these numbers by using an intricate dose reconstruction and reverse dosimetry methodology based somewhat on the PBPK model. So we were not really in a position to describe exactly how these numbers were derived. That would probably be better answered by EPA themselves. However, we can show the numbers as comparison.

PANEL MEMBER GLANTZ: Okay. Thank you.

PANEL MEMBER BLANC: So Paul here. Paul Blanc here again. I have two other questions. One relates to the column -- the green column, sort of the bottom line. And if you recall, we had a discussion about females 13 to

49 that has a not applicable for both of them in the steady state dermal and the steady state inhalation.

DR. KOSHLUKOVA: Yes.

PANEL MEMBER BLANC: And we had a discussion, since the neurodevelopmental issues would be likely to be most relevant to a fetus or would also be quite relevant to a fetus, and the fetus is likely to be related to women of child-bearing age. And we had asked -- or suggested that those rows not be -- not applicable. Then I think there was some discussion back and forth, and I -- it seems as if you're still deciding that that's not applicable. And I was not clear, looking at this, if the not applicable or not available is related to some missing data point that you have because wouldn't the same process be possible to extrapolate to women just using different body weights and other exposure variables, breathing rates, and so forth?

DR. KOSHLUKOVA: Yeah, you're right. We will remove the NA and this will be endpoint applicable.

PANEL MEMBER BLANC: And do you -- is your impression, given how -- your familiarity with the data, that the value for the females of child-bearing age will be higher or lower than that for children?

DR. KOSHLUKOVA: So for the neurodevelopmental effects, based on the studies that we have, they're all --

all valuations are on pups. We do not have moms' effect. We do. We do, but they come at higher doses. So that is applicable for young developing organisms, mature organisms. But since we're concerned about protecting the development -- the developing organism, this endpoint will be applied for pregnant females.

PANEL MEMBER BLANC: Right. Good. I think that would be good. So in fact, it may come out lower or higher. You don't know, because you're going to apply the same tox -- it will be the same point of departure. The only thing that will change will be issues related to breathing rate and other factors, correct? Do I understand that correctly?

DR. KWOK: This is Eric Kwok.

In general, when we divide the point of departure, we look at the endpoint that relevant to the life stage of concern. So for this particular one, the -- when you look at the developmental neurotoxicity study as Dr. Koshlukova pointed out, the endpoint identified in the pups, so meaning it's the developing organisms.

In order to establish an endpoint to characterize the adult, we need to come up with a similar endpoint, and then go from there. So meaning actually --

PANEL MEMBER BLANC: No, I think you're incorrect. The endpoint is still the effect in pups, but

the delivery vehicle is pregnant women.

DR. KWOK: That's true, but when the -- but ultimately, the endpoint -- the reference dose or ref -- the reference concentration will be protective, because in the risk assessment, usually the number that protected the pup eventually will be the driver to protect the -- the woman. But in terms of the endpoint that -- or the reference concentration divide that -- we count like -- make it clear the endpoint is related to the pup protection. And because of that, it count like automatically protect the woman of child-bearing age, because, you know, you protect the pup -- or protect the fetus inside the woman. So in theory, we should protect the mother.

PANEL MEMBER BLANC: But the level that you come up with for that, not currently where it says not applicable, is going to be different than row that protects children 1 to 2, because obviously the way that the dose gets delivered is different. So your calculations have to end with a different endpoint --

DR. KWOK: The --

PANEL MEMBER BLANC: -- for a number.

DR. KWOK: Yes. Well, the calculation -- the number is going to be different, but the endpoint, you know, to protect a woman of child-bearing age has to be

related to the woman of child-bearing age.

PANEL MEMBER BLANC: No, I disagree very fundamentally. What you said -- what I understood what you said was I would agree with, which is if you come up with a number that protects the fetus, it's going to be protective to the women.

DR. KWOK: Um-hmm.

PANEL MEMBER BLANC: But the number that you come up with has to be based on what the effect is to the fetus, which is the target organ of toxicity of the woman. So let's -- let's take as an extrapolation, if we weren't talking about the fetus, let's say that there was a target organ toxicity to the liver, and much less toxicity to the kidneys. In this particular case, you treat the fetus as if it's an organ of the mother, and so your protective value has to be protective to that organ that she has during pregnancy, which is the fetus.

So if not based on some animal study of adult females, it's based on the same data that you have that you're applying to the children, but it is applying to the women who have this organ that has specific target-organ toxicity. And therefore, you use the toxic level for the fetus, but you use the breathing level or the water drinking water or whatever it is that you plug into your model for the adult woman.

DR. KOSHLUKOVA: So I'll make two comments. One of the animal studies the design was such that animals were treated after birth postnatal day 10, so mom was not exposed. And then I -- and the facts were measured later in the development, 60 days, couple of months later.

But I was just thinking of other cases where we have used developmental neurotoxicity endpoints to characterize adult exposure. And one comes to mind for -- from one of our risk assessment documents. It was for a chemical that animals were treated during the development, and postnatally. And then later at 60 days of age, morphometric measurement shows shrinkage in the brain origins.

So that endpoint was used as NOEL for characterization of exposures to all life stages with the assumption that it would protect pregnant women and the fetus. So --

PANEL MEMBER BLANC: So that -- so that's good. You have precedent for doing this. And obviously, you should, to the extent that you -- I think you'll come up with the same numbers if -- even if you limit yourself to the studies that were wholly with exposure during pregnancy only, the Silva study, for example, from 2017.

On the other hand, just -- this may be at a discussion point in your document, but in fact, what is

the comparability of a newborn rat to -- or mouse -- a newborn rodent is probably more to a last trimester human --

DR. KOSHLUKOVA: Correct.

PANEL MEMBER BLANC: -- than to a newborn human. So from either way, I think you're on solid ground. And it's nice to hear that you have precedent for doing this previously. So I think that's wise.

And I think though -- I'll make one other point about acetylcholinesterase, and then I think other people should have the advantage of commenting, because we're a whole committee, and I don't want to monopolize.

On the acetylcholinesterase, pink columns, I noticed that the uncertainty factor for interspecies is still at 1. Whereas, our discussion at the last meeting we spent a lot of time about whether that made sense. And I believe that the consensus was that at a minimum a value of 3 was perhaps more appropriate in terms of the presumptions you were making about the pharmacodynamics in particular. That's my recollection. And I think other Panel members should weigh in on that.

So that's -- those are my two areas, the females of child-bearing age for the neurodevelopmental, and the presumption of a factor of 1 for interspecies on the cholinesterase side.

PANEL MEMBER RITZ: Yeah, this is Beate. I actually agree. We know that the PON paraoxonase metabolism capacity for OP pesticides, and including chlorpyrifos, varies 40-fold within human populations. So there's definitely a difference in susceptibility in humans.

DR. KOSHLUKOVA: Yes. So we're talking -- we're discussing the interspecies. This is the animal-to-human sensitivity.

PANEL MEMBER RITZ: Oh, not -- oh, yeah. Okay. Yeah. Mine referred to intra, that's correct.

DR. KOSHLUKOVA: So we addressed comment on why the interspecies sensitivity -- interspecies uncertainty factor for cholinesterase was removed. The default -- the default uncertainty factor was decreased to 1, particularly in the responses to OEHHA's findings in December, and I will bring --

DR. KWOK: Okay. For the interspecies, uncertainty factor reduced to one, we -- the reason for that is because we're using a PBPK model using the human parameter. And I would like to actually point out one important thing about the model versus the animal data, because in rat, actually, the plasma cholinesterase in rat -- actually, there's a lot of them actually in rat. But there's a paper by Lee in 2005 they showed that in

human, that's not the case.

So actually in the PBPK model, when you run the model, that factor will still activate. So we actually -- the common protection that we observed in rat, and removed it in -- remove it in human when we ran the model. So the model actually give a much better representation about the enzyme kinetics, actually occur in human.

So -- but when Dr. Blanc talk about the factor of 3, could you elaborate a little bit more in terms of why -- for the interspecies why the 3 is a -- is something that we need to consider or...

PANEL MEMBER BLANC: My recollection of the meeting - we'd have to go back to the transcript - was that there were components of the model that you were forced to use in terms of the PKPD model that made certain presumptions and derived from different sources, shall we say. And that going -- so some of it came from -- parts of it came from humans, and part of it came from animals.

And so to say that you could jump from the animal based -- or partially animal based model to humans without any uncertainty was perhaps too conservative. So that is what I remembered from the discussion. In other words, for PKK -- for this model to not require any uncertainty jumping from animals to humans, you would have to have a model which was, you know, very solidly derived from

components of the human experience that in some ways you didn't have particularly for the pharmacodynamic as opposed to the pharmacokinetic pieces of it.

Now, that's what I recall from the discussion. And there was a lot of discussion around the table, so maybe others would want to comment on that. And I sort of got the impression from EPA that you found that argument persuasive enough to back away from the factor of 1, because you -- the last presentation also had the factor of 1.

So -- and also -- and it might be good to bring OEHHA up to the table and have them comment too, because my impression from OEHHA was that they similarly felt some discomfort with the value of 1 being not sufficiently conservative and public health protective.

DR. KOSHLUKOVA: Dr. Blanc, if you look at the screen, we pulled the responses to comments regarding the interspecies uncertainty factor. So I'll go briefly over this. It's summarized nicely here, so that you can see the logic why we felt comfortable to decrease the uncertainty factor to 1. I just want to point out that in the U.S. EPA 2016 risk assessment, they utilized the same model minus the pharmacodynamic part, and also removed the uncertainty factor for interspecies, because it provides -- it derives human equivalent concentrations.

So a lot of this Eric covered. So the PBPK model inputs -- this is from the published studies that came after -- in 2007, the recent studies. We reviewed those and summarized the findings here. The greatest impact on interspecies variation in the model are absorption in the guide binding to acetylcholinesterase and metabolic bioactivation and clearance of chlorpyrifos.

Many of the inputs were derived from humans, and such the resulting output accounted for human specific physiology and metabolism. A notable example is the description of the chlorpyrifos oxon removal by carboxylesterase. This is the finding that Eric mentioned.

The distribution of carboxylesterases in animals differs considerably from humans. In rats, plasma contains high levels of carboxylesterases, whereas in humans carboxylesterases are not found in the serum. The PBPK model correctly accounts for the absence of carboxylesterases in human plasma.

When there were no human specific values parameters were extrapolated from animals. It is a common practice in PBPK model in ending risk assessment in general to use animal parameters scaled to humans when human data are not available. Scaling by three-quarters body weight in carcinogenicity is one example of

animal-to-human dosimetric adjustment.

And in conclusion, our review of the model parameters could not justify the increase of interspecies UF of 1 to 3. That was the responses to the findings and by asked to OEHHA.

PANEL MEMBER BLANC: So, yeah, most of that -- can I just point out that most of what you're saying, of course, is relevant to the pharmacokinetics, isn't it?

DR. KOSHLUKOVA: Yes.

PANEL MEMBER BLANC: So -- and my concern has to do a bit more with the pharmacodynamics and being assured, since you have derived other parameters here in the pharmacodynamic piece of it are animal driven, aren't they.

DR. KOSHLUKOVA: Are you referring to the developmental neurotoxicity effects?

PANEL MEMBER BLANC: No, because you have a -- you do have a factor of 10, which takes that, I guess, into account.

DR. KOSHLUKOVA: Yes.

PANEL MEMBER BLANC: A separate factor of 10 is my question. And again, I think -- I'd like to hear OEHHA weigh-in on this specific piece of it, if they might.

DR. TING: Hi. This is David Ting. I'm Chief of the Pesticide and Environmental Toxicology Branch, Office

of Environmental Health Hazard Assessment.

We make that comment that we believe the interspecies uncertainty factor should be at least 3. The reason is that it's basically model uncertainty. As mentioned earlier, that PBPK model was used to bridge this gap between animal and human. And this is a state-of-the-art model, and it tried to use both animal and human parameters.

However, there are limitations in the construct of the model as well as the parameters. And in our comments to DPR, we cited three reasons. One is that not all model parameters were derived from human studies.

Second, differences between the nature and location of absorption of particles. The model assumed most of the chemical, whether by inhalation or oral, and absorpted in the GI tract.

But we believe because most of the particles are actually aerosols, not solids, not solid particles, when inhaled they are probably absorpted in the upper respiratory or middle respiratory region in the lung, instead of in the gut.

And lastly, this PBPK model has not been well validated using human data. There are some human data, but they're sparse, and the validation is kind of limited. And I want to stress that the model tried to do a lot, and

is very sophisticated model. But it's a very tall order to say that it is equivalent to a well designed and executed human study.

Basically, we're saying here that there's very little or no uncertainty in the -- by the output of the model.

I can answer any questions.

PANEL MEMBER ANASTASIO: Could you also comment -- I mean, OEHHA was recommending a uncertainty factor for intraspecies of 30, right? Whereas, DPR had 10. Can -- and the difference was the square root of 10 for the pharmacodynamics. Can you comment on that as well?

DR. TING: Yeah, I can try.

So first of all, I want to emphasize that red blood cell acetylcholinesterase inhibition is used as a surrogate for the environmental neurotoxicity. And first of all, we talk about the pharmaco -- the pharmacodynamic part earlier that the very -- variability among humans could be relatively small.

However, when we move to the developmental neural, we expect the variability between individuals would be much bigger. That's point number one.

Second is about the pharmacokinetic part. And I understand there's a lot of work being done on four

specific enzymes showing that the variability is about a factor of 4 or 5. However, that sensitivity study was based on very limited human samples, and only focus on four enzymes -- systems. And there are many more enzymes, especially when we move from the red blood cell acetylcholinesterase inhibition to environmental neurotoxicity.

There has -- I think U.S. EPA mentioned there could be like five or six potential mechanisms. And there are many, many enzyme systems involved. And the variability for those enzyme systems could be much bigger. So for both PK and PD, when we think about the developmental neuro, instead of red blood cell acetylcholinesterase, we expect the variability could be much bigger.

PANEL MEMBER BLANC: Well -- Paul Blanc here just to -- just to come -- tie this back, and then really eager to hear the other Panel members. I think that if I were DPR, I'd say in terms of the argument about the interspecies variation vis-à-vis neurodevelopmental toxicity, there is a factor of 10 that's specific to the lack of data on neurodevelopmental toxicity.

However, I think that Dr. Ritz's point about the cholinesterase effects varying by a factor of 4, which is not necessarily specific to neurodevelopmental, just if in

you're talking about cholinesterase effects, it's relevant to that, could certainly be an argument for a factor of 30 instead of 10.

I think that the most convincing part of -- and the most -- and it was extremely helpful to hear you reaffirm that, oh, OEHHA, in terms of the interspecies factor does not support a one-on-one extrapolation, and suggests that a conservative -- more conservative approach is, in fact, a factor of three taking into account that this model has not been validated in humans, and derived some of its parameters from animals, and only part of its parameters from humans.

And your point about aerosols being absorbed into the upper airway tract is absolutely right on, and is probably a home run in that regard in terms of an assumption of the animal models.

So now I'm going to get off and let people talk.

PANEL MEMBER GLANTZ: Just add that I agree with what Paul said.

PANEL MEMBER BLANC: And Stan says he agrees.

