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FIFRA SCIENTIFIC ADVISORY PANEL (SAP)

MEETING ON CHLORPYRIFOS: ANALYSIS OF BIOMONITORING DATA.

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DAY 1 - April 19, 2016

MR. FRED JENKINS: Good morning, everyone. We're about to get started if I could ask everyone to please get seated.

Good morning again, everyone. I want to welcome everyone to this FIFRA Scientific Advisory Panel meeting. The topic of this particular meeting is Chlorpyrifos: Analysis of Biomonitoring Data.

My name is Fred Jenkins, and I am your Designated Federal Official for this meeting. Before we get started, I want to take a couple of minutes to go over a few administrative items.

As the DFO, I serve as the liaison between the panel and the Agency, and I'm responsible for ensuring that the provisions of the Federal Advisory Committee Act are met. I want to extend my thanks to this entire panel for agreeing to participate, as well to the public for coming.

The FIFRA SAP is a federal advisory committee that provides independent scientific peer review and advice to the Agency on pesticide issues. It's important to note that the panel only provides advice and recommendations to the EPA, and that all regulatory decision making and implementation

authority remains with the Agency.

We have worked with appropriate Agency ethics officials to ensure that all appropriate ethics regulations are satisfied for this meeting.

Panel members have been provided the provisions of the Federal Conflict of Interest Laws, and each participant has filed a financial disclosure report. I, along with our Deputy Ethics Officer, and in consultation with the Office of General Counsel, have reviewed those reports to ensure all ethics requirements are met.

This meeting provides an opportunity for public comment. We will have several public commenters who will be speaking during the public comment period. If you have not made prior arrangements and you wish to make public comments, please let me know or someone else with the FIFRA SAP office staff. Those are my colleagues seated here to my right. If you want to provide public comments without having made prior arrangements, we ask that you please limit your comments to five minutes.

There is a public docket for this meeting. The docket number is listed on the agenda. All background materials and other related documents

are available in the docket. Slides of EPA presentations that you will see will be available in the docket as soon as possible.

At this point, I want to introduce and extend my thanks to Dr. Jim McManaman to my left, who is serving as the session chair of this FIFRA SAP meeting. Thank you.

DR. JAMES MCMANAMAN: Good morning, everyone. This looks to be an exciting meeting, and I welcome everyone on behalf of the panel.

I am a professor of reproductive sciences at the University of Colorado School of Medicine, and I have expertise in neuroscience and developmental biology. I will ask each panel member to introduce themselves and say a bit about their expertise.

DR. DAVID JETT: Good morning. I am Dave Jett. I am the Director of the Countermeasures Against Chemical Threats program at the National Institutes of Health. My expertise is in neurotoxicology, specifically developmental neurotoxicology. And in my previous university professor life, I did study chlorpyrifos for a while.

DR. MARION EHRICH: Marion Ehrich. I'm

from the College of Veterinary Medicine, Virginia-Maryland College of Veterinary Medicine, Blacksburg, Virginia. I teach both pharmacology and toxicology and help run our toxicology diagnostic laboratory. I work with pesticides as well.

DR. SONYA SOBRIAN: Good morning. I am Sonya Sobrian from the Howard University College of Medicine Department of Pharmacology. I am a developmental neuropharmacologist.

DR. ALVIN TERRY: I am Alvin Terry. I am the chair of the Department of Pharmacology and Toxicology at the Medical College of Georgia, which is now part of a larger university called Augusta University.

DR. LISA SWEENEY: I am Lisa Sweeney. I am a scientist with the Henry M. Jackson Foundation for the Advancement of Military Medicine. I am at Wright-Patterson Air Force Base in Dayton, Ohio, working for the Navy. My expertise is in pharmacokinetic modeling and dose-response assessment.

DR. SHARON SAGIV: I am Sharon Sagiv. I am on the faculty of University of California at Berkeley. I am an environmental epidemiologist, and my research interests are on toxicant exposures in the

prenatal and early life period and neurodevelopment.

DR. DIANE ROHLMAN: I am Diane Rohlman. I'm at the University of Iowa in the Department of Occupational and Environmental Health. My research expertise is in neurobehavioral testing, looking at health effects from exposure.

DR. WILLIAM POPENDORF: I am Will Popendorf, a retired professor of industrial hygiene, Utah State University, with exposure assessment work in pesticides going back well over 40 years.

DR. ISAAC PESSAH: Good morning. I am Isaac Pessah at the University of California, Davis, School of Veterinary Medicine. I'm a professor of toxicology with an expertise in in vitro molecular and cellular toxicology.

DR. STELLA KOUTROS: Hi. My name is Stella Koutros. I am an epidemiologist at the National Cancer Institute in the Division of Cancer Epidemiology and Genetics, and my expertise is in occupational environmental risk factors for cancer, including the effects of pesticide exposure and cancer.

DR. WILLIAM HAYTON: Good morning. I am William Hayton, a retired professor of pharmacy

from Ohio State University with expertise in pharmacokinetics, pharmacokinetic models.

DR. WILLIAM FUNK: Good morning. I am Bill Funk. I am a faculty at Northwestern University in the School of Medicine, and my lab develops and applies biomarker methods for assessments.

DR. JEFFREY FISHER: Good morning. My name is Jeff Fisher. I am with the FDA at National Center for Toxicological Research in Arkansas, and my area of expertise is in PBPK modeling.

DR. RUSSELL CARR: Russell Carr. I am a developmental neurotoxicologist from the College of Veterinary Medicine at Mississippi State University, and I've got a long history working with organophosphates.

DR. JAMES MCMANAMAN: Okay. We have one panel member that is on the phone, Dr. Georgopoulos. Could you introduce yourself?

DR. PANOS GEORGOPOULOS: Yes. I'm Panos Georgopoulos. I am a professor at the Environmental and Occupational Health Sciences Institute at Rutgers, the State University of New Jersey, and my expertise is in exposure modeling including pharmacokinetics and dosimetry.

DR. JAMES MCMANAMAN: Thank you. With that introduction, we will begin the opening statement with the EPA. Doctor Housenger.

DR. JACK HOUSENGER: Thank you. It's a long line of welcomes, but let me welcome everybody as well, particularly the panel for taking the time and commitment to advise us on this important issue. There's a lot of stakeholder and public interest in this, and I welcome those people in sitting through and listening to the deliberations over the next few days.

Finally, for Fred, our Designated Federal Official, the SAP staff for putting this together, and my staff, not only the ones here on my right, but the people in ORD that have been involved in putting together this presentation. It's a lot of work, and as I'm going to mention a number of times, it's under a deadline that we have to meet, a court-ordered deadline.

This meeting is important in a number of aspects. Number one, chlorpyrifos is a very important agricultural chemical. It's the number one insecticide used in the United States. And how we're planning on evaluating the data is important about the

fate of chlorpyrifos, and ultimately how we regulate it. So we want to ensure that our approach for evaluating the study before us, the Columbia study, and how we use the information is scientifically valid.

We've been to the panel a number of times on chlorpyrifos regarding the Columbia study, I think twice before, and also on the PBPK model and gotten the advice of the panel on it. We've taken the past advice on how to use the study, and we have taken this -- and how we move the science forward, which we'll be discussing over the next few days.

The issues that we will be bringing forth are complex. It's doing business in a way we typically have not been. So in a lot of ways, this is groundbreaking.

Like I mentioned, we are under a court-ordered deadline, and this was set in response to a public petition for us to revoke all tolerances for chlorpyrifos and cancel all registrations. In November of last year, based on a 2014 Human Health Risk Assessment in response to this deadline, we proposed to revoke tolerances for chlorpyrifos because they did not meet the standard for safety as set under

the Federal Food, Drug, and Cosmetic Act. At that time, our point of departure was acetylcholinesterase inhibition.

The dietary risks at that time were driven largely by exposure to water and water that had been contaminated with chlorpyrifos for use. FFDCA, the Federal Food, Drug, and Cosmetic Act, requires us to conduct an aggregate risk of food and water when we are making our safety determinations. Like I said, water was the driver at that point.

While we would have preferred to complete further analysis on our assessments, the court-ordered deadline did not allow us time for that to happen. So in our proposal to revoke the tolerances, we specified the remaining components of our science assessments. The most critical of the pieces will be the ones that we are discussing today, the biomonitoring data, which we have used to derive a point of departure, which is fundamentally different from our earlier assessment.

As the panel convenes over the next few days, we ask you to keep in mind that the recommendations provided must be incorporated into our Human Health Risk Assessment, which will support our

final decision, and that final decision has to be made by the end of this year. So our work is cut out for us, and certainly yours is, too. And we look forward to your advice and recommendations over the next few days.

DR. JAMES MCMANAMAN: Thank you, Mr. Housenger. Do panel members have any questions for him at this point?

(Whereupon, there was no response.)

DR. JAMES MCMANAMAN: Okay. Next up is Ms. Vogel.

MS. DANA VOGEL: Good morning. My name is Dana Vogel, and I am the Director of the Health Effects Division in the Office of Pesticide Programs. My presentation today is going to give you an overview of the regulatory history of chlorpyrifos, highlighting the extensive scientific analysis we've done, including the multiple peer reviews that we have taken over the past approximately nine years or so.

So to begin, chlorpyrifos is an organophosphate pesticide that was first registered in 1965. Skipping forward, in June of 2000, there was a proposal -- we entered into an agreement with the technical registrants to eliminate and phase out

pretty much all the residential uses of chlorpyrifos. That would include the indoor uses in homes or in apartments, that type of use. There was also some mitigation done at that point in time on certain foods as well as some mitigation that was done for worker safety, including the addition of some personal protective equipment and engineering controls for some uses.

The next regulatory milestone is we issued our registration eligibility document in 2006. And in September of 2007, we received a petition from NRDC and PANNA to revoke all tolerances and cancel the registrations for chlorpyrifos.

So now I'm going to talk a little bit about, as we move forward since 2007, all the different peer reviews that we have taken this chemical to. The first one that I will note today was the 2008 Scientific Advisory Panel where we presented an issue paper updating the human health effects for chlorpyrifos, and this was focused on new science that relates to infants and children and pregnant women, and it was based on a review of experimental laboratory toxicology data on animals as well as epi studies that had become available since the

issuing of the 2006 RED. The focus at that point was evaluating both acetylcholinesterase and non-cholinergic modes of action.

The next SAP we had related to chlorpyrifos was in 2009 where we brought approaches for risk assessment for semi-volatile pesticides. And this SAP was focused on toxicity and exposure methodologies that we were using and proposing to evaluate bystander exposure that people may have experienced for volatilization exposures of chemicals, conventional chemicals that were applied that may re-volatilize, and then we were trying to put together some approaches for how we would do those kind of assessments.