PANEL MEMBER RITZ: Yeah, and this is Dr. Ritz again. Actually, the factor for paraoxonase is 40-fold in humans. And given that that, as was explained before, is not the only enzyme system involved. There are many, many more with lots of variation in humans that can bring in

quite a bit more uncertainty.

DR. KWOK: This is Eric Kwok. Because there's a lot of topic been raised, so I try to see whether I can answer in the order it was raised.

Regarding, you know, you had commented about the absorption. Actually, the human version of the PBPK model, the parameter developed based on the control human study. So actually they parameterized the model to gauge the -- actually to develop -- to divide the absorption factors. So it's not -- it's not an estimation per se. Actually, it's based on the controlled human study dermal absorption. They actually used the model to devise a permeability coefficient.

The second regarding the animal data, and I think the model actually tried to incorporate the most relevant human data. In the last meeting, I make a point that, you know, the essence of the PBPK model is try to capture the most important event that we can. And then anything else is pretty much for bookkeeping purposes to maintain the mass balance. That's the most important thing.

So for the chlorpyrifos metabolism, the main thing actually is the metabolism, meaning the activation process and the deactivation process. These are the most important enzyme involved in the process.

So as long as the model correctly captured the

activity in terms of how chlorpyrifos converted into oxon and how oxon is deactivated, I believe the model actually served the purpose.

The -- in response to Dr. Blanc about the pharmacodynamic, the data are based on the understanding of the model parameters, and I believe that derived from the animal data. So mainly actually the enzyme activation/deactivation I believe it come from the animal study.

But that by itself, the only thing I can say is that it is not unusual that as I respond to OEHHA in the absence of human data, we will try to use the animal data. This is -- the practice not unique to chlorpyrifos PBPK model per se. It's kind of a common practice when we construct the PBPK model.

And the example, even in U.S. EPA, that they applied to the PBPK model, based on the best available information include the variable human data and animal data to develop their -- the process, and eventually translate into the -- their -- the regulatory effort that they intend.

So in -- regardless, with respect to the absorption, what the intraspecies variation, the enzyme, I would like to use the data presented in Poet 2017.

Okay. The figure actually currently shown on the

screen is a graph presented in the paper by Poet 2017. What it show actually is the --

PANEL MEMBER GLANTZ: Excuse me, this is Stan. Do people control the zoom on your computer, because we're only seeing like part of a part of the graph. So I think if you zoom out -- yeah, that's much better.

Thank you.

DR. KWOK: So, Dr. Glantz, can you see everything now?

PANEL MEMBER GLANTZ: Yes.

DR. KWOK: Okay. So this graph actually -- first of all, I would like to start on the right-hand panel. That's the coefficient variation of the parameter. So it -- categorizing the four major global parameter, that factored into the PBPK model in terms of biochemistry, physiology, metabolism and all the parameter.

Now, the metabolism, as the legend indicate, is pretty much involved in the activation and deactivation of the chlorpyrifos. As you can see, the variation actually in the coefficient of variation can be large. But if you look at the left -- yeah, the left-hand side of the panel, which is the RBC inhibition, you can see actually the kind of variation for -- let's say, for instance, for the metabolism, the second bar on the right. And you look at the -- you count on the left-hand side, the first bar

corresponded to metabolism, they don't show a one-to-one type of translation.

So meaning even though you have a lot of variation in the input parameters in terms of metabolism, it's not necessarily translating to the same level of variation that you observed in the RBC cholinesterase inhibition.

So this is the -- these -- so we understand actually there's a lot of variation in terms of enzyme activity in human. And also in the same paper, it also presents some kind of analysis.

And so again, the -- this table is also from the same paper by Poet 2017. The four enzyme, why they are there is because they are the most important involved in the activation and deactivation of chlorpyrifos.

So the table 2 actually show that the kind of variation originally in the in vitro data published by Smith. So they -- it's an experiment. It's in vitro data, so they cover a range of observed activity. It's a reflection of the actual experimental data.

So the second one, they went on and to do a little bit more. It's a parametric distribution. So what they did actually is to use the Monte Carlo resampling, you know, from the data, and then to see the kind of variation that are observed from these four enzyme.

And then the last one they did the parametric bootstrap. Actually, they -- what they did is they -- they used the original data again. But they do the bootstrap method to randomly sample and to come up with a set of 20 parametric bootstrap. And from that -- and then to determine the kind of variation.

So after they all this, then they use it to -- the bottom table 3, to come up with the data -- the data extrapolation factor, the DDEF. So as you can see, the DDEF actually basically is a comparison of a medium value versus the first percentile, meaning the most sensitive individual.

As you can see, when you look at the DDEF across the different life stage, meaning the adult male/female, infant, non-pregnant female. They're in the range of 3 to 4 approximately.

So because of that -- you know, because we are proposing the intraspecies of 10, we believe that that should be sufficient to cover the variation based on these exercise of -- or the data present in this particular paper.

So to recap is that, you know, because -- even though there's a lot of variation in enzyme activity within the human population, but because of the -- I would say it's fair to say because of the homeostatic mechanism.

So the variation they observed in the individual enzyme activity, not necessarily translate into the ultimate variation observed in the cholinesterase inhibition.

And because of -- and also because of these analysis in terms of the variation, the results suggested that the variation, after you consider everything, the maximum they get out of this is approximate -- approximate, a factor of 4.

So because we have proposing a factor of 10, we believe that that is sufficient to cover the variation they observed based on the amount of information available to us.

One more thing.

PANEL MEMBER RITZ: So this is Dr. Ritz. Can I ask a question?

DR. KWOK: Sure.

PANEL MEMBER RITZ: So this data is animal data in rats or mice, correct?

DR. KWOK: It's human data, not animal data. The enzyme you're talking about are human data. The human in vitro data, the enzyme. You're talking about the PON1, the CYP enzyme and not --

PANEL MEMBER RITZ: Yeah. No, that what's in table 3 is that from humans?

DR. KWOK: Yes. Yes, in a sense that because

this is a model generated output based on the human parameter that fit into the model.

PANEL MEMBER RITZ: But is that just modeled or is this actually based on actual observational data?

DR. KWOK: Model, not the actual -- the -- not from the -- not from the actual human observation is the model generated output based on the human data.

PANEL MEMBER RITZ: Yeah, but what is the human data the model is based on?

DR. KWOK: Is the four enzyme that they studied using the human -- the enzyme -- the enzyme divided from the human tissues. It's the in vitro data. That's -- that's --

PANEL MEMBER BUCKPITT: In vitro human hepato -- microsomal data.

DR. KWOK: Yes. Yes. Thank you.

PANEL MEMBER RITZ: Okay. So I assume they did not use hundreds of individuals, correct?

DR. KWOK: That's correct. And I think that's the reason why they want to do the bootstrap process.

PANEL MEMBER RITZ: But the human population is genetically extremely variable. And to base a model on let's say five or 10 samples is probably not going to capture variability in the genetic diversity of these enzymes or others that may actually influence the

expression.

DR. KWOK: The only thing I can point out that in the Smith paper, there are like 30 different samples, and they cover a different age group. So it --

PANEL MEMBER RITZ: Do they cover different races, because we know that these metabolic enzymes actually are very different between racial subgroups?

DR. KWOK: Let me check really quick. Look at the...

DR. KOSHLUKOVA: Race was not reported. But if you look at the last column, there -- those four pathways have been reported to add to the -- most of the variabilities in their response for metabolism of chlorpyrifos. So the in vitro data is limited by the model -- the bootstrapping generated differences, for example, conversion to oxon by 98-fold between individuals, or hepatic clearance of -- or hepatic enzymatic activity of PON1 up to 58.

So the model generates ranges in enzymatic activity ranging from 58 to 98-fold. So it certainly for covers four defaults observed variations in PON1 activity, wouldn't you say?

DR. KWOK: I do want to add one thing right now actually. Right now I'm looking at the Smith 2011 paper. I'm more than happy to send you that. And table 1

actually it does actually -- it did actually list out the race. It is -- the 30 samples divide from African-American, White, Hispanic, American Indian, four different.

PANEL MEMBER RITZ: But no Asians, right?

DR. KWOK: No.

PANEL MEMBER RITZ: Okay.

PANEL MEMBER GLANTZ: Well -- so this is Stan. I mean, I think the points that are being made -- I mean, I think the bootstrap approach is fine, but it does depend on the input data. And if you're not capturing these ranges of biological variability in those sample that's underlying the bootstrap, then you're going to underestimate the variability.

Well, I don't understand that, you have to bring that up.

PANEL MEMBER BLANC: Has anybody -- Paul here.

PANEL MEMBER GLANTZ: Come over here so they can hear.

PANEL MEMBER BLANC: I guess also I don't think I clearly heard in all of that the response to the OEHHA point about the GI absorption versus the upper airway absorption, but I could have missed that.

DR. KWOK: Dr. Blanc we are about to bring up a slide about the inhalation absorption.

PANEL MEMBER BLANC: In -- that's underlying the animal model?

DR. KWOK: Among the -- yeah, this is the -- this is based on the animal -- animal data.

So can you see the --

PANEL MEMBER BLANC: But I think it underlies your PK -- it's inherent -- it's taken into account in our PKK/PD[SIC] model or not? I mean, that was the OEHHA question.

DR. KWOK: The inhalation absorption, the model actually did factor that into consideration. So is that -- can you -- can you see the figure 1 actually on the screen now?

PANEL MEMBER BLANC: Well, let's see. Can I see figure 1 on the screen?

Yeah.

DR. KWOK: Okay. So let me walk you through.

PANEL MEMBER GLANTZ: Okay. Wait. Is anybody talking? We don't hear anything.

DR. KWOK: I'm --

(Laughter.)

DR. KWOK: I'm --

PANEL MEMBER GLANTZ: I was trying to make sure I didn't push the wrong button.

(Laughter.)

DR. KWOK: I'm waiting for Dr. Blanc, cue for ready.

(Laughter.)

PANEL MEMBER BLANC: What are you waiting for, I'm sorry?

DR. KWOK: Oh, okay. I'm sorry, because I just want to make sure that you're looking at the graph.

PANEL MEMBER BLANC: Yes.

DR. KWOK: Okay. So this graph actually is summary data from three different animal studies. On the very left panel, the bottom label is the chlorpyrifos oxon, the rat were -- the rats were exposed to the chlorpyrifos oxon vapor, so -- for six hours, nose-only exposure. The middle is a second experiment, the rat were again exposed to, but this time chlorpyrifos vapor, six hours, nose-only exposure.

And then on the very right, we've got a slightly bigger green rectangle. The rats were exposed to the chlorpyrifos aerosol, again nose only exposure.

The three lines actually represent the peak blood concentration of TCPy, which is a metabolite of chlorpyrifos. The second one is -- the second line with solid triangle is the blood concentration of chlorpyrifos in rat. And the bottom one is the peak blood concentration of the oxon.

Now, for the -- so as you can see, the line actually -- the peak blood concentration appeared to be correlated very well with concentration regardless of the physical form of the chemical, meaning either it doesn't matter whether this is vapor or aerosol.

So that kind of, you know, indicated that the -- the -- actually, the physical form may not be that important.

PANEL MEMBER BLANC: But wasn't the OEHHA point have to do with some presumptions made about GI tract inactivation?

DR. KWOK: Yes. In the model actually the -- the model actually is -- 2014 -- '14 here. The model is -- the model -- the PBPK model assumed that, you know, the inhalated[SIC] aerosol get into the respiratory system. And most of them actually get coughed back up, and they swallow into the GI tract.

PANEL MEMBER BLANC: Well, that's a false assumption right there.

DR. KWOK: The -- but the -- when they actually did that, they used the model to match with the animal data. So --

PANEL MEMBER BLANC: I'm just saying that's a very bizarre assumption, because an aerosol that you got into the upper airways would then be absorbed through the

mucous membranes. It wouldn't be like a particulate -- a solid particulate that you cough up. So it wouldn't be like silica particles or something.

But also the issue of the lack of a true validation of the -- or true or maybe there has been a validation of this model in experimental human exposures to show that you can be assured that one-to-one extrapolation without any uncertainty is appropriate. That was another critique of OEHHA in this regard.

DR. KWOK: The -- I think the only thing I can add is that the -- the -- in terms of the respiratory exposure, based on my best understanding, that they tried to -- you know, the model actually fit the data. So I think that's part of the -- I mean, the model represent -- you can -- there's a different way to actually model the -- to model this other process.

So I think, in general, if the model fit the data, then you're probably correct per se, instead of, you know, you assume certain process in the model, it turn out the model not even closely aligned with the data. So I think that's the piece of evidence that I can provide at this point.

The -- the -- and the -- in terms of the validation of the model in human, the data available is very limited, but it's presented in the paper by Poet in

2014 in Xenobiotica. So they did -- they acknowledged that, you know, the amount of data available for the validation of the -- the inhalation model is limited. So that's all I can say at this point based on the information that are available to us.

PANEL MEMBER BLANC: Well, okay, how about the other Panel members? What I would be very curious to hear from the other Panel members whether hearing the point of view of OEHHA and the data that have been presented, whether people feel that is sufficiently conservative to have a one-to-one transition from the animal application or the animal model to the human, or whether some amount of additional uncertainty should be factored in when jumping from the animal model to the human model?

I think it's -- it would be important for me to hear other persons' thoughts about that, even the people on the panel who consider themselves more exposure people. You've been around the block awhile, so...

CHAIRPERSON KLEINMAN: Well, I have, you know, a couple of questions about the modeling, which might be germane. Does the -- does the model take into account differences in metabolic rates between infants, or neonates, or fetuses versus adults?

DR. KWOK: To the best of my understanding the differences originate from the enzyme -- the metabolism

data where it's coming from, meaning actually the -- because some of the -- like the metabolism, the activation and the deactivation of chlorpyrifos to oxon or the TCPy. It devised from a group of in vitro samples from a very young age.

Let me quick change to see if I can put that up.

They said the age of 0.04 years, so they'll be two months old. A couple months old all the way to like 75. So it covers a wide range of life stage. And because the enzyme activity data comes from a different life stage, and then eventually factored into the model, so I would say, yes.

CHAIRPERSON KLEINMAN: Okay. Because I was reading an article by Flaskos, where he's summarizing a lot of other data. And it's showing that -- that in infants, they have a reduced capacity to deactivate the oxons, which are the active form. So that although they may form the oxon at about the same rate, which I think is what the model is predicting, they don't get rid of it as easily.

And so the toxic effect can be much greater. And, in fact, if -- you know, they cite some LD50 data that shows that the young animals have a five times lower LD50 than an adult. So it seems like the -- you know, if -- you know, children or neonates are going to be our

target population, we really -- you know, using the adult metabolic data doesn't really give you an additional amount of safety.

DR. KWOK: I just want to reiterate that the enzyme activity data that went into the model, it covered a wide range of age groups, no just adult, in terms of the enhanced sensitivity in children. But again, I would like to point out we still focus on the cholinesterase inhibition, because now we're talking about the pharmaco, you know, the dynamic portion of it.

If I remember correctly, I think the model simulation not necessarily show an enhanced sensitivity in children. Because of the complex nature of the interaction of given, you know, enzyme, I -- it's not unexpected, but I don't have enough information at this point to give you a quantitative answer.