In 2010, we brought a very important SAP, our draft framework for how we would incorporate human epi and incident data into our risk assessment. And this was a very important SAP. It was the conceptual foundation of how we would evaluate multiple lines of evidence and integrate epidemiological and incidence data into our risk assessments using a weight of evidence approach and adhering to the principles of systematic review. Moving on, as you can see, there were many peer

reviews that have happened for this chemical over the years. In 2011, we brought the chlorpyrifos PBPK model and its linkage to the CARES model, which is a probabilistic exposure and risk assessment model. So here we are linking the hazard and the exposure together.

In 2012, subsequent to the 2011 SAP, we also did a paper review to help us better understand some of the results from the different epidemiological cohort studies. We did a paper review of MRI and neurobehavioral experts to see if there were certain things we wanted to understand better the results of some of the publications. And in 2012, as we did after the RED, we again took a closer look and a more in-depth look at the science as it relates to infants, children, and pregnant women, pulling together again and taking a closer look at the experimental lab data as well as epidemiological studies.

So in 2014, as Jack mentioned, I believe we issued our revised risk assessment for chlorpyrifos. This risk assessment was issued in late December. It was focused at this point on the red blood cell acetylcholinesterase inhibition as the critical affect for our point of departure. It also

made use of PBPK model, and we used the PBPK model to derive human specific points of departure for different age groups, different routes, and different duration of exposure. So the PBPK model was also used to derive an intra-species factor for some life stage, not including women of childbearing age.

And we also at this point in the 2014 risk assessment, we retained the FQPA 10X safety factor, and that was principally due to the uncertainty that we had related to the epi studies and the potential for neurodevelopmental effects that were seen through those studies.

So as I mentioned, we were working on the risk assessment, and at the same time while we were working on the risk assessment that was due through our registration review program, we were also at the same time working on our response to the PANNA and NRDC petition to revoke all tolerances. Both that work is very complementary, so it has been going on in parallel.

Getting into a little bit of the timing of the petition response, as Jack mentioned in his comments, in 2015, the Ninth Circuit ordered us to respond to the petition by the end of October of 2015

and issue any final actions by the end of this coming December. So that's pretty much what is motivating us to finish all the work we have by the end of the year.

At that point in time, when we responded in October, what we did was we used the basis of that was the 2014 risk assessment. In late 2015, we did propose to revoke all chlorpyrifos tolerances based on the 2014 risk assessment because there were risks of concern noted in that assessment.

We also noted, as Jack mentioned, that there was some additional science work we were working on, and that would be continuing to go on and we would plan to complete that prior to the end of the year. That science work is what you are going to be seeing here today in our analysis that we have done in part.

I'm going to step back just for a moment to our most recent 2012 FIFRA SAP, as I believe it's important to go over some of the details of what was said in 2012 from the SAP and how it laid the path for it for the analysis that you are seeing today.

So just a couple of quotes here from the 2012 SAP. They did -- I'm sorry. I think I skipped ahead a little bit on my slides. In 2012, the panel did acknowledge the limitations of these three

longitudinal children's cohort studies that you will be hearing a lot about today, that being the Columbia, the Mt. Sinai, and the CHAMACOS. But they were also in general agreement that the data from these studies alone were not sufficient to derive a point of departure.

I will note that since then, we have gotten some new information, and we have also some new science available, new analysis that we believe enables us to reduce some of the uncertainties with the biomonitoring data and use it in a different way. And that is, again, what you will be hearing about through this current SAP.

Moving on to my next slide, as you can see some additional quotes, while they did acknowledge the limitations, the SAP also encouraged and urged the Agency to explore additional ways to use these studies to inform the chlorpyrifos risk assessment, especially in particular, they noted the Columbia data. And the quote is there.

They also encourage us to make use of the PBPK model to further characterize the Columbia dose estimates, and you will see that acronym throughout the day today, CCCEH; and when we discuss

that, we will be talking about the Columbia data.

So following up on the recommendations from the 2012 SAP, we have been working on chlorpyrifos. We pretty much never stopped working on chlorpyrifos, to some extent. What we have done here is our latest science analysis where we are using the PBPK model. And EPA's exposure assessment approaches that we use throughout our day-to-day, our regular risk assessment work, these exposure assessment approaches have been extensively peer-reviewed. They, themselves, have been brought to many SAPs. We're using them in a way to look at the -- we're using them with the PBPK model, and believe the results provide support for using the cord blood data for our point of departure.

You will also hear about today some additional information on why we think that's appropriate and some case studies that we have developed to illustrate how we are using -- how the PBPK model could be used to predict internal dose from existing potential chlorpyrifos exposures.

So our outline of presentations for today, next you're going to hear from Beth Holman who will discuss the epi literature review that we have

done. We will move on to Cecilia Tan who will explain her work that she has done with the PBPK model. And then we will have some evaluations of the Columbia blood data and predicted exposure through the different exposure pathways from Wade Britton, Rochelle Bohaty, and Danette Drew. And then we'll end the day, hopefully, with Dr. Anna Lowit talking about our point of departure, uncertainty factors, FQPA, and case studies. So that is our plan for the day.

DR. JAMES MCMANAMAN: Thank you. Any questions for Ms. Vogel?

(Whereupon, there was no response.)

DR. JAMES MCMANAMAN: All right. So let me encourage anyone who is using a phone to mute them. As you've noticed, we have had some interruptions in the presentations. So please mute your phones. Thank you.

So the next presentation is Dr. Holman.

DR. ELIZABETH HOLMAN: Good morning. My name is Beth Holman. I work as a scientist in the Health Effects Division in the Office of Pesticides. I'm going to be giving you an overview of EPA's epidemiological literature review today.

First, just to give you an overview of

my presentation, first I'm going to be giving you some additional background and history of EPA's review. Second, I will be giving you an overview of the three U.S. prospective cohort studies that are the main focus of the epidemiological literature review. Third, I will be talking about the specific focus of this literature review in terms of the specific adverse health outcomes that we will be focusing on in our assessment. Then I will be talking about the overall synthesis of the epidemiological literature review. And finally, I will be talking about some of the specific results coming out of Columbia University's prospective cohort study since they are the primary focus of the remainder of our analysis and presentations.

So first, just some additional background and history. In 2008, the FIFRA SAP was involved with a preliminary review of the literature for chlorpyrifos with a particular focus on women and children. They concurred with EPA's conclusion that chlorpyrifos likely played a role, but was not the sole contributor to the neurodevelopmental outcomes that were seen in the three U.S. prospective cohort studies. They also stated that epidemiology studies

should not be considered as the basis for characterizing the point of departure.

Then in 2010, as noted previously, OPP developed a draft "Framework for Incorporating Human Epidemiologic & Incident Data in Health Risk Assessment." This framework provides a foundation for evaluating these multiple lines of scientific evidence, including epidemiology data. The two key components of this framework are problem formulation and the use of modes of action/adverse outcome pathways. Again, this framework was reviewed favorably by the SAP in 2010. It is also worth noting that this framework is consistent with updates to the World Health Organization's mode of action/human relevance framework.

Next, as noted previously, in 2011, the Agency released our preliminary Human Health Risk Assessment for chlorpyrifos with us focusing on the acetylcholinesterase inhibition potential for chlorpyrifos. This is consistent with the recommendation from the 2000 SAP that this was the most appropriate endpoint for setting the point of departure for the purposes of risk assessment.

Also in 2011, again, the PBPK model was

reviewed by the FIFRA SAP. And we will be talking about this more in our later presentations.

Next, in 2012, EPA updated and expanded their review of epidemiology data. This included adding papers related to the intelligence quotient as well as new methodological papers to address measurement error, including socioeconomic status as well as trying to characterize and further validate the studies. And, again, this 2012 update used the draft epidemiological framework analysis approach.

In 2012, the SAP concurred with EPA and the 2008 SAP conclusion that chlorpyrifos likely played a role in these neurodevelopmental outcomes that were seen in the three U.S. cohort studies.

Then in 2014, we issued our updated draft Human Health Risk Assessment which included retaining the 10X FQPA [sic] safety factor.

In 2015, EPA conducted an updated epidemiological literature which expanded our assessment beyond chlorpyrifos to other organophosphates, or OPs. But to be clear, this did not change our overall 2014 conclusions.

Just to be more clear about what was done in our different assessments, in our 2012/2014

epidemiology data review, the assessment focused exclusively on chlorpyrifos with the three U.S. cohorts being the primary basis of this assessment, specifically, the Mt. Sinai, Columbia, and CHAMACOS cohort. Again, the 2012 SAP review concurred with our conclusion that these three cohorts were the most robust available evidence. All of this is captured in the 2014 updated revised Human Health Risk Assessment for chlorpyrifos.

Then in 2015, we expanded our review beyond chlorpyrifos to other OPs. This included adding new results from the three U.S. cohorts. In addition, we expanded our review to include study designs to include non-U.S.-based studies as well as other U.S. -- as well as other study designs. Specifically, we added one cohort from Mexico, one U.S. case control study, and four cross-sectional studies: one from the U.S., two from China, and one from Canada. All of this is captured in our 2015 updated literature review.

So based on the 2012 SAP review and the available studies that were assessed in 2015, we continue to conclude that the data from the three U.S. cohort studies are the most robust available

epidemiology data.

Before I tell you more about this 2012 review, I just want to tell you a little bit more about these three U.S. cohort studies. First, some definitions.

DAPs are dialkyl phosphate metabolites. These are metabolites of multiple organophosphates and are therefore a non-specific measure of OP exposure.

Second, TCPy is a chlorpyrifos metabolite.

And third, PON1 is a genotype expression.

So, again, the three prospective birth cohort studies were designed to examine environmental exposures and adverse health outcomes. Specifically, the Columbia cohort was conducted from 1998 to 2004, and, again, is denoted as CCCEH in this presentation. It was conducted in New York City. It includes a multi-ethnic population, and they primarily tested for chlorpyrifos in cord blood collected at birth.

The Mt. Sinai cohort was from 1998 to 2001, again, from New York City, multi-ethnic population. They tested for TCPy as well as DAPs and PON1.

Finally, the University of California, Berkeley, known as CHAMACOS, was conducted from 1999 to 2002. This cohort was conducted in a California agricultural region with a Mexican-American study population. It focuses on the children of agricultural workers. And, again, like Mt. Sinai, they tested for TCPy, DAPs, and PON1.

In terms of some additional characteristics of these populations, they generally needed to seek prenatal care early in their pregnancy; there was a residency requirement; and they had to deliver at participating hospitals. Overall, they needed to have a low prevalence of risky health behaviors and comorbidities, including no history of diabetes, hypertension, HIV, or history of birth defects, and no smoking or illegal drug use. Again, this is a multi-ethnic population, and, overall, these are younger mothers with an average age of about 25 years.

Next, getting back to the 2012 SAP review of these studies, these are three quotes from the SAP's review. Overall they concluded that the Agency's epidemiological review was very clearly written, accurate, and generally provided a thorough

review of the literature. Again, the 2012 review concurred with the 2008 SAP and Agency conclusion that chlorpyrifos likely played a role in the neurodevelopmental outcomes seen in these three U.S. cohort studies. Overall, they noted nine strengths in the cohort studies. And, again, this is a quote from the SAP review. Again, they noted nine key strengths, and I just want to highlight a few of them.

One is the longitudinal design, which allows us to have a clear understanding of the temporal relationship between chlorpyrifos exposure and these adverse neurodevelopmental outcomes. Second, the use of biomarkers as well as self-reported exposure. Fourth [sic], the relative consistency of findings across populations. Fourth, the strength of the associations found across the studies.

Continuing on, in addition, I also want to note that they noted as a strength the control of multiple confounding variables including other environmental exposures and other pesticides. And also just to highlight, they noted a strength of the minimization of bias in assessing these outcomes and exposures and the likelihood that this would bias the results towards the null and have the potential to

underestimate the effect overall.

Also just to note, there are, of course, uncertainties associated with these cohort studies, and these will be the focus of -- we will be discussing these uncertainties in detail in our later presentations.

Before going any further, I want to be clear about which specific adverse health outcomes we have focused our epidemiological literature review. Multiple outcomes were assessed in the studies, including fetal growth, neonatal neurological development, infant motor and mental development, attention disorders, autism spectrum disorders, and intelligence measures. Consistent with the 2008 and 2012 SAP evaluations, we are focusing on this analysis on neurodevelopmental outcomes. So basically, we are not focusing on fetal growth. We are focusing on the other five measures that are listed here.

The reason we are not focusing our assessment on fetal growth is that there has been inconsistent evidence of OP exposure and an association with adverse birth outcomes across these three cohort studies. Specifically, the Columbia University Study observed an association of an inverse

association. They saw that with increasing cord blood chlorpyrifos, this was associated with decreased measurements of birth weight and birth length.

In contrast, in the Mt. Sinai and the CHAMACOS cohorts, they either saw no association between the exposure and these outcomes, or they saw evidence of a positive relationship, i.e., that increasing DAPs resulted in higher birth weight or higher birth length.

Given the lack of consistency across the cohorts for these growth metrics, we consider these, the link between fetal growth and IP exposure, to be tenuous. We continue to monitor the literature for these fetal growth outcomes. But, again, they are not the primary focus of our assessment.

Next, I just want to give you an overview of the specific methods and analysis used in these studies, including exposure assessment, confounding adjustment, statistical analysis, and overall bias considerations.

In terms of the exposure assessment, the cohorts were looking at differing exposure profiles, pathways, and routes. They were using multiple biomarkers to reflect different windows of

exposure. Again, DAPs are a non-specific measure of OP exposure, and TCPy is a chlorpyrifos metabolite.

Across each cohort, a self-report questionnaire was collected as well as TCPy and urine. In Columbia, as part of their validation study, they collected TCPy -- TCPy and meconium, as well as tested for chlorpyrifos in air. However, the primary focus of Columbia's study is chlorpyrifos in cord blood collected at birth.

In the CHAMACOS cohort, they also collected acetylcholinesterase and butyl cholinesterase in cord blood. And then, again, Mt. Sinai and CHAMACOS, both tested for DAPs in urine using -- DAPs in urine were tested for using CDC methods, and both of these cohorts also tested for PON1 genotype and phenotype expression. But to be clear, the only cohort study which tested directly for chlorpyrifos is Columbia.

Next, in terms of the overall methods used to control confounding in these studies, at the individual level, they used statistical adjustment to account for a number of variables such as race and education. They also tested for statistical interactions. In addition, in the Columbia University

Study, they conducted a multilevel model, which allowed them to account for group and individual level variability for socioeconomic status.

Finally, it's important to note that by design, these cohort studies have an ability to control for confounding. Specifically, biomonitoring data were collected from individuals within each cohort. The unexposed children in the epidemiology studies are those whose biomonitoring data are low and often below the limit of detection. Therefore, the unexposed children are derived from the same populations and location in the same living and economic conditions as those exposed or highly exposed children are.

So in this way, important issues such as socioeconomic status are similar across the entire group of both the exposed and unexposed.

This slide just summarizes some of the specifics of the variables considered in these studies in terms of the confounding variables. Again, demographic information, including socioeconomic status. They also took a look at the stimulation in the child environment and in the postnatal environment. In addition, in one or more of the

studies, other pesticides were assessed, including diazinon, propoxur, and pyrethroid pesticides, as well as other exposures, including polyaromatic hydrocarbons and lead.

In terms of the statistical analysis conducted in the studies, the decisions were appropriate to the research questions and characteristics of the data. This included having to account for missing data when needed as well as accounting for cases where the measurements were below the limit of detection, or LOD.

EPA considers the sample size of these studies to be adequate to assess the main effects that were being studied in these cohort studies. But we do acknowledge they were likely underpowered to evaluate effect modification or interactions.

In addition, sensitivity analyses were conducted to evaluate alternative modeling options such as loss to follow up, where study participants were in those studies at the beginning of the study, but they were lost and did not continue with the studies later on.

Next, this slide summarizes some of the different threats to validity and why EPA believes

these are strong studies. Specifically, in terms of selection bias, the retention rate was moderately high for birth cohorts, 60 to 80 percent at age 7 years of the child. They also compared included individuals versus excluded individuals and concluded they were generally comparable.

Next, in terms of information bias, they took efforts to evaluate the potential for error in outcome and exposure measurements. Again, by design, these studies do reduce the potential for differential thought bias.

In addition, it is noted that Columbia's validation study further increases our confidence in this study data.

And, finally, the confounding, which, again, was controlled for using a number of different methods, as summarized previously.

Next, moving on to the specific adverse health outcomes that we're looking at across these three U.S. cohort studies, again, we are looking at neonatal neurodevelopment, infant neurodevelopment, attention problems, autism spectrum disorders, and intelligence measures. In this table, we've listed whether or not the specific study assessed the outcome

or not.

With the exception of neonatal neurodevelopment where Columbia did not assess these outcomes, and attention problems where Mt. Sinai did not assess these outcomes, these five outcomes were assessed across all three U.S. cohort studies.

Next, I'm going to give you a brief overview of the specific measurement techniques that were used to test for the specific health outcomes. First, neonatal neurodevelopment.

This was done using the Brazelton Neonatal Behavioral Assessment Scale, or BNBAS. These were assessed two-to five-days postpartum. They were conducted by trained neonatologists in a hospital setting. Again, these measurements were only made in the CHAMACOS and Mt. Sinai cohorts.

Moving on to infant neurodevelopment, this used the Bayley Scales of Infant Development. This assesses for both mental and psychomotor development, and it was assessed at six to 36 months across the cohorts. Again, it was measured in all three U.S. cohorts.

Moving on to attention problems, a combination of tools was used across these studies.

First, a combination of maternal report and direct observation using a number of different methods; and then, second, using DSM-IV ADHD symptoms. These were assessed at three, three-and-a-half, and five years in the CHAMACOS and Columbia cohorts. Again, these were not assessed in the Mt. Sinai cohorts.

Moving on to autism spectrum disorders, these were assessed in all three U.S. cohorts. It's important to note here that the recently updated DSM-V defines the autism spectrum disorder, or ASD, and this disorder now encompasses several disorders that were different diagnoses under DSM-IV. Under DSM-IV, there was the pervasive development disorder, or PDD, which was a catch-all where the other categories did not fit. So depending on which study you're looking at, the authors may use the PDD or the ASD criteria and terminology.

Moving on to intelligence measures, this was again assessed in all three U.S. cohorts. These measures were assessed using the Weschler Intelligence Scale for Children, specifically verbal comprehension, perceptual reasoning, Working Memory, processing speed, and Full-Scale IQ. These were standardized across the U.S. population and were

assessed at ages six to nine years.

Moving on to the results from these studies, I'm going to be giving you a summary, high-level summary of the results from the three U.S. cohort studies, which are, again, the primary basis of EPA's conclusions with regard to the epidemiological literature review. In addition, I will be summarizing the results from the 2015 updated literature review, which we consider to be supporting data.

First, neurological effects near birth. This was assessed in the CHAMACOS and Mt. Sinai cohorts. And, again, it was not assessed in the Columbia cohort. Overall, they observed associations between prenatal DAPs and these neurological effects near birth.

In addition, in a cross-sectional study from China, they also measured neonatal neurodevelopment and assessed it three days after birth. They observed statistically significant associations with prenatal DAPs which, again, with DAPs being a non-specific measure of OP pesticide exposure.

Moving on to mental psychomotor problems, again, these were assessed in all three U.S.

cohort studies. Each of these three cohort studies reported evidence of prenatal chlorpyrifos, or DAPs, and an association with impaired mental and psychomotor development. But to be clear, this was not consistent by age at time of testing with testing having occurred from six to 36 months across the three U.S. cohort studies.

In addition, in a cross-sectional Chinese study, they looked at a developmental quotient score for children aged 23 to 25 months. They observed no association with postnatal urinary DAPs.

Next, with regard to attention problems, attention problems and ADHD were reported with suggestive or positive associations in three prospective cohort studies, two from the U.S., one from Mexico. Again, attention problems have not been assessed in the Mt. Sinai cohort. Again, the three cohort studies were assessing prenatal exposure, whereas the cross-sectional study was assessing postnatal exposure.

Finally, in addition, in a Canadian cross-sectional study, they did not observe an association between postnatal DAPs and parentally reported attention problems. However, the authors did

note that their outcome assessment for these attention problems may not have been sensitive enough.

Finally, with regards to autism spectrum disorders and intelligence measures, across the three U.S. cohorts and a U.S. case-control study, they reported suggestive or positive associations between OP exposure and autism spectrum disorders. To be clear, the studies varied in the magnitude of the overall strength of the association, but they did consistently observe positive associations between OP exposure and these disorders.