CHAIRPERSON KLEINMAN: Flaskos, I'll give you a copy of the paper. A little chewed up, but serviceable.

There is also -- oh, go ahead.

DR. KOSHLUKOVA: We'll get back to you with more details on this. But just recalling the data, what the model predicted was that young children will -- the endogeny of the enzyme activity is such that they would have lower ability to detoxify. However, they also have a lower level of converting chlorpyrifos to oxon until I

believe was age of six months, so...

PANEL MEMBER GLANTZ: Well, so this is Stan. I mean, the concern that I have -- I mean, I can -- that there are a lot of parameters in the model. And I -- I can see how, when you did your simulation, that when you put all the uncertainty and all the parameters in, they would tend to balance out. So the mean estimate wouldn't be affected much, so that's plausible.

But I don't understand why the variance in the estimates doesn't increase, because, you know, you're piling uncertainties on top of uncertainties. And then if that's the case, shouldn't you be picking your -- your -- your uncertainty factor or safety factor not based on the mean effects in the model, but rather on the upper bound estimates of -- you know, of the -- well, depending which way take, it's either the upper or lower bound, to come up with what the uncertainty factor you were going to be using in the risk assessment was.

Because I can see a thing where -- where with a lot of parameters varying randomly, they would balance out. But -- but then, you know, like if you're looking at this picture, you know, it just -- it's just hard -- so why are you getting, if you're looking at your outputs, you know, on the -- on the left side, why is that so small? Again, could you zoom out, because we couldn't see

the whole picture.

And then again, the other thing which a couple people pointed out, is that you're doing your bootstrapping off a fairly limited sample. So, you know, to the extent that that's not representative of the full variability and range of responses in the population as a whole, that's also going to underestimate things. So I think all of this argues for having a bigger uncertainty factor in the overall risk assessment.

PANEL MEMBER HAMMOND: This is Kathy Hammond.

Yeah, I think that the variability in human population really is an important aspect of this. And there's clear evidence that there is a lot of that variability. And Beate made the point that we're like -- this was -- the data were based on five people with much more limited diversity than we have on even just the California population.

So I think we do have to have a certain humility when we think about how well we're characterizing that intraspecies variability. And so that would make me lean a little more towards including a measure of that variability, and be -- yeah.

PANEL MEMBER RITZ: So this is Beate. I wanted to say it's not just the genetic variability, it's also the age-related variability in these enzymes, as well as

these enzymes being targeted by other substances, including drugs. So we have certainly chronically ill people whose PON1 activity might actually not be top, because they are taking certain drugs or, you know, they have other kinds of illnesses. And none of that is reflected in these models.

CHAIRPERSON KLEINMAN: So have we given you enough to go on in terms of where we think, you know, what our opinions are about the uncertainty factors, and should we move on, or do you want to discuss this a little further?

DPR ASSISTANT DIRECTOR VERDER-CARLOS: Just -- well, just clarification. So you want a discussion on the additional uncertainty factor of three for the interspecies? Is that what -- is that where we --

PANEL MEMBER GLANTZ: Well, I think -- I think that we're suggesting you should use the additional uncertainty factor. Not just discuss it, but you should use it. I'd be interested in hearing what everybody else -- Paul is nodding his head here.

PANEL MEMBER BLANC: Yes. What I'm hearing as a fellow Panel member is that the Panel members who have spoken on the subject seem to support factoring in some additional uncertainty. And I've heard -- I sort of translate as that it probably is a factor of 3. And I

haven't heard someone say there's so much uncertainty that it should be 10. Consistent with past policy and that this is also consistent with the input of OEHHA. And we definitely like to see OEHHA and DPR work on the same page, which is why I think it was so encouraging last time to see OEHHA and DPR come together on having the -- the endpoint -- the principal endpoint of the recommendation be neurodevelopmental toxicity, which is the green column 2 in the presentation that we saw, which now I think would move to be the first column of any such table.

But I need -- I don't want to read -- and I don't want to read into the comments that I've heard, but that's certainly what I heard from Dr. Hammond, Dr. Ritz. And I haven't heard anything, I don't think, from Joe on this particular point yet. And I would interpret Michael's comments similarly to support additional uncertainty being factored in.

PANEL MEMBER LANDOLPH: Yeah, Paul, this --

PANEL MEMBER GLANTZ: Just so we can move on, the question would be does anybody not think it should be 3, whose on the Panel?

PANEL MEMBER LANDOLPH: Yeah. No, this is Joe. I would easily support an extra factor of 3. No problem, because of the, you know, neurotoxic symptoms that the applicators, and the sprayers, and some of the bystanders,

the farmworkers are getting. So, yeah, easily I could accept 3.

CHAIRPERSON KLEINMAN: I'm kind of thinking of this as -- you know, in terms of the uncertainty for the interspecies factor is there are two different things. One is just the differences related to age, and all of the things that go into it, different breathing rates, different absorption rates, things like that. And then there's another component of sensitivity.

So I would kind of come up with, if I wanted to do it, staying with the factor of 10 sort of thing. I would say that a square root of 10 would make a reasonable, you know, absorption factor, assuming that the model takes into account the difference in sensitivity reasonably. So that would be the square root of 1 times square root of 10. So it would be 3 point something or other.

DR. DuTEAUX: So this is Shelley. So I can just clarify, when you're talking about age differences, breathing rate differences, absorption differences, and sensitivity, you're talking about within human variability, correct? So we're talking intraspecies uncertainty factor, is that correct?

PANEL MEMBER BLANC: I don't know exactly what Mike was implying, but the rest of this discussion has

been about the interspecies uncertainty factor.

DR. DuTEAUX: Right, that's why I was trying to clarify.

PANEL MEMBER BLANC: So --

PANEL MEMBER HAMMOND: No, I guess I was -- I was speaking intra -- this is Kathy. I was speaking intraspecies.

PANEL MEMBER BLANC: Okay. Well, then, Kathy, maybe you could -- since most of the discussion has about the interspecies, and whether or not we can trust the model that they have to be directly extrapolatable from animals to humans at a one to one level without any extra uncertainty, I think I voiced, Stan's voiced, and Dr. Ritz has voiced clearly that there's enough uncertainty derived from how the parameter estimates have been gotten on the inter -- in animals, and also on the lack of convincing validation in humans using that exact same model that we would favor an uncertainty factor of 3 going from non-humans to humans, so that an interspecies uncertainty factor should not be 1, it should be 3.

PANEL MEMBER HAMMOND: Yeah, I certainly believe that if you're going from animals to humans, you need an interspecies variability. But my understanding was that the discussion from DPR was that they were using human values in the models. And that's why I thought it was

intraspecies. I thought that that's what Dr. Ritz was also talking about, the variability among the human beings by age and as well as other factors.

DR. DuTEAUX: This is Shelley --

PANEL MEMBER HAMMOND: That to me --

DR. DuTEAUX: Sorry.

PANEL MEMBER HAMMOND: There may also be, if you want to add to that the animal factors, but I think this was looking at the human input factor.

PANEL MEMBER RITZ: Yes, I was talking about the human input.

DR. DuTEAUX: Okay. This is Shelley again. Just to clarify, because we need to go back and revise the document, we need to be crystal clear about the changes that the Panel would like, and it sounds like there's still some discussion.

PANEL MEMBER BLANC: Right. Well, why don't we break it out then. Can we just talk about -- because I do think that despite this confusion and some of the comments being on different parts of it, that if we just break out the interspecies extrapolation that I am not hearing from the Panel that they are comfortable with a factor of 1 to 1, and that there is uncertainty jumping from the animals to the humans for several different reasons, and that based on that, we should, on that level, use a value of --

we recommend using a value of 3.

And then we should come back to the interspecies factor, which I believe is 10 as it is. And then we can discuss whether 10 is sufficient. The OEHHA comment was that they thought that should be 30. So you're right, we should be clear about our sense on that one or not. But let's first deal with the animal one, the interspecies.

DR. KOSHLUKOVA: This is Svetlana. Are we -- is the discussion now focusing on the -- toxicodynamic for -- the pharmacodynamic portion of the interspecies uncertainty factor.

Dr. Blanc?

PANEL MEMBER RITZ: So what I understood - this is Dr. Ritz - is that one of the major problems with that model is that it was only considering gut absorption and not lung or nasal or whatever else.

DR. KWOK: Dr. Ritz, can you repeat your last statement. I'm not sure I understand the -- the model actually consider all the portal of entry, so meaning the skin absorption, the inhalation absorption, and all absorption. You can either run it concurrently or you just isolate one exposure route at a time.

PANEL MEMBER GLANTZ: But I think they both get captured in 3.

CHAIRPERSON KLEINMAN: So, Alan, do you have any

feeling on this?

PANEL MEMBER BUCKPITT: I'm perfectly comfortable with a factor of 3. And again, if you look at the Smith data that was used for the metabolism, there are very few older individuals. There's only two individuals over 50, so they don't cover the full range of human metabolism.

So I was under The impression that we were talking about human, human extrapolations, and that your model was based mostly on human data, but hasn't been validated with exposures.

DR. KWOK: Not all the routes, okay, like oral. There's some control human study available to validate the oral exposure.

PANEL MEMBER BUCKPITT: But not the inhalation exposures?

DR. KWOK: Not at the same level of detail. I mean, in terms of the data that you could uses -- compared to what available to the animal -- or to the human oral study, they're not in the same level in terms of the information available for it, yeah.

PANEL MEMBER BLANC: Okay. So let -- this is Dr. Blanc again. If I could just summarize the discussion that is pertinent to the interspecies extrapolation, bearing in mind that we're going to come back to the intraspecies uncertainty factor which is currently 10.

We're talking with the interspecies factor, which in the current modeling was set at 1, a direct one-on-one extrapolation.

We've heard that the current model is derived from some human -- a lot of human, but also some animal data, and that it's -- and that this model, which is not wholly derived from human data, has not been completely or fully satisfactorily validated in humans. So you've got two sources of uncertainty, one is that parts of it come from animals and not all of it comes from humans, and that it certainly has been validated only to a limited extent in humans.

And for -- those two things are what compel me to want to have additional uncertainty in the interspecies extrapolation to --

PANEL MEMBER GLANTZ: Of 3.

PANEL MEMBER BLANC: -- of 3 -- a value of 3, not a value of 10. I'm -- you've partially suspended my disbelief, but not wholly. So if it would be easier for the group, I'm happy to make a motion that the Panel reflect the consensus view that not 1 but a value of 3 for uncertainty should be applied on the interspecies extrapolation. And then we can go from there and circle back to the intraspecies value which is currently 10. Would that help people, if we had such a motion on the

table?

PANEL MEMBER GLANTZ: Yes. I'll second it.

CHAIRPERSON KLEINMAN: Okay. We have a motion on the table.

PANEL MEMBER BLANC: And Dr. Glantz has seconded it.

CHAIRPERSON KLEINMAN: And seconded.

PANEL MEMBER GLANTZ: And that way we can just get everybody to weigh in, and then we've given DPR some clear guidance on this point.

CHAIRPERSON KLEINMAN: Since we've got so many people on the phone, let's just do a voice vote. So let's go around the table first.

Kathy

PANEL MEMBER HAMMOND: For the moment I'll pass. I'll come back. I want to think about that. I mean, I think we have had a problem here. I think that the UCSF contingent has been talking interspecies, and all the rest of us have been speaking intraspecies. And so to have the motion be about something most of us have not been talking about doesn't really make a lot of sense to me.

CHAIRPERSON KLEINMAN: Well, just from the point of discussion, it -- you know, it seems to me that there -- you know, the con -- a confusion factor is if we accept that the model is a pseudo-human, then we could say

that there is an -- there is no interspecies difference.

Now, Dr. Blanc is indicating that he feels that it's an imperfect surrogate, in which case there'd be a higher amount of uncertainty for that.

On top of that, then what several of us were talking about seemed to fall into, as Dr. Hammond has pointed out, a -- the -- you know, more in the intraspecies differentiation, which already has a -- an uncertainty factor of 10, I believe, associated with it.

So we could...

PANEL MEMBER GLANTZ: I think the point -- well, the reason for the motion was to try to pry these two issues apart. And I think what you said summarizes the position that, you know, Paul and I have been talking about pretty clearly. And plus you added some other reasons that it's a good idea to do 3.

CHAIRPERSON KLEINMAN: All right. So we were continuing to go around the table.

Cort?

PANEL MEMBER ANASTASIO: Yeah, this is Cort. I would agree with a factor of 3.

PANEL MEMBER BUCKPITT: I would agree with a factor of 3. This is Alan.

PANEL MEMBER LANDOLPH: Joe Landolph. I agree with a factor of 3 also.

CHAIRPERSON KLEINMAN: Okay. So we have a majority --

PANEL MEMBER RITZ: Oh, this Beate. I do too.

CHAIRPERSON KLEINMAN: -- for a factor of 3.

Okay. So our recommendation is --

PANEL MEMBER BLANC: Well, let the record show also that I also agree with the motion that I made.

(Laughter.)

PANEL MEMBER GLANTZ: Me too. Although, it is -- let the record also show that Paul agreed with himself for a change.

(Laughter.)

PANEL MEMBER BLANC: Okay. Thanks.

CHAIRPERSON KLEINMAN: Rare, but not unprecedented.

Okay. All right. Having done that, then perhaps we should been -- move to the other elephant in the room, which would be the intraspecies. And is there a feeling that the factor of 10 is not large enough to cover the varying differences?

PANEL MEMBER HAMMOND: May I just say I don't think that we should be voting on each of these points. I really think that's an inappropriate way to --

CHAIRPERSON KLEINMAN: I don't want to vote on them. I just want to discuss --

PANEL MEMBER HAMMOND: Right, because that's --

CHAIRPERSON KLEINMAN: Yeah, that was another point that we've got.

PANEL MEMBER HAMMOND: -- not that we -- yeah.

PANEL MEMBER GLANTZ: Well, this is Stan. The only reason I suggested Paul make a motion was to -- in an effort to try to pry these two questions apart and give DPR clear guidance on the two separate questions. I mean, I agree that we usually don't vote at this level of detail. But I do agree with the comments somebody made that we were mixing up two separate issues, and that was confusing. And so I think the act of making the motion separated them. And I think the -- Mike now wants -- so we've dealt with one, now I think Mike should deal with the other one and see, you know, if people are happy with the 10 or want something different.

I mean if everybody is happy with what they've got, then we can just take note of the fact that people are happy.

PANEL MEMBER HAMMOND: My apologies to you, because you've had a very clear presentation, but I've gotten confused in some of this. Could you please review for us, Dr. Svetlana, the -- what our factors are, where we are in your great table. Just bring that back up.

Yeah. Magic table, and just -- could you just

say again where we are and what we've said, just to help me.

Thank you.

DR. KOSHLUKOVA: So this is the colored table. We're going to be focusing on looking from the left column, the very last row, steady state inhalation, and we're focusing on children for now, 1 to 2.

Okay. So if -- now we're moving to the second -- to the uncertainty factor column, the one to the left to the second row. For the PBPK-PD point -- derived point of departure, we used a 1 for interspecies sensitivity. This is going from humans to animals -- I'm sorry, animals to humans. And this was -- shall we go over the reasons?

PANEL MEMBER HAMMOND: Actually, just putting it up there is very helpful. Let me try to say it to make sure that I understand it, if that's okay?

So in the -- we're looking in the pink columns, the second row of data, and there are three uncertainty factors. We've just finished discussing the inter factor. And the consensus of the Panel was that instead of 1, we think that it should be 3. And the intra -- what we're talking about now is the intraspecies. And the question is whether 10 is sufficient? And it sounds me pea like we -- the discussion has been that that is -- that 10 is sufficient. Although, OEHHA had suggested 30. I think --

I think that is correct.

And then -- and that leaves again the fact that we're going to a different outcome leads to another factor of 10. So I'm going to -- am I interpreting that right.

DR. DuTEAUX: Just to clarify -- this is Shelley -- the 10-fold factor to cover developmental neurotoxicity is because there is some uncertainty whether the point of departure for acetylcholinesterase is protective of developmental neurotoxicity.

PANEL MEMBER HAMMOND: Right.

DR. DuTEAUX: So we've added that additional 10 to protect potential --

PANEL MEMBER HAMMOND: That's exactly how I understood it, yes. Yes. So what I'm hearing from the Panel, but if I'm wrong, that's fine, but I'm just trying to sum this up, is that the Panel is saying that the interspecies uncertainty should be 3, and the intra the Panel seems to be fine with 10. And I think that the -- changing the outcome, you know, from -- going from the cholinesterase to the neural tube issue, that there should another factor of 10. So that in the end, there would be a factor of 300. All right. And if -- you know, maybe we could kind of tie this up with that, or if people on the phone disagree or anyone here.

PANEL MEMBER ANASTASIO: This is Cort. My

understanding is that there was some question of whether intra should be 30, and not 10. So my --

PANEL MEMBER HAMMOND: That's correct.

PANEL MEMBER ANASTASIO: Yeah.

PANEL MEMBER HAMMOND: OEHHA has said 30.

PANEL MEMBER ANASTASIO: OEHHA has 30, and I believe that several members of the Panel have expressed support for the factor of 30 as well. Perhaps, those --

PANEL MEMBER BLANC: Dr. Blanc here. Yeah, I would say -- first of all, what you said is correct that the issue on the table seems to be 30 versus 10. My own view is I'm closer to Dr. Hammond's view that 10 is sufficient, bearing in mind that there's another factor of 10 for developmental neurotoxicity a special uncertainty if one is looking at the acetylcholinesterase pathway. And to me that takes into account certain of the arguments that I've heard about a factor of 30 as opposed to 10, because some of that is driven by vulnerabilities, which would mostly touch on developmental neurotoxicity, which is already embedded in the factor of 10. And so that's why I'm okay with 10 instead of 30, even though there may be greater fold variability in enzymes related to the cholinesterase pathway. But I think it would be important for me to hear, particularly from Dr. Ritz who voiced that in particular just to be sure that I'm not missing the

boat.

PANEL MEMBER RITZ: Yeah, I was just looking at the Smith article again. And they did have a lot of children in there, but not a lot of elderly. But yeah, generally, I would say the 10 is probably okay.

CHAIRPERSON KLEINMAN: So in terms of the -- where that 10 comes from for the intraspecies, is that, you know, following up on what EPA originally did taking 3, 4 pharmacokinetics and 3, 4 pharmacodynamic differences.

DR. KOSHLUKOVA: So if you look at this table here, you -- what U.S. EPA did in 2014, they calculated point of -- they calculated point of departures for different population subgroups. For general population -- for general populations, excluding children and pregnant women, they used the data-derived extrapolating factors coming from the PBPK model. Not exactly what you see in this table, but pretty close.

For chlorpyrifos, they used a data-derived extrapolating factor of 4, and for the oxon of 5. So that's how they calculated the final reference dose or concentration.

For the females of reproductive age and children, EPA did not use the full uncertainty factor of 10, because they felt that the model did not -- because the model

didn't use the pregnancy compartment.

DR. KWOK: Just to add on to what Dr. Koshlukova talked about, the model actually has two different versions. One is a pregnant version, the other is a non-pregnant version. In 2014, U.S. EPA used a non-pregnant version, just female. The 2017 paper by Poet actually add on to the pregnancy portion of the model, but still we're not sure everything in the model represent the pregnant female is enough for us to move forward with that. And because of that, that's where the 10 come into the picture, is because it kind of like covered the pregnant female. That not currently covered by the non-pregnancy version of the PBPK model.

DR. KOSHLUKOVA: So how do we use the model this would have been 4 -- 4? Based on the new -- based on the new data -- the new published pregnancy model, it showed that pregnant women -- pregnant female difference between the median and the most sensitive, the first percentile in terms of 10 percent cholinesterase inhibition is 3. So the -- and then it appears that the other subpopulation groups, the differences between the median and the most sensitive is about 4.

So we did not -- we stay with the 10, because there were still some concerns regarding the fetal compartment.

PANEL MEMBER BLANC: Dr. Blanc here. I mean, I think that there are probably a lot of ways to get to 10. So I think you should be -- you know, you should be supported in having taken that public health protective approach. And that we're certainly not discussing going below 10. And it is helpful for you to say that, in fact, your value of 10 is a bit more conservative than the EPA's value in some of their calculations. And so that takes us back to the question, is 10 sufficient and having -- and although OEHHA put forward one argument for why it might be 30, I think so far I've stated that I find 10 sufficient. I think Dr. Hammond said that, Dr. Ritz said that.

PANEL MEMBER GLANTZ: Stan said that too.

PANEL MEMBER BLANC: Stan in the back here is also supporting 10, so I think that leaves the Panel members who have not clearly spoken to this matter to say what they -- what they think, and then maybe we can put this too rest and give our stenographer a carpal free -- carpal tunnel-free period.

CHAIRPERSON KLEINMAN: Cort, do you have any comment?

PANEL MEMBER ANASTASIO: No, except to say it seems that 10 is relatively standard and so it seems appropriate here.

PANEL MEMBER BUCKPITT: I think 10 is appropriate.

PANEL MEMBER LANDOLPH: Yeah. This is Joe Landolph. I can live with 10 also.

CHAIRPERSON KLEINMAN: Okay. So let's move on.

Were there other issues that you wanted to bring up, so we have more?

DR. DuTEAUX: Yes. This is Shelley again. There is just a few other items that we took from the January 23rd meeting. Besides the direction to include the developmental neurotoxicity endpoint, and develop an RfC, which you see the draft numbers on the green columns. And now we have a charge from the Committee to go forward with changing the uncertainty factor -- the total uncertainty factor to reflect 300 instead of 100, which doing some quick math that would change the bottom column, the RfC, from 28.5 for children aged 1 to 2, to approximately 9.5 micrograms per meter cubed.

So the other items that we wanted to make sure the Panel knew we were -- we were working on include -- well, we actually in the December draft, the number that's on the very far left bottom column, the 2850, the 2-8-5-0, that's our new number. It's corrected from some model corrections that we did. So the document will reflect that number currently in the version that you have, the

December version. It says 2370, so we do have to make that correction throughout the document, including all of the tables of the aggregate MOEs. So we'll be making that correction.

We also understand from Dr. Araujo -- sorry, if I pronounced --

DPR ASSISTANT DIRECTOR VERDER-CARLOS: Araujo.

DR. DuTEAUX: Araujo. Sorry, I apologize for massacring his last name. He wanted us, as did Professor Ritz, to look additionally at human epidemiology, items that came from not only the agricultural health study, but other potential human facts, including cardiotoxicity lipidemia, Parkinson's Disease, which we had already presented some preliminary findings on, respiratory effects, so to fully -- or more fully account for human epidemiology, not just neurodevelopment in human infants and children.

We will be adding the quantitative exposure analysis from the epidemiology studies on cord blood and maternal plasma. This was also briefly our draft evaluation was briefly discussed during the January 23rd meeting where we will formalize that and add that into the next version of the document, as will the new developmental neurotoxicity studies in the animals. We've referred to that, and we have a table of some -- I believe

it's seven studies approximately from 2014 to 2017.

So we will be doing a thorough analysis of those data, and developing the point of departure from those studies and the reference concentration. And we will potentially include a discussion on the window of susceptibility, if we can derive such information from those studies. At this point, it looks like there is no specific window of susceptibility from those animal studies.

In addition, based on the January 23rd meeting and also our meeting with Professor Anastasio we need to go back and look at the air monitoring data, and either provide a summary or detailed explanation of those data, and why we used modeling outputs as opposed to the monitoring data. And if I remember correctly, our meeting with Professor Anastasio, he also suggested we look at secondary drift, and perhaps model that as well as just the prime -- as the primary drift as well.

Okay. And he's nodding in agreement.

And just to help, because we have had continuing discussions with registrants and stakeholders about the scenario of exposure, what we need to do is more clearly define the difference between a 21-day steady state inhibition of acetylcholinesterase versus what parameters we used for an exposure scenario. There was some distinct

confusion between saying that a 21-day exposure was not consistent with the label use recommendations for chlorpyrifos in this State.

So we need to further clarify and discuss that we were not intending to say that a 21-day exposure was an exposure scenario. It's simply the model parameter that gets to a steady state decrease of cholinesterase. So those are some of the issues that we took from the January 23rd meeting, again based somewhat on our draft discussion of several points, as well as comments that we received from meeting individually with Panel members.

Is there anything else from my colleagues here sitting at the table that we need to add?

PANEL MEMBER BLANC: Well, just -- Blanc on the phone. Just to reclarify, that based on the discussion today, there are three things, one of which is that the interspecies will increase to 3, as you've acknowledged. The other is that you will put in the -- in the -- in what is currently the green column the values for females, based on the toxicity to fetuses, where it currently says not applicable or not available. And -- so that's four rows.

And the final, and perhaps to me the major thing, is that as you draft your document, it won't present two equally promoted sets of values. It will pro -- it will

present a primary set of terms for -- derived from developmental neurotoxicity and as a contextual back-up will provide your acetylcholinesterase derived values. So that the table will have to change not only in terms of what is the first set of columns, which will be developmental neurotoxicity, but also in terms of how those columns are headed, one of which says "Human" and one says "Animal". They're both human. It's just the sources of some of the data.

So I think it's important for DPR to be very clear that that's what the Panel is indicating you need to do in terms of what is your primary pathway. That's certainly my view, and that's how I've interpreted all of the comments, or the bulk of the comments, that the Panel has made at the last meeting.

And I want to be clear from the other panels that I haven't -- Panelists that I haven't misread my colleagues on this.

PANEL MEMBER HAMMOND: This is Kathy. I just have a question for the Chair related -- this is coming out of Paul's comments. And I'm trying to figure out where we are? We haven't really discussed exposure as a Panel yet. And I have a lot of questions -- things to talk about there. Is that something we're doing at another meeting or -- I'm just not --

CHAIRPERSON KLEINMAN: Well, I --

PANEL MEMBER HAMMOND: It sounds like we're kind of wrapping up for the day, is that right?

CHAIRPERSON KLEINMAN: No, we're not wrapping up at this point. We said that we would deal with -- begin with discussing where we were from last week, but the plan was to start to address some of these other questions, which we had not touched on, and that's something I would sill like to do.

Now, one of the things that I discussed with Jim on the phone is that we originally planned, I think, this thing to run till, what, 3:30?

(Discussion off the record.)

CHAIRPERSON KLEINMAN: So before we go further, I wanted to get a sense of whether people were going to start fainting from lack of food? And if there was a need for food, maybe we could arrange to, you know, just get some sandwiches or something later or -- or should we -- yeah, I guess I wanted to get a feeling for do we want to just plow through till 2:30 and keep going or do people need a break?

Because we didn't have the stenographer, we didn't take a break yet. And maybe that would be a good idea to take a five-minute break. And that way I could talk to Jim about logistics. Everybody can do a --

PANEL MEMBER GLANTZ: Okay. Well, this is Stan. Just -- I mean, I'm fine to do that. I mean, I just want to concur with Paul's sort of summary of what I think we all agreed to on the first -- you know, on these issues. And I think if there's anybody who doesn't agree with that, it would be good to hear from them, because then DPR would get a pretty clear view.

And then my understanding was after we did this, then we were going to go on to the exposure stuff. And I'm happy to take a break. But I think just to -- so we have complete clarity, you know, does anybody disagree with, you know, Paul's statement right before you started talking, Mike, in terms of the first part of this discussion?

CHAIRPERSON KLEINMAN: I don't see anybody jumping up and down.

PANEL MEMBER GLANTZ: Okay. Well, so I think that -- I think -- you know, I think we've actually made quite a lot of progress. And I wanted to thank DPR and everybody else. And, you know, if you guys want to take a break. We've been sneaking out when nobody was looking.

(Laughter.)

CHAIRPERSON KLEINMAN: Svetlana had a comment.

DR. KOSHLUKOVA: I have a question to Dr. Blanc regarding the headings "Human" and "Animals". Can you

clarify what -- what is your request for us?

PANEL MEMBER BLANC: Well, all I'm saying is it's a little misleading, because both of them are relevant to humans, because that's what we're talking about. And, in fact, the data that drives what is currently the first set of columns and will become the second set of columns is, in fact, derived in part from animals, but we're applying -- this has to do with human risk. So I'm not going to get down in the weeds and suggest that you call it, but you know that's my point.

DR. KOSHLUKOVA: Okay. Understood. Thank you.

DR. DuTEAUX: And this Shelley. We'll likely just delete that row to better clarify. And the order of the rows, at least the pink row and the green row were in chronological order in terms of the versions of our document. This particular table, or a version of it, will be included in the -- in our final TAC evaluation document, maybe with or without the EPA one, because we do have another table in our document that compares other world regulatory agencies, and the values that they have come up with, and that might be a more suitable place to compare EPA against PRMA, which is Health Canada, versus Australia, versus EFSA, which is the European Food Safety Agency. So comparing those national organizations might be a more appropriate thing.

PANEL MEMBER GLANTZ: Yeah, this is Stan. I completely think -- agree with you. I think that's a really good idea.

DR. DuTEAUX: And just for clarification, even though I know Professor Blanc expressed his opinion, I believe what we heard from Professor Landolph was slightly different, in that we needed to present a full description of the data sets for both endpoints and -- and describe in the risk appraisal section the strengths and the weaknesses of both data sets. From that, I believe one could then glean, or assume, or come to the conclusion that one endpoint is stronger than the other.

But again, this is -- this is something we typically do in our risk characterization documents. If there are two especially two well-supported endpoints, we provide the argument for both. And that's what we did for 1,3-dichloropropene. We showed that on one hand, a portal of entry effect was well supported, as was a systematic effect. And --

PANEL MEMBER BLANC: Well -- Dr. Blanc here -- certainly I'm not arguing that you shouldn't discuss acetylcholinesterase. You have to make it clear in your documents that the -- that the value you're supporting is ultimately based on the neurodevelopmental and not present them as equally pros and cons, and that going forward one

could choose either one upon which to base regulatory action.

So I, as a Panel member, will not be satisfied with a document which is unclear as to what is being recommended. It needs to be -- it would need to be one or the other with a second as a sort of contextualizing approach, which we've often done both with you guys and with OEHHA, and it's always very helpful. I just don't want you to misinterpret that as being equivocal about ultimately what approach should derive the recommendation. And it should be the neuro -- developmental neurotoxicity endpoint based on the NOEL or LOEL depending on what study you use from the animal data for neurodevelopmental. That's my point of view.