Finally, for intelligence measures, measured at age seven years, in the three U.S. cohort studies, they reported an inverse relationship between the respective measures of chlorpyrifos or DAPs.

Overall, across the studies, it's important to note the difference in our understanding of prenatal versus postnatal exposure. At this point, we have a number of studies that have observed a link between prenatal exposure to chlorpyrifos, or OPs, measured as either chlorpyrifos, TCPy, or DAPs, and adverse effects on neurodevelopment through age seven years, with some additional more limited evidence up to the age of 11.

However, our understanding with regards to postnatal exposure is more limited. A smaller number of studies have assessed postnatal exposure to OPs. Specifically, postnatal exposure was assessed in the CHAMACOS cohort, as well as in three cross-sectional studies, one from China, one from the U.S., and one from Canada. To be clear, postnatal exposures were not assessed in either the Columbia or Mt. Sinai studies.

As far as across the studies that did look at postnatal exposure, the only study that saw an association was in the U.S. cross-sectional study where they looked at NHANES data and observed a positive association between attention and behavioral problems and DAPs.

So overall, across the epidemiology data that we looked at, we note the strength -- that overall, the strength of the observed associations, which are high in some cases but not in all; we note consistency in a number of the measures of neurodevelopment, including the Brazelton, which is the neonatal neurodevelopment; ADHD-like behavioral problems; Bayley, which is the infant neurodevelopment; and IQ measures, including Working

Memory.

And, again, to note that across these cohort studies, in particular, alternative explanations for these results were evaluated, including the potential impact of confounding variables.

Again, the three U.S. cohort studies are the primary basis of our conclusion. We note that the strength of these studies in terms of the study design, both with regard to our understanding of the temporal relationship between the exposure and the outcomes that were measured, as well as by design -- that differential misclassification is considered to be less likely. Again, we do note the issue of prenatal versus postnatal exposure, and that is considered to be a data gap which we'll be talking about more in our later presentations this afternoon. In terms of biological plausibility for these outcomes, the mechanism of action is unclear, but there are several plausible hypotheses.

And, then, finally, we are going to be talking about this more in just a minute, but it is worth noting that the studies were conducted across the period of time when the residential uses for

chlorpyrifos were canceled. So we'll be talking a little bit about the data from the Columbia study, which allows us to look at the impact of that. But to be clear, these studies were not designed to assess the influence of the cessation of its residential exposure.

So, finally, I want to give you more details on the Columbia University findings as these are the focus of the remainder of our presentations, as well as our issue paper.

First, a little bit more background. Again, the Columbia study, known as the Mothers and Newborn Study of North Manhattan and South Bronx, again, conducted by Columbia University, again, referred to as CCCEH, they measured parent chlorpyrifos in cord blood, as well as other indicators.

Again, the other two birth cohorts from the U.S. generally measured these non-specific measures of chlorpyrifos and other OPs, specifically, TCPy and DAPs. Therefore, EPA considers the Columbia study to be the most relevant to the chlorpyrifos human health risk assessment and is therefore the focus of this analysis. The other two cohort studies,

as well as the additional epidemiological literature that I talked about just now provide important supporting information. And, again, these conclusions were concurred in terms of the Columbia study being the most relevant for chlorpyrifos. The 2008 and the 2012 SAP concurred with this conclusion.

Next, it's important to note that the Columbia study was conducted before and after when the pesticide manufacturers voluntarily canceled use of chlorpyrifos in the home environment. So this graph here is showing us the results from Whyatt et al. (2004). On the y-axis, they plotted the umbilical cord chlorpyrifos level. The light blue bar on the left is from the results from before the cancellation of the chlorpyrifos residential uses. And the right dark blue bar is from after the cancellation.

So overall, they were able to show that, as you can see, after the residential uses were canceled, the levels are lower.

Looking at this data in more detail, this table shows the distribution of the chlorpyrifos blood levels both in cord blood and maternal blood. The first half of the table shows the results from 1998 to 1999, which is before the cancellation of the

residential uses. The second half of the table shows the distribution after the cancellation of these uses.

We will be talking about these results in more detail in later presentations. But for now, two key points: One, the numbers are lower after the cancellation of the residential uses in 2001; and, two, the cord blood and maternal blood numbers are similar.

In terms of the correlation between the cord blood and maternal blood as you saw just now, it suggests that maternal blood is a reasonable surrogate for cord blood given that they are similar. The Columbia University researchers conducted a statistical analysis of this and found that maternal blood and umbilical cord blood were highly correlated. These together suggest that tracking the blood concentration of the mother is a reasonable surrogate for the fetus. You will be hearing about the surrogacy issue in later presentations.

Finally, I just wanted to highlight some of the specific findings in the Columbia University Study.

The Rauh et al. (2006) study, followed 254 children through the age of five years and used a

dichotomized statistical approach. They split their study participants into two groups. The low group, which included concentrations of chlorpyrifos and cord blood less than or equal to 6.17 pg/g, whereas the high group had greater than 6.17 pg/g.

Overall, they observed statistically significant deficits of 6.5 points on the Bayley Psychomotor Development Index at the age of three years when they were comparing these high to low groups. It is notable that these decrements persisted even after adjusting for group and individual level socioeconomic variables.

In addition, in this same study, at age three years, when comparing the same high to low exposure groups, they observed increased odds of mental delay; psychomotor delay; attention disorders; ADHD; and the pervasive developmental disorder, or PDD.

In addition, it is also worth noting that in a follow-up study at age 11, there was also increased odds of mild to moderate tremor in the arm when comparing the same high to low exposure groups.

In a more recent study, Rauh 2011, they looked at the relationship between prenatal

chlorpyrifos exposure and neurodevelopment. This included a total of 265 of the Columbia participants at the average age of seven years old. The participants included in the study included a complete set of data including prenatal maternal interview data as well as these prenatal chlorpyrifos marker levels.

Overall, they described the log of the Working Memory Index of children as being linearly associated with concentrations of chlorpyrifos in cord blood. They derived both the slope as well as a 95 percent competence interval for this relationship. Overall, for each standard deviation increase in exposure, they observed a 1.4 percent reduction in Full-Scale IQ and a 2.8 percent reduction in Working Memory.

So, in conclusion, across the epidemiological literature review, the current database strengthens the 2008/2012 conclusion that chlorpyrifos likely plays a role in the observed adverse outcomes on child neurodevelopment.

Second, given the study design, study conduct, and the methods used, EPA believes that these three U.S. cohort studies, which are, again, the primary basis of our conclusions, that they likely

under- than over-estimate the association.

And, finally, the new data from 2012, as well as our 2015 update, support and extend our previous conclusion.

And, again, just to note that we did retain the FQPA 10X safety factor in our 2014 Human Health Risk Assessment in order to account for the uncertainty associated with the potential for these neurodevelopmental outcomes.

Questions?

(Whereupon, there was no response.)

DR. JAMES MCMANAMAN: Thank you very much. So does the panel have any questions? Dr. Ehrich?

DR. MARION EHRICH: So you separated the children into low exposure and high exposure. Was that based on that six or the level of detection, or what was -- how did you separate -- how were the children separated into low and high exposures?

DR. DANELLE LOBDELL: I'm Danelle Lobdell, epidemiologist with ORD, Office of Research and Development.

So originally, they came up with that stratification that -- with the less than 6.17 pg/g in

their fetal growth study. So they had done a series of exposure assessments initially when they were first starting looking at how things were looked at. So in that very first study of fetal growth is where they came up with that, and they maintained that low and high group throughout the rest of the studies based on those preliminary studies.

DR. MARION EHRICH: Okay. It seems that all the data from this was based on analytical work done right at the beginning. So on that study you're talking about where they got the 6.17, they actually had some values below the detection that they called half values that they included in. Is that an okay thing to do?

DR. DANELLE LOBDELL: Yes. That is one of the techniques that is used in epidemiologic analyses as far as below the limit of detection. One of the things they will do is do half of that limit of detection in order that you have a value so you don't have so many zeros making your analyses skewed.

So that is a typical statistical way of attributing and helping formulate that as far as environmental epi studies. So that's one of the techniques that can be used. There's different ones

that can be used, but you will see that quite typically.

DR. MARION EHRICH: I guess my statistics is different --

DR. ANNA LOWIT: This is Anna Lowit. My name is spelled wrong.

DR. JAMES MCMANAMAN: We can correct that in the written comments.

DR. ANNA LOWIT: Approximately 30 to 40 percent of the cohort is below the LOD for chlorpyrifos in cord blood. So what Danelle speaks about is accurate for those. The papers where they've done this dichotomous high versus low, in the 2011 paper, the Rauh 2011 paper that uses the linear aggression across the Working Memory, at the low end below the LOD, they've done an imputation approach that creates more of a distribution. I don't think we have a slide with the plot. But it's certainly in the papers. So instead of a half LOD, it's more of an imputation approach.

DR. MARION EHRICH: I have more questions on this chemistry because usually you don't quantitate. I work in a forensic lab. You don't quantitate on a level of detection. You quantitate on

a level of quantitation. And when I go back to look at those papers, have you seen their original data where they have the chromatograms and their calibration grams and so forth? The calibration curves are 1000-fold higher than what they are giving in their papers. So I'm not quite sure.

The only thing that was in the issues paper was that table 1, and that's not like these levels that are talked about in the paper, the publications from that group.

As somebody who signs off on these, I would like to see the chromatogram; I'd like to see the level of detection, which is just a blip, and that's either yes or no; the quantitation which would be the calibration curve. And none of that seems to be available in the publications from that particular group.

DR. ANNA LOWIT: And we are not in possession of these chromatograms. The data were conducted at CDC at the time when Dana Barr was there. But we are not in possession of the chromatograms.

DR. JAMES MCMANAMAN: Thank you. Dr. Terry.

DR. ALVIN TERRY: Yes. I sort of

concur with that, at least from my understanding of this. There seems to be a lot made of these exceedingly low numbers, and I collaborate with analytical chemists, as well. I think it would behoove you to have analytical chemists rigorously look at this to see whether or not this is within the limit of quantitation or -- you know, any of the papers I am familiar with, pg/g would be very, very low on any scale.

DR. JAMES MCMANAMAN: Since this is public record, would it be possible to get copies of those for the panel, you know, search the Internet or something like that to pick up the original publications? Are they available, or are they confidential?

UNIDENTIFIED MALE: We don't have access to the raw data. We recently, well, we've been in conversations with Columbia to get that data. This morning I sent, based on an interview with a spokesperson from Mailman School of Public Health that said they would make the data available to us and sent a letter to the dean. But currently, we don’t have the raw data before us.