PANEL MEMBER LANDOLPH: Well, this is Joe Landolph. You have both of them already discussed in your document, right?

DR. DuTEAUX: We can more -- we actually need to more fully develop the developmental neurotoxicity and develop charts of the margins of exposures and things like that.

PANEL MEMBER LANDOLPH: Right. So -- excuse me.

DR. DuTEAUX: So because the document will be go on -- will go oh to health based regulation or risk management directives, they need to see what those numbers

would be that would then affect the use of this pesticide in the State.

PANEL MEMBER LANDOLPH: Right. So you already have the binding to a acetylcholinesterase --

DR. DuTEAUX: We have the --

PANEL MEMBER LANDOLPH: -- mechanism fully discussed?

DR. DuTEAUX: We have those numbers fully discussed. However, it was -- it was -- we've had to correct that number. So all of the tables in the document have to be updated.

PANEL MEMBER LANDOLPH: Yeah, that's okay. But, I mean, you already have it in there.

DR. DuTEAUX: My recommendation would be to just leave it in there, and then, you know, justify why you're using the neurodevelopmental toxicity endpoint.

DR. DuTEAUX: (Nods head.)

CHAIRPERSON KLEINMAN: Okay. On that note, I think we should adjourn. I spoke to Jim and he suggests that we take a 30-minute break, so we'll reconvene at 1:00. And there is a sandwich shop down -- or cafeteria down below first floor, if anybody wants to get something there, and then we will be back at 1:00 o'clock.

(Off record: 12:30 p.m.)

(Thereupon a lunch break was taken.)

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

(On record: 1:10 p.m.)

CHAIRPERSON KLEINMAN: All right. I'd like to reconvene. And let me see, are our telephone panelists back on?

Paul?

Jim will go ahead and alert them that we're getting started again. But what we'd like to do now is turn to some of the other issues. And there were a lot of discussions about the exposure assessments. And while we're getting the pictures up, I thought it would be useful to have the Panel start off with comments on the exposure assessment if they have any. I know Kathy has some. And maybe start out with some of our questions and then give DPR the opportunity to present a little more data because we really didn't talk about it in detail in our last meeting. It was presented in a couple of slides. And so there are questions about the model -- the drift model, and also on the actual exposure assessment.

So I thought it might be good to just sort of go around the table and start with getting some ideas on -- you know, out there that we are -- we have some concerns over.

So, Kathy.

PANEL MEMBER HAMMOND: I guess -- this is Kathy

for the scribe. So are you going to present how you did the exposure assessment in the models? Was that intended or not?

DR. BARRY: This is Dr. Barry. I can --

PANEL MEMBER HAMMOND: I would -- I mean, I just would say that I found that the document was incomplete in terms -- I -- within the document, I really couldn't follow how you did what you did. I mean, it was kind of saying we use certain models without an explanation of the models and what they did.

DR. BARRY: Okay. So which part of the exposure assessment are you talking about, producing the air concentrations and the deposition or the actual calculation of the exposure?

PANEL MEMBER HAMMOND: I guess probably the air deposition, right?

DR. BARRY: Okay. Because there's a really detailed memo at the end where it's all laid out, so --

PANEL MEMBER HAMMOND: Do you mean in the appendix?

DR. BARRY: Yeah, um-hmm.

PANEL MEMBER HAMMOND: Oh, I didn't find that.

DR. BARRY: It's appendix --

PANEL MEMBER HAMMOND: Yeah. No. Appendix B, right.

DR. BARRY: Which appendix? I don't remember which --

PANEL MEMBER HAMMOND: I guess I didn't find that complete, no.

DR. BARRY: So the -- you're talking about the memo that I authored didn't answer your questions? It's appendix 2.

CHAIRPERSON KLEINMAN: Well, part of what we want to do is have this information on the record. So if it's in a memo, we need to get it --

DR. BARRY: Yeah, it's appendix 2, and it's a -- yeah -- okay. So you -- do you want background on the direction?

PANEL MEMBER HAMMOND: Actually -- well, I mean I suppose at this point, I'm not -- hmm. I'm not prepared to talk about that at this point. So.

DR. BARRY: Okay.

PANEL MEMBER HAMMOND: So if you want to -- and if you're not prepared to present --

DR. BARRY: Oh, no, I can talk about it, but I --

PANEL MEMBER HAMMOND: Okay.

DR. BARRY: -- but I don't think I was aware that we were going to be walking through in detail. But --

PANEL MEMBER HAMMOND: I mean, I -- again, depending on what's the most useful here, I can -- I have

a list of things I can talk about --

DR. BARRY: Okay.

PANEL MEMBER HAMMOND: -- from the exposure. Is that better, more useful for you all to do at this point?

DR. BARRY: Yeah.

DR. DuTEAUX: Well -- or if, in general, you wanted Dr. Barry to go over some of the major conclusions, we do have maybe four or five slides that she could start off with, and then if there's questions.

PANEL MEMBER HAMMOND: I don't mean to kind of ambush you, if you're not prepared.

DR. BARRY: Oh, no, it's okay. I don't think I understood that we were going to be doing a formal presentation. I thought we were going to have a discussion, so -- which is fine, we can --

PANEL MEMBER HAMMOND: I think we usually start with a formal presentation and then a discussion. That's all. But that's okay. I mean, I can -- as I said, I can just jump in or whichever you prefer.

DR. BARRY: So we have some background slides.

PANEL MEMBER GLANTZ: This is Stan. I'm back and Paul will be here shortly.

DR. BARRY: Okay.

CHAIRPERSON KLEINMAN: Thank you, Stan.

DR. BARRY: All right. So as I think --

PANEL MEMBER RITZ: And, hello, this is Beate and Jesús is also here just so you know.

CHAIRPERSON KLEINMAN: Welcome, Jesús.

DR. BARRY: So we're focusing on inhalation. So we'll focus on the AGDISP model, because that's what was used for the inhalation. And it's the Lagrangian principle model. It models the droplet cloud after it's been released from the nozzles on an aircraft. Well vetted. It was -- began being developed in the '60s by the military, and then has gone through several iterations and improvement to be the version that we're using now, 8.28.

So the AGDISP algorithms have been validated using the spray drift task force field data that was collected in 1992 and '93. It's judged to perform well. It tends to overestimate deposition, particularly in the far field. And it was reviewed pretty extensively by the U.S. EPA in 1997.

So -- yes, go ahead.

PANEL MEMBER HAMMOND: May I ask a question? I found myself confused in the term -- the use of the term "deposition".

DR. BARRY: Horizontal deposition.

PANEL MEMBER HAMMOND: What?

DR. BARRY: Horizontal deposition.

PANEL MEMBER HAMMOND: So deposition surface settling.

DR. BARRY: Settling. Settling. Um-hmm.

PANEL MEMBER HAMMOND: Not lung deposition.

DR. BARRY: No. No. That's --

PANEL MEMBER HAMMOND: Because it's a model that's supposed to modeling concen -- air concentrations. But then it does go further to say -- no. I'm sorry that I'm misunderstanding.

DR. BARRY: Okay. I need to answer the questions. Okay. So the model is a mass conserving Lagrangian first principles model, which means that it has a certain amount of mass that the released from the aircraft based on the gallons per acre. It's liquid formulations. Okay. So it's a liquid tank mix -- excuse me, a liquid tank mix. You could have dry flow -- anything that can be put into a liquid tank mix. So you have however gallons per acre was put into the -- you know, the aircraft tank, and then the active ingredient, which in this case is chlorpyrifos.

So then you have this -- you have the application process, which is flying, you know, back and forth along a field, assuming the wind direction is perpendicular to the aircraft. So it's kind of a worst case pushing things offsite. Okay. So in terms of drift.

So the mass is released at a certain rate. So you have a certain total amount of mass that's released during the application. That mass is conserved, and it goes into the off -- anything that goes off-site either gets gravitational settling, which is where the horizontal deposition comes from or what's left in the air. The way the air concentrations are estimated is that you have a flux plain, and the model calculates what's passing that flux plain in terms of the air concentration, the mass that's in the cloud of --

PANEL MEMBER HAMMOND: So the model does estimate air concentration --

DR. BARRY: Yes.

PANEL MEMBER HAMMOND: -- as well as deposition?

DR. BARRY: Oh, yeah, yeah. Yeah.

PANEL MEMBER HAMMOND: And I know that in fact you end up being interested in both, because later the dermal and food and all of that is important for the deposition. But you -- I thought you started out saying you were doing inhalation discussion.

DR. BARRY: The reason that I'm using this model is that we're looking at inhalation as the TAC process. This model is the state-of-the-art for estimating air concentrations associated with spray drift. It's -- it is the latest version model that would do that, so I hope

that clarifies things.

Okay. So the -- there is another model. It's AgDRIFT. That's what we use for the orchard airblast and the ground boom for the horizontal deposition, because unfortunately when the spray drift task force did their studies, Ag -- there's two models, AgDRIFT and AGDISP. And AgDRIFT is what the spray drift task force developed. It's a proprietary kind of black box-ish type model that EPA uses for labeling. But that's what's used for horizontal deposition for orchard air blast and ground boom.

So we still have to use that model, but the -- the algorithm used to estimate the air concentrations is not the most recent, most developed cutting edge version. That's the -- the AGDISP is a separate model, 8.28.

So I hope that's not too confusing, but there are two models being used. The one for air concentration AGDISP 8.28, and the one for -- and horizontal deposition for aerial air -- for aerial applications. And then for horizontal deposition, ground boom, and orchard airblast, we're using AgDRIFT, because it's the only tool available. And it's based on field data. I reviewed the field data. It's been vetted. It's basically, you know, what's used by EPA to label.

PANEL MEMBER HAMMOND: So DRIFT is what gets

deposited, and the AGDISP model is what's the air concentration, is that what you're saying?

DR. BARRY: AGDISP does both.

PANEL MEMBER HAMMOND: It does both.

DR. BARRY: Um-hmm. But AgDRIFT for orchard airblast and ground boom only does horizontal deposition. That's all there -- that's all that's available.

PANEL MEMBER HAMMOND: There's no air -- and that's --

DR. BARRY: And that's why we have that --

PANEL MEMBER HAMMOND: Okay. And that's the reason you're using -- okay.

DR. BARRY: That's why we have the charge question, yeah, because we don't have a model that really estimates air concentrations associated with orchard airblast and ground boom. So I hope that helps.

And the reason 8.28 is what we've moved to is that they've improved the physics of how they understand what happens to the droplets, as they evaporate in the droplet cloud that is ultimately formed from the nozzles when it's released from the nozzles of the aircraft. Okay.

PANEL MEMBER HAMMOND: All right, and so some questions on that. This says it's for droplet evaporation. So when you say you're improving that, is

that the particle size distribution and how that changes --

DR. BARRY: Yes.

PANEL MEMBER HAMMOND: -- from evaporation?

DR. BARRY: With time and distance.

PANEL MEMBER HAMMOND: With time and distance.

DR. BARRY: They're accounting for the higher humidity in the -- they accounted for the higher humidity in the droplet cloud that they weren't accounting for before. A couple of things have happened. The time still has been reduced and how it calculates that, and then also how it handles the evaporation has been improved.

PANEL MEMBER HAMMOND: Okay. So there is a -- from that, there's a dis -- particle size distribution, which is calculated at various distances and --

DR. BARRY: Yes.

PANEL MEMBER HAMMOND: -- and various heights?

DR. BARRY: Yes.

PANEL MEMBER HAMMOND: So I would really like to see those distributions, because that's coming -- it comes up later in some of the exposure discussions.

DR. BARRY: Yeah, and some of that information is in appendix 2 in the back of that memo. There's a set. It's only less than 10 microns, because at the time we weren't really sure what we were going to be doing with

the droplet data.

PANEL MEMBER HAMMOND: Okay. Because I actually think that that's a limitation that -- a serious limitation.

DR. BARRY: Okay.

PANEL MEMBER HAMMOND: Can the model predict large -- larger size particles?

DR. BARRY: Oh, yeah, yeah. Yeah, I only reported less than 10 microns because it was what was relevant to the discussion we were having when we completed the draft that you have.

PANEL MEMBER HAMMOND: I was going to say --

DR. BARRY: But I --

PANEL MEMBER HAMMOND: I was going to say that's -- actually, I think, larger sizes are important as well --

DR. BARRY: Yeah, and remember --

PANEL MEMBER HAMMOND: -- and maybe we'll have that discuss -- I want to get to that discussion.

DR. BARRY: Yeah, and remember that we don't assume a differential of droplet spectra. We assume spectra. We assume everything gets absorbed right now. We don't -- we don't account -- we -- I'm not accounting for droplet spectra.

PANEL MEMBER HAMMOND: So it's 100 percent of

whatever is in the cubic meter around my face --

DR. BARRY: Yes.

PANEL MEMBER HAMMOND: -- is assume that inhaled that.

DR. BARRY: Yes.

PANEL MEMBER HAMMOND: There's no -- okay. Okay. I guess that wasn't fully clear to me either. All right.

DR. BARRY: And that's a question we've had, because we've gotten comments. That's why one of the charge questions asks that, because, you know, we've gotten comments about that. And --

PANEL MEMBER HAMMOND: And I certainly saw those in the recent comments we got as well.

DR. BARRY: Um-hmm. Um-hmm.

PANEL MEMBER HAMMOND: And I do want to address those eventually, but I couldn't understand what you'd written well to get that.

DR. BARRY: Okay. Okay. So this is here to talk about again the horizontal deposition that is related to orchard airblast and ground boom. So those horizon -- unlike AGDISP, which is a Lagrangian principes, the model tracks ensemble of droplet clouds, and how the droplets settle.

The AgDRIFT model is an empirical model. It's based on horizontal deposition curves that were developed

with the spray drift task force field data. So just so you understand the difference between the horizontal deposition values for air blast and ground boom versus aerial. So aerial is much further along technic -- you know, in a scientific and technical sense.

PANEL MEMBER HAMMOND: And when you adapt these and use them, do you correct for different vehicles and the volatility of different -- the vehicle in which the pesticides is included?

DR. BARRY: You mean for ground boom and orchard airblast?

PANEL MEMBER HAMMOND: Um-hmm.

DR. BARRY: No. We use what comes out of the model according to application type, which is different kinds of orchards or how high the boom is on a ground boom, and what the application rate is. And the reason for that is that these are based on a observed values. So it's what was recorded on -- what was captured on horizontal sampling media in the field studies. And then statistical analysis was done in order to fit those curves.

PANEL MEMBER HAMMOND: But were field studies done using this -- the same composition as what we're looking at for -- in this document?

DR. BARRY: Okay. Yeah, I know. Okay. Thank

you.

PANEL MEMBER HAMMOND: In other words, the solve of the vehicle in which the chlorpyrifos is in and --

DR. BARRY: Yes.

PANEL MEMBER HAMMOND: -- the chlorpyrifos itself.

DR. BARRY: Okay. So one thing that is -- underlies all of this is that it assumes that basically spray drift is AI independent. Okay. So --

PANEL MEMBER HAMMOND: Is what independent?