DR. JAMES MCMANAMAN: Okay. Thank you.

Other questions? Yes.

WILLIAM POPENDORF: Just another comment on the imputation. A second reason for doing that is to allow logarithmic transformations because you can't transform zero. On a linear scale, half a value below one, in this case, you know, if you look at those scales, doesn't make much difference.

But I wanted to clarify the other point on the 6.17. My understanding was that was based on dividing the cord data into thirds, and that was the division between the upper third and the lower two-thirds; is that correct?

DR. DANELLE LOBDELL: Actually, that is correct in the fetal growth paper. And then what they actually ended up doing is dichotomizing that and maintaining that dichotomization between low. But originally, you are correct.

DR. JAMES MCMANAMAN: Dr. Pessah.

DR. ISAAC PESSAH: I concur with the concerns raised about the number of measures below LOD. But I think there is another issue and that these were chlorpyrifos measurements; is that correct? Was there any record of chain of custody, the time the blood was collected to the time it was actually

analyzed, given that chlorpyrifos is unstable?

DR. JAMES MCMANAMAN: Speak into the microphone, please.

DR. DANELLE LOBDELL: I am unclear as far as, you know, their exact procedures as far as collection. I know, you know, as far as the cord blood was concerned, it was collected, you know, of course, on day of delivery. I don't recall their systematic procedures. But I'm sure they had some. So that will be something we will have to look more into as far as what has been described.

DR. JAMES MCMANAMAN: For the record, the answer to Dr. Pessah's question was about whether it was chlorpyrifos that was measured, and there was an acclamation that that was the case; that was true. Just for the record.

Dr. Jett.

DR. DAVID JETT: I just wonder if the Agency would like to comment on how the magnitude of these levels compare with the other two epi studies if there are comparisons that can be made.

DR. ANNA LOWIT: So as Beth walked through in some detail, the Columbia cord blood results are unique to the other cohorts in that the

important metric is parent chlorpyrifos in cord blood, which was not measured in the other cohorts.

Columbia did not start measuring TCPy in urine until after the cancellation of the indoor. So there's a little bit of an apples and oranges comparison across the cohorts.

DR. WILLIAM HAYTON: I have a question about the concentrations in blood. Is it blood or is it plasma? I read one of the Columbia papers, and it seemed pretty clearly stated that the blood was centrifuged, plasma was collected, and then forwarded for analysis. And they are not the same thing. So I would like that clarified.

DR. ELIZABETH HOLMAN: I believe you are correct. Measurement was directly in the cord blood plasma.

DR. WILLIAM HAYTON: Okay, because the white paper, I mean, if you're looking for -- what's the reference -- fluid and in the PK modeling, too, it makes a difference whether it's plasma or blood. And it seems to me those designations are just -- in the white paper, they are used to be synonyms. Sometimes it's talked about as plasma concentration, sometimes blood concentration.

In the PK modeling, is the reference fluid then going to be blood, or are we looking at tissue blood partition coefficients, tissue plasma partition coefficients?

DR. JAMES MCMANAMAN: Before beginning, that was Dr. Holman's answer to Dr. Hayton's question and then Dr. Hayton's response to Dr. Holman.

DR. CECILIA TAN: This is Cecilia Tan, U.S. EPA. To answer Dr. Hayton's question about in the PBPK model whether it's blood or plasma, I believe that the data that was used to calibrate and evaluate the PBPK model, it is plasma. So it is comparable to the biomarker data.

DR. JAMES MCMANAMAN: Okay. Just to encourage you to state your names. Thank you for doing yours. But the meeting is being transcribed, so it's hard to keep track of who is speaking if we don't have the names.

Yes, Doctor, go ahead. Dr. Carr.

DR. RUSSELL CARR: You mentioned that the purpose of this was not to measure the values before cessation -- before cancellation of registration and after cancellation of registration. But yet, that data is available. And maybe if we had

that smoking gun, it might make this a little bit stronger because we have data from kids who reached seven years old prior to cancellation and data from kids -- after seven years old, after cancellation. The cohort goes all the way out to 2006 based on other studies. They found that IQ at seven years old is affected by pHs and maternal care, phthalates, all originally dating from the same cohort.

One issue I have with the IQ data in the 2011 Rauh paper is that when we talk about compounding variables, she lists hers out, and it's lead, PAHs, and environmental tobacco smoke. There is no mention of diazinon or any other organophosphate insecticide. And I'm just kind of concerned that was not included for analysis.

DR. ANNA LOWIT: I will cover a piece and then defer to Danelle for part of that. That's a very long, complicated question.

The first part of your question was about the individuals in the cohort in the pre- and the post-cancellation. So to clarify what you heard from Beth is that the cohort, itself, was not designed to look at the before and after. From a statistical point of view, it's not designed that way. However,

we do know that because the cancellation occurred somewhere during the study, that there are children born before and after. In fact, we know that only one child was born who has a value in the quote/unquote, high group born after the cancellation, actually. That child was born very close right after the cancellation occurred.

So upon the cessation of that internal -- that in-home environment, as that was removed from the in-home, you see those striking bars of it and the striking decrease in the cord blood.

But from a statistical point of view, you wanted to be more evenly distributed, the before and the after, to be stronger. That's what Beth was clarifying. But we do know -- I mean, it is clear, the before and after. We agree with you.

So I will defer to Beth -- to Danelle on all the confounding issues, and Beth, also.

DR. ELIZABETH HOLMAN: To be clear, in terms of the Rauh 2011 study, as well as the Rauh 2006, it's important to note, so in terms of lead, in terms of a confounding factor, lead was only available for 89 of the children that were assessed. Confounding is only an issue when it is associated

with both the chlorpyrifos measure and with the intelligence measure.

In the case of the intelligence measures, it was not significantly correlated with either the chlorpyrifos level or the intelligence measures. But, again, they only had it available for a subset of the data for 89 children.

In terms of the -- and similar results were obtained for the Rauh 2006 study, which was for the relationships with mental and psychomotor development.

In terms of polyaromatic hydrocarbons, both environmental tobacco smoke, and to a lesser extent, were correlated with chlorpyrifos. But they were not significantly correlated with the intelligence measures.

In terms of diazinon, you are correct that that was not discussed explicitly in the 2011 paper. However, this was the subject of extensive discussion with regards to the mental and psychomotor decrements in the 2012 SAP review. They specifically assessed whether or not the mental and psychomotor development decrements were still associated if you included both diazinon and a metabolite of propoxur.

And they concluded that it did not have an impact overall whether or not they included those additional -- whether you included those pesticides did not impact the associations that were seen with mental and psychomotor developments with respect to chlorpyrifos exposure.

DR. RUSSELL CARR: But that's only available for the 2006 study.

DR. ELIZABETH HOLMAN: That is correct.

DR. JAMES MCMANAMAN: Yes.

DR. STELLA KOUTROS: I just wanted to give a couple of bigger picture thoughts about what I heard from the panel thus far.

It sounds like some of the panel members have concerns about or want more information about the quality of the assay and the blood collection protocol, and then others still have some concerns about the data or the statistical analysis.

But I suggest that the Agency think about and report back to the panel members what they would like us to be considering moving forward here such that we don't have a recapitulation of the 2012 FIFRA SAP and let us know what your starting point is for us. If you are already accepting the validity of

this assay data, maybe you should let us know that. Or if the panel feels uncomfortable -- because it is the basis of so much of what we are asked to do, if the panel needs more information to make these judgments, you might consider providing that, as well.

DR. ANNA LOWIT: So I will start and if Dana or Jack want to add, I will invite them to do so.

As you heard from Dana's presentation first thing this morning, we've been reviewing these studies since 2007 and 2008 timeframe. Two separate panels have reviewed the studies, and to some degree, have asked some of the same questions and have looked into these details about confounding and about other OPs in some great detail.

So to some extent, particularly, the 2012 SAP went into those in so much detail, and we have not in our issue paper, we brought those back and have not spent a long time developing that on behalf of all of you.

We would request that in large part, you defer to the 2012. Although we acknowledge that they continue to publish and there are new studies, and we also knowledge that, as we move to change how we do our risk assessment on these, that questions

will continue to rise.

I don't know if Jack or Dana would want to . . .

MR. JACK HOUSENGER: I was just going to concur with Dr. Koutros on the aspect of the analytic side. But I was going to add, possibly a way to answer the question certainly of Dr. Pessah would be, do you know if the study was conducted under GLP, and if not, back up your question to ask them. Good laboratories practices.

DR. ANNA LOWIT: I don't believe it was; although that would be an easy thing to check into. But keep in mind, all the analytical work was done at the CDC labs, and they have a long history of collecting blood and urine samples. So although we don't know how the samples were handled, I think it's a reasonable assumption that the Columbia investigators would have followed whatever protocol was given to them by CDC at the time.

DR. WILLIAM POPENDORF: By the way, that asked that question.

DR. JAMES MCMANAMAN: Marion.

DR. MARION EHRICH: Still have some problems with the analytical because everything refers

back to that Barr 2002 paper that came out of the CDC. But that group published again in 2010 and they have chlorpyrifos limited detection at 21 ppt, which is pg/g, and their linear curve at 21 to 6400 parts per billion, which is 1000 higher. In the 2011 paper, they concentrated their samples 200 fold. In the 2002 or 2001, the first paper, the Barr paper that's always used as a reference, they concentrated 400 fold, yet you are getting three significant figures for your cut off when you're concentrating something -- you have to dry it down, and then you have to re-suspend it.

There needs to be more looking at that particular analytical data because sometimes -- your calibration curve should go down to your limit of detection. And when that's in parts per billion and your limit of detection is given as parts per trillion, that gives this panel member, cause for pause here, to say the least.

DR. SHARON SAGIV: I think given some of these analytic concerns and the fact that this is based on one study, the Columbia study, I think that does -- it's a little bit troublesome. I wonder what people make of the TCPy measure that's the metabolic analyte for chlorpyrifos and why that hasn't been

examined. What do you make of that biomarker? Just because that would allow for a couple of other studies to be considered for chlorpyrifos.

DR. ANNA LOWIT: So in relation to the TCPy question, TCPy is not specific to chlorpyrifos. It's also the metabolite of chlorpyrifos methyl and triclopyr, also pesticides. It's also important when you look at TCPy data, TCPy is actually prevalent in the environment without further metabolism. So it's common for people to either expose in the diet or in their environment for TCPy.

So it's very difficult to interpret TCPy data from biomonitoring studies because you don't know what their exposure was before the study began or what their direct exposure to the TCPy is. It's often much higher than you would predict from just a straight up chlorpyrifos exposure.

DR. SONYA SOBRIAN: I have a question about your sample sizes. In your earlier studies, in the Whyatt studies, it looks like you are looking at the cord blood and maternal blood between 180 and then 90-something subjects. But if you look at the behavioral data from the studies in 2011, you're looking at 265 children, and you're trying to

correlate the changes in the behavioral measures with the blood levels; and the numbers don't add up. Can you speak to that?

DR. ELIZABETH HOLMAN: I believe the difference there is that you are talking about the validation study, which -- versus the studies where -- including all the study participants that have been collected across the years.

DR. SONYA SOBRIAN: It's just difficult to get some idea of what the actual sample size -- with the original sample size was somewhat and what the attrition rate was and how you -- you're looking at cord blood measures, and you're trying to correlate, at least if I understand, you're trying to correlate those with changes in behavior, in the 2011, with cognitive. But how do you know what is in the larger sample when you haven't -- your numbers for the validation sample are small?

DR. DANELLE LOBDELL: As far as the studies over time are concerned, they do indicate how many -- what is the follow-up, how many have not been retained over time within each of the individual studies. They also do comparisons between who has lost a follow-up and who has not, and if there are any

differences between those groups; and they have not seen anything as far as their attrition is concerned. So that is definitely highlighted and noted within and throughout the studies.

So, you know, given over time, you know, some of the earlier studies may be a little smaller because they haven't quite analyzed and brought in that data from those just into the cohort early on. So you are going to have some discrepancies in numbers early on in the early studies. And as the cohort grows and they bring in more of that data and it gets analyzed and brought in as they grow older, then you're going to see some of those larger numbers also.

But when you do validation studies also, you will do a subset of that and, you know, usually you take random sample of that.

So I don't know exactly how to answer your question, per se, knowing that, you know, to account for the differences in numbers, it's very common practice to take a subset to look at that validation representing the whole group as a whole.

DR. JAMES MCMANAMAN: A question?

DR. SONYA SOBRIAN: Just one more

follow-up. I guess the question is how confident are you that the validation study reflects the later number of children?

DR. DANELLE LOBDELL: I don't have any reservations and what they've done in their methodology and that aspect.

DR. JAMES MCMANAMAN: Dr. Pessah.

DR. ISAAC PESSAH: I have a question about, again, it's analytical, on cross validation.

Obviously, these samples were measured over many years; is that correct? That's my understanding. I imagine the instrumentation at CDC changed over those years, and has there been any attempt to cross-validate earlier samples to make sure that you get the same answer?

DR. ANNA LOWIT: Our understanding is that -- all that was done at CDC. As we've noted, we don't have access to that. Our understanding is that it was the same method used the entire time. And I am unaware whether or not they did any cross-validation across time or not.

DR. ISAAC PESSAH: As I understand it, the method was not identical.

DR. JAMES MCMANAMAN: Somebody want to

respond to that? That was a question to whom?

DR. MARION EHRICH: I cited two papers from that group. One is Barr et al., Journal of Chromatography be in 2002. That's one they used primarily for the references. And occasionally they move to citing Perez in Journal of Chromatography B. This is in 2010. But it's from the same group because Barr is the last author on this particular paper. And that's one that really has the calibration curve in it for chlorpyrifos, which is not present in this other one, even though some of those Whyatt papers from that group at Columbia say the method has been validated and so forth by this 2002 paper. It really is not there for chlorpyrifos.

So I'm just not comfortable with the analytical end of this whole thing. I'm sorry. But that's the way it is.

DR. ANNA LOWIT: We can go through the papers one by one and verify their methodology if it's something you would like us to do.

DR. JAMES MCMANAMAN: Well, it seems like we're off about a thousand fold in terms of validation. So there's a burning question for some panel members about the accuracy of the data. Yes.

DR. JEFFREY FISHER: Dana Barr is now at Emory. She was at CDC. She's still around. I think she would be a good person to talk to.

DR. JAMES MCMANAMAN: Thank you. Other questions?

DR. DAVID JETT: I wanted to go back to a couple of things Russ brought up, and then your comment about going back to other SAPs.

I'm still thinking about this issue of confounding exposures. I know this was covered in the other SAP, but it's hard for me to answer a question now about exposure scenarios without thinking about that. It's my understanding they did analyses on other agents, chemical agents, exposures.

I guess the general question is how were they chosen, and did you focus on agents that would potentially have an effect on an outcome that you were interested in based on what we knew about chlorpyrifos? Was that the general approach?

DR. DANELLE LOBDELL: Essentially, as far as the compounding is concerned, you would look at both its relationship between the exposure and the outcome. So confounding by definition means that it has a relationship with both. If you don't see a

relationship with one, then there is not confounding.

So for some instances, you may have some compounds that were measured and are related to neurodevelopmental outcomes. But if they're not related to the exposure chlorpyrifos, then they would not be considered a confounding within the models that you're looking at.

So that was a big basis of the discussions, actually, back in the 2012 SAP. And they looked through all the different types of exposures that were measured within the Columbia study, and there was a huge discussion between that in regards to what was going on and why or why not they were included in the models.

DR. DAVID JETT: But the selection of those in the Columbia study, we don't really know the rationale there? These are compounds that were measured, and then you tried to make that relationship of is it confounding or not.

DR. DANELLE LOBDELL: So I can't speak directly, so that's why I'm kind of hesitating a little bit. I cannot speak directly as to what they specifically did as far as thinking about confounding control. I can only speak to what they have put

within their papers, themselves.

In thinking about -- so we in general, nowadays, we use what we call DAGs to try to formulate what some of those relationships are. But those were just coming into being not quite when this study began.

But you use the literature, you use -- again, they looked at things and measures that they did have -- that they did actually measure within their cohort. But as far as classically thinking what they went through, I can't speak to that.

DR. SHARON SAGIV: I can tell you what groups that -- we do these studies. They usually see what they measured first. If they haven't measured lead, you can't look at compounding by lead.

They also think about how these exposures co-occur. So, for example, if you have an exposure that's much more prevalent in a lower socio-demographic population, then you would probably look at exposures that were also co-occurring in those low, low SES populations. That's how you kind of come up with which exposures to look at as confounders, as multi-pollutants. But usually it's whatever you have.

I did have sort of a question and a

comment. The first comment I had, and this is in regards to the neurodevelopmental outcomes, is that I think for the cohort studies, they didn't look at clinically diagnosed autism spectrum disorders. I think that's a distinction I think we should make for the record. In case-control studies, they certainly did. But for the -- I know Columbia did not do an ADOS or anything like that. They looked at CBCL or BASC, and they used symptoms that are consistent with ASD to -- but those aren't clinically diagnosed ASDs. So I just wanted to put that out there.

The second sort of question I have is you included a lot of different neurodevelopmental assessments, some of which are very early on in newborns and some that are in infants. Did you weight those equally with what you would see in, say, three- and seven-year-olds? Especially the NBAS, those are taken right at birth.

I mean, I think that most of the studies have found abnormal reflexes. That was the prevailing association they found. But I wouldn't necessarily weight them as high as a seven-year-old neuro outcome.

So I just wondered if you took that

into consideration.

DR. ANNA LOWIT: We haven't ranked them, per se, is what you're getting at with respect to weighting them. As described in the paper, and you will see in the presentation later on, as it relates to how you would use the data in a risk assessment, I'm not sure weighting them, per se, is really that important, per se. It's looking at the totality of the evidence and the weight of that evidence and the fact that there are multiple things found that are positive associations across the same children over multiple years is part of the strengths of the totality of the evidence.

DR. JAMES MCMANAMAN: I have one last question for Dr. Holman. Is the -- are the associations between chlorpyrifos levels in the blood and the adverse outcomes; you said they are highly correlated. Same level on all?

DR. ELIZABETH HOLMAN: Just to be clear, which studies are you referring to?

DR. JAMES MCMANAMAN: I can't remember whether you identified the particular studies or not. But you said there was -- the adverse outcomes were hardly correlated with chlorpyrifos levels. So I was

just wondering whether all adverse outcomes where they had the same level of correlation, same level of association.

DR. DANELLE LOBDELL: I just want to kind of clarify. You're indicating outcomes right now. But I think that the correlations that she was speaking of was the correlation between the maternal blood and the cord blood and that they were highly correlated throughout that time period. I believe that is what you may be referring to more so than the outcome.

DR. JAMES MCMANAMAN: I wrote a note saying that she mentioned that the associations were highly correlated with levels. But I may have misunderstood what she was saying.

DR. ELIZABETH HOLMAN: No. When I showed that table of the cord blood and the maternal blood measures, the intent was to show that they were similar and that the Columbia researchers did statistical analyses to determine whether they were correlated, and they were highly correlated.

In terms of the adverse health outcomes, across the two specific studies that we were talking about, the Rauh 2006 paper looked at multiple

measures where they had the high and the lower exposure group. And when comparing the high to low exposure group, they found at age three years, they found multiple associations with elevated risks of various outcomes, which I can talk about again.

DR. JAMES MCMANAMAN: So in those multiple associations, where the correlations, did they -- is the correlation between the level of chlorpyrifos and the adverse outcome, did they match?

DR. ELIZABETH HOLMAN: Yes.

DR. JAMES MCMANAMAN: Did some have a different level of correlation than others?

DR. ELIZABETH HOLMAN: Yes. No, there were different levels of correlation depending on the outcome. If you look -- I can find the specific slide number --

DR. STELLA KOUTROS: I think they're just a little confused because your terminology is a little bit different than what they are expecting. So what you're describing is the magnitude of the effects and the association between the exposure and the outcome.

DR. JAMES MCMANAMAN: Exactly. Sorry.

DR. STELLA KOUTROS: And I think he

just wants to know the magnitude of those associations, not the correlation.

DR. ELIZABETH HOLMAN: It's on slide 55, and it's the magnitude of the association is -- so it's comparing the same high and low exposure groups with that 6.17 pg/g cutoff. And depending on the outcome, for each of these, I've listed the odds ratio comparing the high to low exposure group followed by the 95 percent competence interval. So in each of these cases, they are considered to be statistically significant.

DR. JAMES MCMANAMAN: Okay. Thank you. Dr. Pessah.

DR. ISAAC PESSAH: So I actually did have a question about the correlation between cord blood and the maternal blood. Those samples were collected at labor and delivery, obviously, for the cord blood. What about the maternal blood? There are huge differences during pregnancy in terms of lipid. And if you don't account for that, I don't see how you come up with a correlative value. I assume that they were both collected . . .