DR. BARRY: Is active ingredient independent. So if you have a tank mix that's liquid, that it won't matter whether it's chlorpyrifos, or whether it's glyphosate, or, you know, any other AI, you have a tank mix that was applied by orchard airblast or by ground boom, and then you -- you did the application, and you had samplers out there downwind, you collected the horizontal cards, it'ss -- the results are expressed in fraction of application rates. And it's not associated were a particular AI. So it is generic. It's assumed to be generic.

PANEL MEMBER HAMMOND: I'm going to ask a favor of you. Please don't use all those acronyms that I don't know.

DR. BARRY: Oh, I'm sorry. Okay. So --

PANEL MEMBER HAMMOND: Say words. I tell my students I know two acronyms, EPA and OSHA.

(Laughter.)

DR. BARRY: I will remember that. So it's generic with respect to the pesticide being applied, the active ingredient. So -- and that was the whole -- that was the whole premise of the spray drift task force in developing that data set. And it is really the foundation data set for all spray drift research at this point.

PANEL MEMBER HAMMOND: Do they use the same carrier vehicle in all --

DR. BARRY: It was water.

PANEL MEMBER HAMMOND: What?

DR. BARRY: It was water.

PANEL MEMBER HAMMOND: It's always water?

DR. BARRY: Um-hmm.

PANEL MEMBER HAMMOND: Is that what it is?

DR. BARRY: The experiments are done with water, the ones with these --

PANEL MEMBER HAMMOND: The experiments are done with water. Is the actual application done with water?

DR. BARRY: I would say commonly. Of course, there are oil based application and things like that

PANEL MEMBER HAMMOND: That's what I was wondering.

DR. BARRY: But, you know, I couldn't give you -- I'm not going to hazard --

PANEL MEMBER HAMMOND: How about for chlorpyrifos?

DR. BARRY: I'm not going to hazard what water based and what's not, because I don't have that information.

PANEL MEMBER HAMMOND: Because that would make a different, because it would change particle size over time, right? You have different evaporation rates, and particle size --

DR. BARRY: Well, maybe.

PANEL MEMBER HAMMOND: -- distributions, which would then lead to different settling rates versus not?

DR. BARRY: You might get less drift. It might be less horizontal deposition if they're not settling. So I mean, we can have a whole conversation about what would happen about that, but the fact of the matter is that this data was based on water-based applications. So -- and that's for orchard airblast and ground boom, the horizontal deposition. So what's lacking from those two application groups, or methods, is the air concentration aspect of it.

So anyway, getting back to the field studies. They were conducted under a cooperative research agreement

with EPA, both with the pesticide -- Office of Pesticide Programs and Office of Research and Development. Those data were reviewed by a spray drift -- a scientific advisory panel. I participated on that panel. I reviewed the data as a peer reviewer. You know, so, you know, I will stand by the quality of this data basically, and it -- and, you know, why we're using what we're using.

I don't remember what the next slide is.

(Laughter.)

DR. BARRY: Okay. These were my scenarios. And this is with respect to orchard airblast and using the air concentrations generated with the AGDISP model, which is why it's six pounds per acre, because you can't apply six pounds per acre by air for chlorpyrifos. It's not labeled for that.

But for orchard airblast, there is an application -- there is a use that's allowed for six pounds per acre. It could be any -- it could be application rate. This is just an example.

So the air concentrations were generated using the fixed wing aircraft algorithm, the model, AGDISP. And the swath width was 60 feet. I used 50 swaths, which is 3000 feet wide, which results in about 207 acres. And roughly in that -- the mass released in that particular Application would 1236 pounds. And at 145 miles an hour,

it would take about 11 minutes.

So you can see it goes on really fast. And you can imagine the air concentration might be kind of high associated with that application, which this is getting to arguing, you know, the use of that fixed aircraft air concentrations, as opposed to the orchard airblast application, 16-foot width, 60 swaths, that results in 640-feet wide, about 22 acre -- 21 acres. And you're going to release about 127 pounds in that time, and it will take about four hours at three miles an hour.

So -- go ahead.

PANEL MEMBER HAMMOND: So sorry.

DR. BARRY: Oh, no, no, no.

PANEL MEMBER HAMMOND: The -- I have an image of what an orchard airblast is, but I don't know if it's the right image. So could you please describe -- I think I know what it is.

DR. BARRY: Yeah, and I don't have a -- I'm sorry, I didn't bring a photo, but it's -- if you can find something on the internet maybe. It's a big piece of equipment. Probably taller than me or maybe my height, and then it's got -- the whole -- the whole point of an orchard airblast application is that you want to go up and into the foliage. And it's --

PANEL MEMBER HAMMOND: Oh, is it going into the

foliage from below --

DR. BARRY: Yes.

PANEL MEMBER HAMMOND: -- or over the foliage?

DR. BARRY: No, no. What I'm talking about is in. There are some that go over. That would be vineyards and things like that. There are -- those are called wraparound, and yeah, there are some wraparounds. The drift associated with wraparound is not as high as orchard airblast -- the airblast.

So here we go. Those are not quite -- yeah, yeah, the guy driving. Yeah, there we go. One over, one over. No, to the left, to the left. Down. Yeah, that's good. That one is good. So, you know, these are typical.

So fine droplet spectra. The thing about airblast is that you don't get a lot of horizontal deposition outside or the orchard because -- just because of the nature Of the application.

You know, you do get material left in the air. There's no doubt about that, but it -- but the whole process goes on much more slowly. And if you think as an air dispersion modeler, wind speed doesn't stay in a direct position. The -- the orchard airblaster is changing positions. The same thing with ground boom actually too, it's changing position pretty slowly, three, four miles an hour, whereas the aircraft, you know, again

1200 pounds of the material boom into the air in 11 minutes, so -- which is why it's a worst case scenario in terms of air concentration.

So where was I going with that?

That was why I argued to use the fixed wing as the surrogate for air concentrations for orchard air blast -- oh, here you go -- orchard airblast and ground boom.

Yeah. Yeah. So the basic -- the basic thing to remember is that the process is much slower than an aerial application. And you have choice for -- you have a chance for air dispersion to occur that would -- doesn't necessarily occur when you're doing an aerial application.

Okay. Maybe while I'm talking, what's the next slide. And do you need a -- do you need a ground boom -- a ground boom application? Do you have a sense -- it tends to -- yeah. Okay. Because those go downward, yeah.

PANEL MEMBER HAMMOND: I just wasn't sure.

DR. BARRY: Yeah, yeah. It's good to see it obviously.

Okay. So this -- this slide is here because one thing that EPA didn't do was use the model beyond -- there are sets of deposition. And you're allowed like 20 swaths is the maximum for orchard airblast, 20 swathes, so 20 back and forths. But those end up with being pretty small

applications, because the if you're only 16 feet times 20. So those are a lot smaller than what our use patterns were showing. You know, so -- so I elected to overlay, you know, deposition from multiple swaths. And then what I did, and what's outlined in the memo, is figure out how far back you have to be before none of the material from that upwind swath ends up off-site. And that's where we ended up, you know, with the number of swaths. It's either 40 or 60, depending on the application method. So this just illustrates, you know, the idea of how that was done.

So for -- and that wasn't necessarily with -- necessary with aerial, because 50 swaths is huge, 207 acres, so I didn't have to do that with aerial. But with ground boom and orchard airblast, you know, it was necessary to go beyond one set -- one set of 20 swaths. So that's just a visual of how that was done.

So we did account for larger applications than the typical set that's in the models.

This is like Christmas. I don't know what's coming.

(Laughter.)

DR. BARRY: It's like I don't remember. This is from January. Oh, this also underpins the idea that using the fixed wing aircraft air concentrations is a health

protective assumption, because what happens is as -- if you have a process -- and this is for a point source. So if you've got a moving source, it's even more.

As averaging time goes up, your air concentration goes down. If you have a fixed -- if you have a fixed receptor, you know, air concentration goes down. So if I have an aircraft that's putting material into the air very quickly, that -- you can imagine, if you're a receptor downwind out in the field, you're going to potentially be exposed to a higher air concentration than if you're standing downwind of an orchard air blast in one fixed place and the thing is going back and forth, and it's three miles an hour, and 127 pounds, rather than 1200 pounds.

So I just wanted to give, you know, the Committee of an idea of what happens with averaging time, and air concentrations in the process of having mass released from an application.

Yeah. Okay. So we were asking about droplet spectra, and I think Cort had this question also. So this is not a particular height. This is the entire cloud, because we've had discussions and comments about how it needs to be cut at a particular height, and, you know, to account for breathing height. But I'm not -- yeah, we could have a discussion about that.

But -- so this shows what happens with that cloud and the droplet spectra with increasing distance. So the blue --

PANEL MEMBER HAMMOND: So just as a comment, the last side and this slide are not in the memo, right?

DR. BARRY: I think we might have -- I developed this, I think, after the last --

PANEL MEMBER HAMMOND: Yeah, and that's part of what -- these are some of the things that I think are important.

DR. BARRY: Okay.

PANEL MEMBER HAMMOND: Okay.

DR. BARRY: Yeah, I think I developed this after the last meeting, and after meeting with Cort too, because he had the same question.

(Laughter.)

DR. BARRY: Great minds think alike, right?

So the blue curve is basically field edge or 10 feet. And the red curve -- field edge or at 10 feet. Basically, 10 feet is as good as field edge in my opinion.

Okay. And then the red curve is at 100 feet, and then the green curve is at 1000 feet. So you can see that you're getting settling of the bigger droplets, which means that more of the cloud is smaller -- smaller droplets -- there's two things happening, the big droplets

are settling -- the bigger droplets are settling, and then also the droplets are left reducing because of evaporation.

So, yeah, as you go downwind, you're -- the 50th percentile, you know, decreases. So that can be accounted for or not. Right now, DPR is assuming that 100 percent of the cloud gets absorbed at the breathing height. So, you know, the question is do we account for it or do we not account for it? If we do, how do we do it?

PANEL MEMBER HAMMOND: And that was one of the comments, right?

DR. BARRY: Um-hmm. One of the charge questions.

PANEL MEMBER HAMMOND: Would you like me to comment on that?

DR. BARRY: Um-hmm, sure. Yeah, definitely.

PANEL MEMBER HAMMOND: Well, first of all, there was a comment -- there's a statement about respirable and inhalable. What do you mean by inhalable? How are you defining inhalable?

DR. BARRY: That's a good question.

PANEL MEMBER HAMMOND: I mean, I have -- there is a definition that I use in my classes --

DR. BARRY: Right, but I think you talked about that --

PANEL MEMBER HAMMOND: But I want to know what

yours is.

DR. BARRY: -- in January.

PANEL MEMBER HAMMOND: What?

DR. BARRY: I think you talked about that already.

PANEL MEMBER HAMMOND: Oh, did we? Okay.

DR. BARRY: I think you did, but I don't -- I didn't know what we wanted to use to tell you the truth, so I just summarized less than 10 microns -- 10 microns or less just as a summary in my appendix of my memo, but I mean, I all -- I'm open to interpretation, and if we adjust at all.

PANEL MEMBER HAMMOND: So, yeah, I mean, I actually think your decision is a wise -- it makes sense. But the -- to say respirable is what generally makes it into your keep lungs. I do remember talking about this. And the inhalable is what can enter the body at any point, and at even 100 micron particles, 50 percent can pass through the nose, and even more through the mouth.

DR. BARRY: Um-hmm.

PANEL MEMBER HAMMOND: And since we're not talking about the target organ here is not the deep lung, right? It's not the alveoli. So therefore, you know, going into respir -- the respirable is not necessary, in my view, that we -- you know, the people are absorbing a

dose that could be relevant, if they're larger.

So, yeah, I think some people use the terms interchangeably, and I saw some issues there.

And I -- yeah.

DR. BARRY: I started looking it up. I'm like, okay, we need to discuss this. Right, because I thought 100 also.

PANEL MEMBER HAMMOND: And if you would like, I can send you some material on that, you know, in terms of it's something that some people, like Bill Hines at UCLA has done a lot of work, in actually measuring what really can get into the body.

DR. BARRY: And what gets into the body is what's important.

PANEL MEMBER HAMMOND: And it's much more -- much larger -- much higher percentages of larger particles than people think.

DR. BARRY: Um-hmm.

PANEL MEMBER HAMMOND: It's -- they're not going to make this at the alveoli. So like if it's silica, it doesn't matter, you know, for silicosis, but it does -- but if we're talking about a pesticide, then it can matter.

DR. BARRY: Yes, um-hmm.

PANEL MEMBER HAMMOND: So that makes sense.

DR. BARRY: Yeah.

PANEL MEMBER HAMMOND: And I thought it was interesting -- okay, that's -- yeah -- no, that's a different point that I've got there. Okay.

PANEL MEMBER ANASTASIO: Sorry. This is Cort. Just to add to what Kathy was saying, yeah, so this is all related to charge questions number 5, right? And -- right. And you assumed that --

DR. BARRY: (Nods head.)

PANEL MEMBER ANASTASIO: -- any size was inhalable?

DR. BARRY: Or into -- yes, um-hmm -- or into the body, yeah, um-hmm.

PANEL MEMBER ANASTASIO: Right. And I would agree with that. I mean, if you look at this, 100 micron cutoff, you've got 90 percent of the mass even if field edge is inhalable. So I think the way you treated that was is the right way.

DR. BARRY: Okay. That was kind of why we left it the way we did, you know, in the draft you have.

Okay. So I don't know if we need this one. This --

PANEL MEMBER HAMMOND: Just I think because it's related. You haven't talk about it, but I think it's related to that. There's been some criticism of your not

including the vapor phase or that you should only include the vapor phase. I've seen both of those comments, right?

Now, you chose not to include it, correct?

DR. BARRY: We did not include it because of the acetylcholinesterase approach to begin with. And that was -- that was consistent with EPA's call, because originally they were looking at vapor also. But then a new -- a study was submitted, the nose-only vapor study that showed that there was not more -- 10 percent acetylcholinesterase inhibition was not reached at the saturated vapor pressure, because EPA had done some modeling --

PANEL MEMBER HAMMOND: Right.

DR. BARRY: -- based on a flux study. And they were actually producing concentrations -- estimated air concentrations that were higher than the saturated vapor pressure, so -- yeah, so that -- you know, that had to be looked at obviously.

And then in the course of that, a new study on the effect of the vapor was also submitted. And that's when EPA set aside that we're -- in the context of acetylcholinesterase, we're not going to worry about this.

As we move away from that, as we've discussed, you know, something that needs to be considered, and that's secondary drift. That's not primary, because we're

talking about primary and secondary actions here now.

And, you know, that can be looked at a number of ways. We can use our own air monitoring study network results for that, because, you know, that represents that other ambient part. We can look at the flux study. There are problems with the flux study unfortunately that the -- I'd have to go back and review it. I haven't looked at it that closely in several years.

But, you know, it's a possibility to do dispersion modeling. So, you know, there's ways that can be dealt with, but we should all be clear that the spray drift is still going to drive it. The spray drift, the primary drift is definitely going to drive it.

PANEL MEMBER HAMMOND: Right. No, it's pretty clear -- I mean, I actually -- you know, it's pretty clear to me that you're -- even if it's saturated that the vapor is a small percentage of the total, right?

DR. BARRY: Yeah.

PANEL MEMBER HAMMOND: But I think you may as well add it in, because people definitely take it in. But I think to exclude the particles is -- doesn't make sense. So, you know, I would add it in knowing you're adding in a small number, but you have -- you haven't neglected the vapor, so people don't think that, you know, it's there.

DR. BARRY: Yeah. Yeah, and that point is

definitely well taken.

PANEL MEMBER HAMMOND: On the other hand, if just assume that everything is inhaled that gets -- well, actually the vapor will travel further -- that's another thing --

DR. BARRY: Yeah, yeah.

PANEL MEMBER HAMMOND: -- than the particle. So that's actually another piece.

DR. BARRY: And It's a different process. You know, it's a different time in the whole process too.

PANEL MEMBER HAMMOND: Right. So there may need to -- you probably do need to look at that as a separate thing, because -- yeah, it becomes different.

DR. BARRY: Um-hmm.

PANEL MEMBER HAMMOND: But I agree that it will be in the -- the near vicinity. It clearly is a small percentage of the total, but I would count it as part of the total, and do it for that purpose. But at some distance, it may be the majority.

DR. BARRY: Oh, yeah, yeah. I would definitely agree with that.

PANEL MEMBER ANASTASIO: Well, just -- again, this is Cort. Just to follow up, you know, very short time scales after application, yes, mostly aerosol. But then all that material that deposited on the field, right,

then you get the secondary drift, the vaporization. So I think integrated over the longer exposure times, it may not be negligible.

DR. BARRY: Right. And they -- but we have to be in the context of our -- the time period of our RfC though, right? The one-hour I think is what we're looking at.

PANEL MEMBER ANASTASIO: But -- yes, but although when we talked on the phone, didn't you tell me acute could be up to, what was the longest period, a week?

DR. BARRY: Oh, yeah, Eric.

DR. KWOK: It's kind of a working definition when we define the short term. So we define anything at the timeframe less than a week, call it short-term. So as Dr. Barry referred to, it really depends on the actual focus in terms of the exposure time, so -- but, in general, we define a time frame so that we can actually match the exposure timeframe of the toxicological endpoint they usually identify, because as you realize, animal study they are not conducted at the same time frame the exposure occur. So we have to make some kind of like accommodation, so that when we pull an environmental animal study, that it will be reasonably matched with the exposure timeframe that we are talking about.

PANEL MEMBER HAMMOND: Now that the endpoint is

changing, that might have to be reconsidered what's the appropriate timeframe. I mean, it may not change, but I'm just saying that you need to think it through.

DR. KWOK: Yes, yes.

DR. BARRY: Yeah. The timeframe of the DNT threat -- number is -- has to be specified. And if it's still an hour, then, you know, we're kind of in the same framework. I don't know what it's going to be not being the toxicologist. I leave that to them. But, yeah, I definitely --

PANEL MEMBER HAMMOND: No, you have to ask your toxicologist to tell you.

(Laughter.)

DR. BARRY: It all depends on the averaging time of the threshold of interest. But yeah, we'll be -- we'll definitely be discussing the secondary movement in the document. So that's -- well, this is just the -- I guess we can talk about this.

These are illustrations of assuming that your -- the wind is all going from every direction towards a single house, which is not what happens in the real world, and then -- do the next one, Svetlana, please.

This is what actually happens. So you can have a lot of applications going on, and only one or two of affect a particular location over a short period of time.

Now, when you start talking about, you know, longer term exposures, then you have to worry about patterns and things like that.

But we're -- the exposure assessment that I did looks at single applications over, you know, one hour time period for air concentration, and one and a half hours for rolling around on the grass of a 50-foot wide swath. So that would be -- you know, it's a different scenario than thinking about a regional pattern, only because of the acetylcholinesterase endpoint, and the dermal endpoint.

So it all goes back to what is the endpoint and what's the averaging time of the endpoint.

PANEL MEMBER HAMMOND: So I think that -- yeah, that's exactly right. And I think there will be that need to, if we're changing the endpoint, to see it cascade through how that affects a lot of the document. It's more than just that table, but it --

DR. BARRY: Agreed.

PANEL MEMBER HAMMOND: -- then becomes this how do we do the exposure assessment.

DR. BARRY: I was already thinking about that.

PANEL MEMBER HAMMOND: What's the relevant time.

DR. BARRY: Yeah.

PANEL MEMBER HAMMOND: Along that line, there was -- I think I remember reading something about there's

an interval -- is that the right term? -- the interval between how often you can actually spray a particular field? Like, it might be 30 days for some crops and some crops can be twice in a month, but, you know, those intervals.

And therefore, that was the interval that you assumed -- whatever that interval was, that was -- you said it was that frequently. But what about did you consider what if -- this might be more orchard airblast than aerial, but you could spray field A on Monday, but on Tuesday you might spray field B, but field B could still be, you know, near and contributing to a school or something nearby.

DR. BARRY: That's a good question. This -- this exposure scenario, and the MOEs are based on a single application in a single day.

PANEL MEMBER HAMMOND: Right, and that's what -- and again, I guess that's what I'm trying to say is I think we -- you might want to consider. You know, you could look at that, and then say, but the next day there might be this exposure, the next day.

And, you know, the developmental effects probably are not on the same timeframe, so that would also contribute to that.

DR. BARRY: Yeah. So that will go back to the

time period of the threshold that we're looking at.

PANEL MEMBER HAMMOND: So I'd just encourage you to also look at other fields being sprayed, rather than just both the same field being sprayed again.

DR. BARRY: Um-hmm. That was all the slides I had. So that was all the slides I had. So if anybody has anymore questions, I'm happy to --

PANEL MEMBER HAMMOND: I have other things, comments I had about the exposure. They're not necessarily just following from that.

You have a comment about granular product was omitted.

DR. BARRY: Um-hmm.

PANEL MEMBER HAMMOND: Could you tell me what a granular product is again. I can imagine, but I don't want to imagine.

DR. BARRY: I think like fertilizer, like fertilizer that you'd put on your lawn. It's like that kind of like pebble -- not pebbles, but I mean --

PANEL MEMBER HAMMOND: Right, so it's applied directly to the ground.

DR. BARRY: Yes.

PANEL MEMBER HAMMOND: So I think maybe you need to say that --

DR. BARRY: Okay.

PANEL MEMBER HAMMOND: -- because one could spray a gran -- I think there are granular products that are sprayed as well.

DR. BARRY: And they can be put on by air too.

PANEL MEMBER HAMMOND: That's what I meant, airborne.

DR. BARRY: Um-hmm.

PANEL MEMBER HAMMOND: So I think that there -- if you had a granular product that was put on through air, then you would want to include it in your things, as opposed -- now, if it's put in on the ground, I guess, that's where the vapor pressure might come into play with that.

DR. BARRY: Right. Yeah. You mean if it was incorporated -- soil incorporated or just put right in the ground?

PANEL MEMBER HAMMOND: Right. Right. Right.

So I think I -- so I think -- again, I would rethink what -- whether there could be significant exposure from that kind of product.

DR. BARRY: Okay.

PANEL MEMBER HAMMOND: But I wasn't sure fully how that went. I'll have to go back. Oh, the house dust. This is kind of skipping now away from the -- sorry.

DR. BARRY: This is Dr. Kwok.

PANEL MEMBER HAMMOND: On house dust there's a nice graph. And you have the -- the changes in the house dust before and after the banning of indoor products.

DR. KWOK: That's correct.

PANEL MEMBER HAMMOND: Pardon?

DR. KWOK: That's correct. Yeah, the graph actually show that before 2000 when the indoor use restriction was severely reduced was this, you know, after 2000. And then because the data actually originated from the CHAMACOS in the same neighborhood. So I think that represented it enough, because they, you know, pretty much under the same environment, they collect the house dust before and after. And the graph show there was a change, in terms of the use, so as to how dust concentration collected, at least at the same community.

PANEL MEMBER HAMMOND: Yes. No. My concern -- I liked the idea of all of that. But the actual graph, what concerned me was that the graph -- I now have to find it -- was of the maximum. Just the dots were of the maximum concentration. And the maximum is a very unstable number. And then you talk about the ratio of the max -- ratio of the maximum before and after, and that's a very unstable number.

In other words, if you collected 10 more samples or 100 samples, you might have a very different maximum.

So actually -- so -- yeah, so those red dots, right, those represent single samples, right?

DR. KWOK: That's correct.

PANEL MEMBER HAMMOND: And so we don't really know. That's not a good estimate. So I would -- I would strongly suggest, since they have a lot of data -- a lot of data is hidden there, you know, that they -- they have more than one dust sample, right, that one do a say a box -- a whisker plot of those data. And that would be a much better representation.

And, you know, there are ways in which you can -- you can statistically look at the data. And if you look at the distribution of the data, and, you know, the geometric means and standard deviations, you can actually predict the 99th percentile, which often will be higher than the maximum of a sample you've collected.

So if you want to do a 99th percentile calculation, you could do that, or 95th percentile, if you wanted to do -- I mean, it's just -- and maybe we don't need to do that for this, but I think that putting a single point, when there's much more data available is just --

DR. DuTEAUX: So this is Shelley. Just asking for clarification. Eric, do you remember in Bradman et al. if they had just summary data, or if they had --

DR. KWOK: I'm pulling up that reference now, because I don't remember.

DR. DuTEAUX: And it might be -- because occasionally, we have difficulty in getting actual data points.

PANEL MEMBER HAMMOND: I would hope that -- I would he would have -- I don't know the paper.

DR. DuTEAUX: But we might -- we might ask you to intervene on our behalf to ask for some raw data would be wonderful.

PANEL MEMBER HAMMOND: I would be willing to do that. I would be willing to do that.

DR. DuTEAUX: Okay. Thank you, but Eric is pulling up the paper right now.

CHAIRPERSON KLEINMAN: Cort, did you have any comments you wanted to make?

PANEL MEMBER ANASTASIO: (Shakes head.)

CHAIRPERSON KLEINMAN: Okay.

PANEL MEMBER HAMMOND: While you're doing that, I'll just talk a couple of other things.

One of your -- I think you want -- again, there are a lot ways in which changing the endpoint will change some of what you want to write in the exposure. One of the them would be, for instance, going back to including women of child-bearing age, having a line for that, for

instance. And I haven't done this completely, but table 34 on page 110, you know, I think you want to then, at that point, include women of child-bearing age, if we're now doing a developmental endpoint. But I just --

DR. BARRY: Yeah, we can expand the tables for sure.

PANEL MEMBER HAMMOND: Yeah, I think just kind of thinking that through. And in the food only discussion -- what?

DR. BARRY: It's 34.

PANEL MEMBER HAMMOND: I have it on page 110, table 34, I think it was.

DR. BARRY: Thirty-four.

PANEL MEMBER HAMMOND: I mean, this is not a big deal. I mean, it just was something -- this is along this line. It's really illustrative more. Maybe that was it. Yeah.

DR. BARRY: Yeah.

PANEL MEMBER HAMMOND: So if you're talking about food consumption --

DR. BARRY: Oh, that's food, yeah, okay.

PANEL MEMBER HAMMOND: I mean, it's for the infant population, but now that would -- you know, clearly, you'd want to have women of child-bearing age in there.

And then in the food-only discussion, it occurred to me that, you know, you used data that came from NHANES and the distributions and what had been seen in the national markets and stuff. But if someone had a home garden, and they were eating out of their own home garden that got sprayed, that actually might be a -- I think that might be a scenario you might want to incorporate, because I think that that's a very probable scenario, right.

DR. BARRY: Svetlana is the dietary person.

PANEL MEMBER HAMMOND: Oh, I'm sorry.

(Laughter.)

DR. BARRY: I'm going to defer to her, I'm sorry.

(Laughter.)

DR. KOSHLUKOVA: So the reason we included in this particular table 34 only infant, because we were at -- we had a specific question from OEHHA whether non-nursing infants had potentially higher exposure because of their consumption of formula, which is made with water. And so that was the question, that's why we specifically included this. And we did a particular analysis to show that the 99th percentile, the non-nursing infants are comparable to -- nevertheless, for the dietary exposure, we have at least 10 or 11 populations of groups, and women are included there.

PANEL MEMBER HAMMOND: And then you're probably

looking that up and didn't hear my other comment about home gardens.

DR. KOSHLUKOVA: Yes, and so the other one --

PANEL MEMBER HAMMOND: But the home gardens might actually have more -- you know, directly deposited from the spraying material on them, which is less likely to be in the market basket that would come for an average U.S. population.

DR. KOSHLUKOVA: Right. So we're basing on consumptions from -- on consumption databases, and NHANES is the one that is the more comprehensive. And it has a very large population, about 60 percent -- 60,000 percent -- participant and it's ongoing and continuous. So if -- we're also cutting -- because of the type of dietary exposure assessment, we're performing a probabilistic one. We're presenting the 99.9 percent also. Hopefully, we're capturing a highly exposed individual at the high end --

PANEL MEMBER HAMMOND: I'm not sure that you would. That's what I'm saying.

DR. KOSHLUKOVA: It's possible that we're not.

PANEL MEMBER HAMMOND: No, I'm thinking -- the reason I'm thinking this, I think that, in general, those things are looking at what's the market basket, and that that is -- you know, may have a very low percentage

likelihood of having the -- having been sprayed on.

But if we're talking about someone who lives where we had all the winds converging, you know, the tornado about to form --

(Laughter.)

PANEL MEMBER HAMMOND: -- at that location, at that house, if they had a garden, you know, and they were eating something that isn't normally sprayed with that crop, and so it -- anything in -- that you buy in Boston wouldn't have that -- wouldn't have chlorpyrifos on it. But because that family has a garden, and that there's drift, then it settles. That's the scenario I'm thinking of.

DR. KOSHLUKOVA: Right. So that's a valid question. But think about the aggregate exposures scenario that we have. We have a child that's sitting a certain distance from the application site. So we're assuming that that child has been home fed by mom diet that contained of 200 and so many commodities that have approved of chlorpyrifos used at the maximum -- it's not in the maximum. It's a distributional residue but all them contained chlorpyrifos. And then the child was standing at the application site getting exposed through the air, and through the skin, and as well eating contaminated food.

So a lot of assumptions are incorporated into this scenario. It's possible that we're missing one really hot commodity.

PANEL MEMBER HAMMOND: I understand what you're saying. But if you're going to say you're going to look at food, you want to look at the maximum food. And I'm suggesting a sightly different scenario of the maximum food, that's all. But I do understand what you're saying. But this is actually not a totally crazy maximum kind of scenario.

DR. KOSHLUKOVA: So what we can do is we can make a comparison between a really high really -- really high dietary consumption. For example, if we're not to perform probabilistic analysis, where we have distribution of consumption as well as distribution of residues, that's one way of doing it. In more crude analysis, we would use distribution of consumption, but we'll also consider only the highest measure residue in -- available in the monitoring databases, so --

PANEL MEMBER HAMMOND: No, no, no. I'm saying not on the databases for that, but for that, for the food itself, think of the -- the databases don't include that home garden that's right near where you sprayed. So you'd have to take the deposition -- at least, in my view, this is my thoughts. You could -- but that I'm thinking you

want to say take lettuce that isn't normally sprayed, and what you would normally get out in the market base when you did all that wouldn't -- the lettuce wouldn't have it. But at home, nice leafy out there, and it's collect -- it's a nice little collecting medium, so that the salads that you get in that home have much more than you would normally -- and that's the scenario I'm thinking of.