DR. ANNA LOWIT: So clearly the cord blood would have been taken at or near delivery. The

maternal bloods, we don't know when they were taken, if they were taken at delivery. But the publications say that some of them were taken as much as two days later. But as we'll show in later presentations, that two-day window may not be as striking as it appears because once you hit what we call the terminal half-life where the clearance slows down -- the half-life is very long. So you get to a half-life of something in the order of four to five days. So a two-day window to collect the mother's blood is not as strikingly off as it may initially feel.

And we'll talk about that quite extensively in the coming presentations.

DR. CECILIA TAN: In the next presentation, I will talk about the comparison between a pregnant model and a non-pregnant model.

DR. JAMES MCMANAMAN: Thank you. Dr. Terry.

DR. ALVIN TERRY: This goes back to your question, Dr. McManaman, and this regression analysis where you say, yes, the higher levels are correlated with the worst neurodevelopmental outcome. But it's important to point out that this is in the evidence of dose effect.

So I was curious about this dichotomy where you have below six or greater than 6 pg/g and then -- is that a typical way the EPA would evaluate scientific data? I mean, people in pharmacology and toxicology always like to see some evidence of dose-dependence. And in this type of work, a temporal relationship, you have neither in this Columbia study that you are placing the most weight on. I just wondered what your thoughts were on that.

DR. ANNA LOWIT: I'll start and get help from others. I'll take the second half of that first.

I think there is, in fact, a temporal relationship here. Around the year 2000 -- remember, the children in the cohort were born over a several-year timeframe, from 1998 through 2004. And around 2000, as we will talk about extensively for the rest of the day, around 2000, the Agency took -- went into a voluntary cancellation agreement with the registrants at the time. What that did was remove chlorpyrifos from the home environment. Prior to that time, individuals could have gone to the store and purchased it. It would have been used by the building managers to -- within apartments of the women. But in

2000, those uses were no longer available, so they were actually removed from that environment. So there is actually a temporality to the data, and, in fact, the temporality is an important component of how we understand that data.

If you look at it up here on the table, and this same slide will come up several times today, if you look at the '98/'99, which would have been the time of the use at the indoor, you can see across the distribution that at the upper tails, you're above 10 pg/g in both cord blood and maternal blood. Just looking at those values, they are highly correlated. There's a nice comparison between them.

However, in the 2001 data, which would have been after the cancellation, you see the values are strikingly different. So it's not even above the LOD until you hit around the 90th percentile.

So there is, in fact, temporality to the data.

With respect to -- this temporality sort of creates a pseudo-dose-response, which is unique in epidemiology, looking at my epidemiology friends, that -- keep in mind the investigators at Columbia could not have predicted in 1998 that in the

year 2000, something major would happen with respect to regulatory action that would fundamentally change what was happening in the cohort. You couldn't have predicted that at the time. So there is this happenstance that happened that for the members of the cohort, there's a pre-cancellation set of children and a post-cancellation set of children, which creates the sort of pseudo-dose-response of the existence of the residential use and the removal from that environment.

DR. RUSSELL CARR: The question is, though, that we don't have the neurobehavioral data to match this. We know that if we remove the chlorpyrifos, the exposure level goes down. But do we have the neurobehavioral data past that point?

DR. DANELLE LOBDELL: They do actually have the neurodevelopmental outcomes measured in all of the cohort members.

DR. RUSSELL CARR: Well, what I'm saying is we have 2001, the levels went down. I'm talking about behavioral data from those children. That's what I'm talking about with the smoking gun, the measurements at seven years old for kids who were not exposed to chlorpyrifos at all. Where's that located?

DR. DANELLE LOBDELL: It's part of the analyses. So they would be included in the non-exposed group that are compared to the highly exposed group.

DR. RUSSELL CARR: Most of the ones, they stop in 1990 to 2001. The age ranges don't go all the way out to 2004, 2005 in those neurobehavioral studies.

DR. ANNA LOWIT: First, Russell, I'd like to see which publication you're talking about. Keep in mind the children in the cohort are continuously followed. So the same kids who are in the paper that they looked at, the three-year-olds are the same children at seven are the same children at 11. So they are tracked the entire time.

DR. RUSSELL CARR: I agree with that. But they've tracked other kids, too, who were born after chlorpyrifos -- the cessation of chlorpyrifos use. I'm saying it would be nice if we had that data.

DR. ANNA LOWIT: You do have that. Those kids are implicit -- can we bring up one of the slides with the greater than less point -- less than six point-something -- one of the high/low slides. We're looking for a slide to talk through that issue.

Earlier, there were some questions about the cutoff, the high versus low -- there we go -- on the low group versus the high group and where those numbers came from and everything else.

Russell, it's important to remember that the high group are basically the children before the cancellation. The low group are basically the children after the cancellation. There is a little bit of crossover. There's one kid in the high group that was born after the cancellation, a few months after it occurred. And there are a few kids in the low group that weren't that exposed.

You see the striking -- and it's in one of Beth's other slides, and it's across that distribution we see that there is this striking before and after. And all those kids are in all these analyses because they're all being tracked. So the low group represents those kids born after 2000 and who are also being observed for the same outcomes.

DR. RUSSELL CARR: I agree that for the cord data they did that; they separated out into those two cohorts. But I have yet to see it done for the neurobehavioral data.

DR. ANNA LOWIT: I guess we're not

understanding your question.

DR. RUSSELL CARR: On the cord blood, there is a paper by Whyatt that separates out where, from 2000 to 2004, they basically stopped seeing chlorpyrifos except for the one child you're talking about. But yet, I haven't seen it to where they take IQ data or MDI data from just those kids from 2002 to 2004 and compare it back to 1999. It's always done by variables, but there's kids prior to '99 that were low-level chlorpyrifos.

DR. ANNA LOWIT: Let me tell you what I'm hearing; you tell me if I'm following.

So you're wanting, instead of using the risk metric of the cord blood, the before and after, you're asking whether or not as a risk metric, they've looked at the before and after?

DR. RUSSELL CARR: Yes, just by the date, the exposure period versus non-exposure period.

DR. ANNA LOWIT: Not to my knowledge. But I guess I would ask you, given the temporality of the cord blood data, what would be the value added of that?

DR. RUSSELL CARR: If chlorpyrifos is indeed decreasing the IQ and causing MDI and PDI

problems, if you remove it, those children past that point should have higher values than the children during the exposure period.

DR. ANNA LOWIT: But they do. Can we put 55 back up -- 54 and 55.

So the metric being used by Columbia is the metric -- at least for the 2006 paper, which is the one that you're looking at -- separated by the low and the high by the 6.17. What that -- in a toxicology study you would look at, in most cases, a control, a low, a mid, maybe a high-dose, correct?

So in this case, it's just, you know, think of it as the quote/unquote, controls and some sort of dose group.

And in a toxicology study, you would note that by the administered dose they received. So either zero for the controls or some sort of metric dosed in the animals.

This is an epi study, so it looks different. We don't have that external dose metric to the children. The external exposure, as Wade will describe in detail this afternoon, we don't know what was on the surfaces in the apartments. We don't know how much was applied along the corners. We don't know

those things, but we're really good at predicting them, as we'll talk about later. So we don't know that administered dose.

So instead of administered dose, what we do have is also very powerful. It's that internal blood concentration, and that is the 6.17. So that becomes equivalent to your tox study. Normally in a tox study, we would talk about it administered dose to the animal. Here we're talking about that internal concentration.

So those low versus high, i.e., control versus dosed children, what we have here on slide 55 are the outcomes of those analyses of that dichotomous analysis for mental delays, so the low versus high, the risk ratio of that. The same thing with the psychomotor delay, the attention, the ADHD, and the PDD metric.

So, in fact, I believe we do have the question that you're . . .

DR. DANELLE LOBDELL: I understand where you're coming from. It's more of instead of using an exposure metric, you're using a time period as your exposure metric is what you're suggesting. So, basically, you're suggesting, and rightly so, I

have not seen the data that looked at post- versus the pre-.

However, you know, as Anna has pointed out, the large majority of the low dose really are coming from the post-. There are definitely some from the pre-period, and that is for sure. But a lot of your post- are within the low dose.

DR. RUSSELL CARR: The Rauh 2006 paper states the children came from 1997 to 2002. In 2002, we were still detecting chlorpyrifos in the majority of the children. It wasn't until after that point, from 2002 to 2004, that the numbers went down.

DR. ANNA LOWIT: No. That's not exactly accurate. Can we put that slide back up with the table?

So, Russell, this is a smaller version of the same -- of a bigger table that is, I believe, called Figure 1 in the issue paper that looks at the cord blood and maternal blood across each year of the study. All we've done for brevity for the slides is to just pull what we thought were the two most important years, the one before the cancellation and the one immediately after.

So if you look down across the

distribution, if you look at the 2001 which would be after, you have to get to the 90th percentile to see a value over the LOD. On your computer, if you open up the issue paper and look at Figure 1 -- I don't remember what page it's on -- but if you look at the data from '98, '99 to 2000 to 2001, there is a striking drop.

DR. ELIZABETH HOLMAN: Just to be clear, I don't think I made this clear when I talked about this slide, they split it into two groups, and the specifics were before cancellation, that was everyone before January 1, 2001, and the after was everyone after 2001. They did a statistical analysis, and this is the mean overall measure for those two groups, and they did conduct the statistical analysis and concluded they were statistically different between the two groups.

DR. MARION EHRICH: Comment on this one. That point six is below the level of detection in the Barr 2002 paper, and certainly below the level of detection in that same group's paper in 2010, which was 21. So most of them will be below what they call their level of detection in the 2010 paper.

DR. ANNA LOWIT: I appreciate that.

We've heard all the questions about the analytical techniques and have reached out to Dana Barr, and we will be calling her at the break to get some questions answered.

So there are two LODs in the study, as we understand it. Some of the samples had an LOD of one; some of them had an LOD of point five.

DR. STELLA KOUTROS: I just wanted to comment on the fact that I accept and appreciate the Agency's 10 past years of work to assess the quality and value and validity of the literature thus far, and accept that the conclusions drawn by the Agency about these data have already been made, and that I agree with them.

DR. JAMES MCMANAMAN: So it seems like -- I don't think Dr. Carr's question was resolved. But maybe it was. But it sounds like there is a discrepancy between the 2006 paper and the data that was reported in the slide. So perhaps we could get the 2006 paper.

Let's take a break because I know that you said you would get this data after the break. But that was assuming we did have a break. So if we don't take the break, you won't be able to.