DR. DuTEAUX: So this is Shelley. And I think you have a -- you're raising a very valid question, and we could probably do it two ways. One is to create some modeling assumptions, kind of joining output from Terry's model, and then the dietary assessment to come up with maybe a probabilistic estimate of what might be in a home garden in one of the high use areas, like in the Salinas Valley.

The other approach we might use is by looping in our enforcement group who have done drift investigations, and they've sampled plant matter, when they've done drift investigations. It's not necessarily consumable plants. I mean, this might be wild geranium that no one would eat. But it might give us an empirical data set, and we could possibly look at both.

This again is adding to the volume of stuff that we'd have to put in the revised document and would need time to be able to analyze it.

DR. KOSHLUKOVA: Point. So what we can do is only add up to the tolerance level. Anything above the tolerance established for a particular commodity would be an illegal assessment.

PANEL MEMBER HAMMOND: No, no, no from home gardens. It's a different story from a home garden, right?

DR. DuTEAUX: No. Well, home gardens are exempt from tolerance.

DR. KWOK: Yeah. This is Eric Kwok. Yeah, I want to -- I want to elaborate on that one again, because I -- it took me awhile. Yeah, the reason why I'm using the maximum, because in the original paper they did actually feed the data with at least some statistical analysis were performed. The 95th percentile value is 1050, the very first dot on the left. So but I using the 98 -- let's see, the 9810, so which is way above the 95th percentile, because -- I mean, I do have the raw data. And to try to be, you know, not underestimate the exposures. That's why I picked the maximum number. As I -- you know, your comments were received. I know it's not a very stable number. But based on this set of data, that's why I picked the maximum.

So for the other one it's the same. Again, in the absence of the raw data, the -- the paper report only

up to the 75th percentile. And the number is 76. And I -- that's why I -- the maximum actually is 1200. So that's why I'm using the maximum probable...

PANEL MEMBER HAMMOND: Sure. I mean, that doesn't surprise me. That's kind of what happens, you know, with these kind of things, but I would -- I think talking about the ratio of those two numbers is taking the data too far.

DR. KWOK: Oh, yeah. Okay.

PANEL MEMBER BLANC: Paul Blanc here. Can I make a couple comments in building on Kathy's points?

PANEL MEMBER HAMMOND: Yes.

PANEL MEMBER BLANC: One is if you could go back to the table on the breast milk, this is apropos of Dr. Hammond's points about how there may be subtle changes in content or emphasis as we focus on the endpoint of neurodevelopmental toxicity. One is a very small point, which is on the table on the diet based on nursing versus non-nursing infants. The data that would be driven by the nursing infants seems to be much less normally distributed. And therefore, you present the mean values, but it might make more sense in the column that has means to put median values, just look -- just looking at the data, if it -- assuming that such data are available to you. They may not be based on how that is reported.

PANEL MEMBER HAMMOND: In fact, if they are available, I would agree with -- I mean, I actually usually like to have both, because they both are real relevant. You know, the median value will tell you more of what the most expected value is. But the mean value actually is more important in terms of getting the actual doses, you know, looking at the average doses people would get, so they're both useful.

PANEL MEMBER BLANC: Yeah. And then the other point is in the text where you talk about samples of cow milk and samples of soy-based infant formula. I wonder if you have any data on values in almond milk, given its widespread use now. It's possible or even likely that you don't, but then I'd say a phrase like, "Unfortunately, data on almond milk were not available", since almonds are a heavy use chlorpyrifos crop. And I have no idea what you see when you sample almond milk, but just curious there.

And then also amplifying another comment that -- that Kathy made is that not only is there the scenario that a day later the same owners other field gets sprayed, but in fact there's very likely to be different owners that are adjacent to each other that are spraying either the same day or very close proximity in time, because we're talking about crop intensive use for crops which are

grown in geographic proximity, and in which the season for the window for applying these pesticides is very close.

I would assume that you have such data -- licensing data available to you that would give you a sense of whether that's actually happening. That is to say, license for use like different licensees within a kilometer of each other, or some metric such as that. I don't know whether that -- I mean, you -- that data are there, but they may not be analyzable in that fashion. I don't know if you can geocode it in that way.

DR. BARRY: So you're talking about a spatial analysis of applications in maybe like a high-use area.

PANEL MEMBER BLANC: Yeah, absolutely. Your worst case scenario in that regard, because just saying that an individual user is prohibited from applying X or Y doesn't get at the question that Kathy raised about what about the next farm over.

DR. KOSHLUKOVA: So this is Svetlana. Regarding the almond milk, we will check what the pesticide database -- pesticide database program has on almond milk, but I'm inclined to say that I don't have this. They sampled soy milk, formula-based milk. We have data on almonds, but not on milk. No, there is no -- we just searched. There isn't.

PANEL MEMBER BLANC: So then I suggest you

extrapolate what would happen if you took those almonds and presumed that if you liquefied them, it would be the same concentration. I don't know how you make almond milk. I guess you grind it up in some way and put -- add water. I actually have no idea. But, you know, absent some value, you might just make a worst case scenario, you know, it's not boiled down, so it can't be higher, I presume, but I really don't know.

DR. KOSHLUKOVA: So would you just consider the residue measured on almonds as a surrogate for almond milk?

PANEL MEMBER BLANC: Yeah, absent anything else. And you'd have to translate it into a, you know, concentration in a -- in some other form. But, yeah, I guess you'd have to figure out how many kilograms of soy milk is equivalent of the kilograms of almond milk as equivalent to kilograms of cow milk, et cetera. Like all of the assumptions that they made that converted it into kilograms per day. Yeah.

DR. KOSHLUKOVA: Okay.

PANEL MEMBER HAMMOND: So Wikipedia tells us that the basic method of modern domestic almond milk production is to grind almonds in a blender with water, and then strain out the almond pulp.

PANEL MEMBER BLANC: Okay. I mean, what does

Wikipedia say about commercial manufacturing, since that's what would also be -- hey, guys, don't you have a lab or something, where you could actually test some almond milk quickly? How long would that take?

DR. DuTEAUX: This is Shelley DuTeaux and we have -- we have an MOU with California Department of Food and Agricultural Laboratory, and they are integral to our fresh frozen vegetable commodity testing program. They also do other testing for drift incidents, et cetera. We will ask if they could analyze some almond milk for us.

PANEL MEMBER BLANC: Super

CHAIRPERSON KLEINMAN: We are going to be losing Cort in a few minutes, so I wanted to -- and Al.

So I'd like to -- you know, just move out to a couple of other things. Are there other issues that either of you need to bring up or want to?

Okay.

When -- changing the parameters that we were using for the uncertainty factors, that's going to change your MOEs, correct?

DPR ASSISTANT DIRECTOR VERDER-CARLOS: (Nods head.)

CHAIRPERSON KLEINMAN: Which means that all of the data tables have to be, you know, recreated. I was just looking, and that's going to require a tremendous

expansion on some of these things. So I just wanted to get some idea of context. When you start thinking about this in the regulatory sense, and we're talking about bystander exposures, not occupational exposures, will this eventually come down to if somebody's living within say 50 feet of a field, that would have to be, you know, taken into account when they figure out how much material they're going to spray?

DPR ASSISTANT DIRECTOR VERDER-CARLOS: Yes.

CHAIRPERSON KLEINMAN: Okay. So that's going to be an interesting table, a lot bigger than what you have now. But the -- oh, and when you start to think about this as a -- you know, for regulatory purposes, do you specify how you're going to sample or -- the material in the air or are you just dealing with you're going to say you've got -- you use the model data, and so you can put stuff out?

DPR ASSISTANT DIRECTOR VERDER-CARLOS: Currently, DPR has a air monitoring network that also measures chlorpyrifos. And our Environmental Monitoring Branch Chief is here, that she can talk but that. But we do measure chlorpyrifos in ambient air for the long term. We started that in 2011.

CHAIRPERSON KLEINMAN: Because relevant to what Dr. Hammond was saying about the inhalable particles --

DPR ASSISTANT DIRECTOR VERDER-CARLOS: Right.

CHAIRPERSON KLEINMAN: -- the way you monitor needs to be taken into account, especially since we're talking about the ability to take in bigger particles than a standard air sampler will accept. A lot of the air samplers have cutoffs or, you know, whether they're inadvertent or not inadvertent.

And there are samplers designed for -- you know, at least for the occupational world that really do a good job on the inhalable, and you get astoundingly more material that you have to take into account. So that's something, you know, I think is worth, you know, adding to, you know, your thinking, at least.

We are -- yeah.

PANEL MEMBER LANDOLPH: Could you also do me a favor. This very nice report from the Department of Pesticide Regulation, the internal memorandum which Shelley talked about last time in the transcript, could you refer to this or add -- add it as an appendix in your report when you finish up just to show what kinds of neurotoxicological damage people are receiving when they get exposed to chlorpyrifos?

DR. DuTEAUX: So are you referring to the Pesticide Illness Surveillance Program --

PANEL MEMBER LANDOLPH: Yes.

DR. DuTEAUX: -- memo?
PANEL MEMBER LANDOLPH: Yes.
DR. DuTEAUX: -- it is in our references. If you'd like us to add it as a full appendix, we can do that as well.
PANEL MEMBER LANDOLPH: If you wouldn't mind --
DR. DuTEAUX: Sure.
PANEL MEMBER LANDOLPH: -- that would be very helpful. Thank you.
PANEL MEMBER BLANC: Paul here. Just a very brief thing in question what Mike just was talking about, it would seem to me that the tables -- the latter tables, which do the calculations, in my view, once you get to that point, you don't need to do the parallel calculations for the less conservative acetylcholinesterase inhibition values that you come up with. I think once you get to the point where you're talking about this stuff, it can just the -- driven by the -- by the safety numbers you came up with for the neurodevelopmental. So I don't think the tables are going to get bigger. I think they're just going to have substituted values.
PANEL MEMBER GLANTZ: And Stan agrees.
PANEL MEMBER BLANC: Stan is yelling in the back that he -- that would be his understanding also.
CHAIRPERSON KLEINMAN: Okay. We've really

touched on a lot of the issues. Were there other issues related to -- I guess -- oh, charge question 6, whether the human epidemiological data could be factored into the thinking in a more quantitative way than it's been -- than it's being used. And, Beate, do you have any feelings about that?

PANEL MEMBER RITZ: Well, we have kind of touched on that, haven't we, by saying that these are -- oh, you mean, the new data, not the Columbia Center and other children's center data that have been extensively used for the -- for the report already for neurodevelopment?

CHAIRPERSON KLEINMAN: Right.

PANEL MEMBER RITZ: Well, I would at least like to see some reference to those newer data on neurodegeneration.

CHAIRPERSON KLEINMAN: Okay.

PANEL MEMBER RITZ: But I'm not sure that that is, you know, already possible to include in a risk assessment document. I don't know. Oh, and -- and, yeah, for these purposes.

DPR ASSISTANT DIRECTOR VERDER-CARLOS: So Dr. DuTeaux already alluded to the fact that we are going to be adding more explanation on the epidemiological studies in the new document -- in the revised document, so -- like she said earlier. So if that is -- if that is all right

with you, Dr. Ritz, then that's what we're going to be doing.

CHAIRPERSON KLEINMAN: Yeah, I think that's, you know, what --

PANEL MEMBER RITZ: Yes.

CHAIRPERSON KLEINMAN: -- should be done. I think that will work.

PANEL MEMBER GLANTZ: This is Stan. And I also agree. I think -- I think we did talk about this last time. And what DPR was talking about is the way to integrate this information is fine.

PANEL MEMBER BLANC: I mean, I -- Blanc here. I mean, I think explicitly you're not using the EPA -- federal EPA mathematical approach, which was to deri -- to try to derive something from the epi data. And I don't think you need to -- you know, bad -- you know, harp on that more. And I think that as long as -- as long as you're doing two things, which you are doing -- three things.

One, you're using the neurodevelopmental endpoint as your key endpoint. Two, although you're using the animal data to derive your quantitative NOEL/LOEL, you're using the epidemiologic data to support the biological plausibility of using the endpoint that you're using. Those are I guess, the two pillars. Oh, and three, you're

further taking into account, the human aspect by adding another factor of 10 -- well, no, that's relevant to the other one. Forget that point, I was off base.

But anyway, if those two things I think are -- are the acknowledgement and incorporation qualitatively of the human epi data, but using the animal data for your numeric quantification.

DPR ASSISTANT DIRECTOR VERDER-CARLOS: Okay. Thank you, Dr. Blanc.

CHAIRPERSON KLEINMAN: Okay. If -- I think we've, you know, covered most of what we intended to do. And now I'm not sure how this works out, but I think we would need to see the next version -- you know, a reversion of the paper.

DPR ASSISTANT DIRECTOR VERDER-CARLOS: Okay. So our understanding is to now go forth and finish the document that we will be giving then to you, based on our discussion today. And we're also going to be waiting for the transcript to make sure we didn't miss anything. But we -- we've started on a lot of the things that Dr. DuTeaux had talked about already.

So we are going to then submit that to you, and let Jim know when that timeframe is. As you know, we have a lot to do, so -- so that's the next step. We don't -- and then based on what we'll -- we'll submit the document,

and then you'll look at it and see if that document is enough.

PANEL MEMBER LANDOLPH: Yeah. Thank you very much for all the fantastic effort you're putting in. I understand how difficult this is, how much work, and how much intellectual effort goes into it. So thank you from me.

DPR ASSISTANT DIRECTOR VERDER-CARLOS: Thank you. Appreciate that.

CHAIRPERSON KLEINMAN: We appreciate all the work.

So that wraps up this particular part. Now, I have a couple of other very minor quick things. One is that on tertiary-butyl acetate, we discussed the material quite awhile ago. OEHHA staff sent me the final document, and I reviewed the changes made, and concluded that they accurately reflected the changes we discussed as a panel. And so I have indicated that to OEHHA. And so that is now officially off our table.

And on AB 617, this is the community outreach and consultation project. A consultation group was formed. I'm a part of that, and I attended a meeting by telephone earlier. And we will be having another meeting later in the month. And so Jim and I will put together a letter to the Panel just to summarize the activities and what we'll

be doing in terms of that so far.

So we will -- we have a date scheduled for April 6th, but I don't know, we'll that be adequate time for you to -- no, that's what was thinking. So we will re-poll the Panel to, you know, come up with some more dates, once you can give us an estimate of how much time you need.

DPR ASSISTANT DIRECTOR VERDER-CARLOS: Okay.

(Laughter.)

CHAIRPERSON KLEINMAN: Sorry. Okay. So are there any other questions or comments that need to be done?

And if not, I would ask for a motion to adjourn.

(Motion and second.)

CHAIRPERSON KLEINMAN: Okay. Moved and seconded.

And all in favor?

(Ayes.)

CHAIRPERSON KLEINMAN: Any opposed?

PANEL MEMBER RITZ: Bye everyone.

CHAIRPERSON KLEINMAN: All right. Thank you very much. We're adjourned.

(Thereupon the California Air Resources Board, Scientific Review Panel adjourned at 2:24 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 15th day of March, 2018.

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