DR. ANNA LOWIT: Before you break, you said there seems -- I guess we're still struggling with understanding where Dr. Carr thinks there is a discrepancy.

DR. JAMES MCMANAMAN: Unless Dr. Carr has been cleared up, I think it's with his interpretation of the 2006 paper.

DR. RUSSELL CARR: My point with before and after is basically throughout toxicology history, you have, for instance, eggshell thinning. You have before and after. PCB exposure, you have before and after. And those sentinel species that we're having trouble with, once you remove the exposure, they recovered. Based on their total publication route, not just chlorpyrifos, they had data from kids who were born 2004, 2005, 2006. I'm saying that data. We can take that data and compare it back to 1999, '98, '99, 2000, just to get an idea.

I know that's not your purview, but as it was mentioned, it would be really nice to have that just because that would be a true smoking gun. If IQs went up, then we're able to say, you know, it's pretty evident.

DR. ANNA LOWIT: Okay. So one last

point, and we will go call Dr. Barr. Keep in mind as you deliberate, that we are under court order to complete this action. That's within eight months. December is eight months from now, so we're under a very short timeframe.

So I would, again, Russell, remind you that the cohort does include the kids born in 2000, 2001, and 2002, which would have been after the cancellation for which they have measured those metrics and they have also done the Working Memory. So we actually have -- I don't know the numbers off my head. But I believe there are actually more kids after -- it's an easy number to get to -- than there are before.

So adding additional children born later, I guess I would, again, ask you how that information isn't already included.

DR. JAMES MCMANAMAN: I'm a little confused now, too. So the odds ratios that you just had up on the slide that I asked about, those were odds ratios for the kids born before and after; is that correct?

DR. ANNA LOWIT: It's the low versus the high.

DR. JAMES MCMANAMAN: Well, I thought the low versus the high were the kids born before and after, essentially.

DR. ANNA LOWIT: It's not a perfect separation, but conceptually, it's basically like that.

DR. JAMES MCMANAMAN: So that's where the issue lies, then, whether that is truly before and after or whether it's essentially before and after, I guess, is the question.

DR. ANNA LOWIT: Well, if it would be helpful, we can actually pull up the full table, not the little short one that we've got in the slides, and talk through the temporality of those data and talk through how '98/'99 are strikingly different from every other year. And even as the year 2000, you can almost see a transition as the numbers incrementally go down, and then strikingly go down further in 2001, and how comparable 2001 are to 2004.

If that would be useful, we can do that. Or if it's not, you all have the tables.

DR. JAMES MCMANAMAN: I think it would be useful. Dr. Sagiv.

DR. SHARON SAGIV: I disagree. I think

that having the actual levels is important. And looking at the temporality, I don't see how that adds to having the actual chlorpyrifos levels unless we are doubting the analytic method. That's the only way I could see that might be -- I don't see why looking at the before and after piece would be value added over looking at the dichotomy of high versus low actual measured levels.

DR. STELLA KOUTROS: I agree. From an exposure assessment perspective in an epidemiologic study, having a binary before and after is much more crude than the measure levels that we have.

DR. DIANE ROHLMAN: I also agree with that. I think if we think of the cord blood measures in the grouping into the high and low, it is really a surrogate for this before and after the regulations. So including both of those is a duplicate. And we have much more rigorous methods, as Stella just pointed out, with the cord blood levels.

DR. JAMES MCMANAMAN: Dr. Popendorf.

DR. WILLIAM POPENDORF: Well, I don't know if this is quite the time to bring it up, but I disagree with the validity of the cord blood data, really. Whether it's to the magnitude that it would

obviate this particular grouping above and below six, I'm not sure. But I think there is some real question about the values, particularly the high values that we'll talk about later, that might be gotten around by just looking at dates independent of a measured cord blood level.

DR. JAMES MCMANAMAN: Okay. With that, I think we should take a break. I hope that the questions that we have, the panel has, are clear, and there is certainly some disagreement. But let's take a break and see if we can sort this out.

(Brief recess.)

DR. JAMES MCMANAMAN: There were questions that were outstanding when we took the break, and we're going to formulate these questions into specific questions that we will ask -- that the Agency will ask the principal author of the papers to clarify over the next hour or so. And we will -- based on the response, we will read that back into the record and see if we can clear up this question, the analytical question.

Right now, given the late time, we're not going to -- take a lunch break at 12:30. I'm not sure how long the next presentation is. Will it fit

within that timeframe, or near that timeframe, I guess?

DR. CECILIA TAN: I can try to do it in 30 minutes.

DR. JAMES MCMANAMAN: So Fred is saying 12:15 for a break, for lunch break. I don't know whether that gives us enough time.

DR. CECILIA TAN: The alternative is for us to collect the questions from the last discussion.

DR. JAMES MCMANAMAN: We're trying to formulate them so they are very clear questions.

DR. ANNA LOWIT: Are we going to get the questions in the next half hour or will it be after the lunch break?

DR. JAMES MCMANAMAN: No. We'll get it before the lunch break. I don't know how long your next presentation is.

DR. CECILIA TAN: I can do it in 30 minutes.

DR. JAMES MCMANAMAN: Okay. Good. Go for it.

DR. CECILIA TAN: My name is Cecelia Tan, and I am a research scientist at the Office of

Research and Development. I am currently on detail assignment with the HED, OPP.

Before I start, I would like to -- I understand there are a lot of concerns about the, reservation about the data, the biomarker data that we have presented. But I would like to ask you, for the next 30 minutes, just assume that there is no problem with the data, and to just focus on whether or not you think our approach is appropriate to link biomarker data, specifically chlorpyrifos concentration in blood to exposure. Thank you.

So my presentation today will cover two topics. The first topic is a brief introduction to this tool, physiologically based pharmacokinetic, PBPK model, and how its capability to link external exposure to internal does allow us to apply this tool in risk assessment or biomarker interpretation. Also, I will provide a brief introduction to the PBPK model for chlorpyrifos.

In the second half, the second topic, we will focus on the two main uncertainties in interpreting biomarker data. They are likely exposure scenarios and time between exposure and sampling. And I will explain how we used the PBPK modeling and

exposure assessment approach in OPP in survey data to address these uncertainties.

PBPK model, physiologically based pharmacokinetic model. The PK stands for pharmacokinetic, and pharmacokinetics is the study of absorption, distribution, metabolism, and excretion, ADME, of chemicals in the body. A PBPK model is a series of mathematical representations of biological tissues, as well as the physiological processes, in the body that simulate the ADME of chemicals that enter the body.

PBPK modeling has been recognized by the Agency that it is a scientifically sound and robust approach to estimating the internal dose of a chemical. And also it is a means to evaluate and describe the uncertainty in risk assessment. These two quotes came directly from EPA report in 2006.

PBPK models, again, incorporate physiological determinants. For example, tissue volume, blood flow rates, and biochemical processes, such as metabolism or protein binding of how they determine chemical disposition. It can be used to simulate the time course of internal dosimetry, such as blood concentration of a parent compound or a liver

concentration of a metaboli under different exposure scenarios, for example, single daily oral exposure or eight-hour-per-day dermal exposure in different species.

In addition to the Agency, the larger scientific community has recognized PBPK modeling as a sound and quantitative tool to support risk assessment. When applying PBPK modeling in risk assessment, the underlying assumption is that an equivalent biological response occurs at equal tissue does, not at the equal external dose. PBPK model can be used to organize available mechanistic data and used to identify data gaps and suggest new experiments.

But the power of PBPK model lies in its capability to predict chemical concentrations under new and inaccessible conditions. PBPK models have been used in the past 20 years or so by academia, industry, consultants, other government agencies to extrapolate from high to low dose, and from animals to humans, different routes, route-to-route extrapolation, as well as across life stage, for example, from adults to infants.

PBPK models are also used to quantify

uncertainty and variability in physiology, for example, a different body weights in a population and ADME, for example, different capability to metabolize. It can also be linked to pharmacodynamic PD models to predict biological endpoints.

I want to emphasize that the PBPK model predicts tissue dosimetry, the concentrations, but not the biological endpoints. You have to link it to some sort of dose-response model.

In addition to risk assessment, another application of PBPK modeling is biomarker interpretation. So for biomarker interpretation, simply having a good model is not enough. When the purpose is to link PBPK -- link biomarker data to exposure, we need to know what are the likely exposure scenarios. We also need to know when and how biomarker samples are collected. Once we have that kind of knowledge, we can either use forward or reverse dosimetry to link biomarker concentration to exposure. In the next slide, I will give you more detail on what I mean by forward and reverse dosimetry.

If the purpose is to link biomarker data to health effects such as what is being done in

epi studies, we can use PBPK model to evaluate whether a biomarker that is measured in accessible media is a good surrogate for target tissue dose, for example, metabolite in urine is a biomarker. Is that a good surrogate for, for example, a parent compound.

Some definitions of forward and reverse dosimetry. Forward dosimetry is using the model and likely exposure scenarios, including the routes, the doses, the duration, and frequency of exposure to predict a biomarker concentration at a specific time point that matches the biomonitoring study and then comparing that prediction with the measured data.

Reverse dosimetry is you start with the biomarker concentration, incorporate your knowledge about the exposure scenarios and that temporal relationship between exposure and sampling to back calculated a range of possible exposure concentration.

Whether we use forward or reverse dosimetry, and even if you have the perfect model, it is critical to have knowledge about likely exposure scenarios in that time between exposure and biomarker sample collection. Here is a figure to further illustrate this point.

So here I have four different curves

representing the blood concentration of a chemical measured in blood over time. These four different curves represent four different exposure scenarios. For example, the green curve is repeated exposure to the same dose over time. And the brown curve represents two exposure events -- it's probably hard to see the little blip in front of the big one. So these are two exposure events at very different doses.

So if a biomarker sample is taken at that point where the red arrow is pointing, you would have measured the same concentration from four very different exposure scenarios. So you really want to know what are the likely exposure scenarios for those individuals who you collected the biomarker samples.

The next source of uncertainty is time between exposure and biomarker sample collection. If we now look at -- it's kind of hard to see the color -- the one in the middle, the orange curve, it is one exposure scenario. And if you look at the blue arrows, that represent taking biomarker samples at different time points. It really just depends on when you take the sample. Even though it's from the same exposure, your biomarker measurements will be different because of that time.

So now let's move on to chlorpyrifos. There is a PBPK-PD model available for chlorpyrifos. This PBPK-PD model was used in the 2014 Human Health Risk Assessment to derive point of departure based on 10 percent cholinesterase inhibition by oxon in red blood cells.

The scenarios that we look at are food exposure to chlorpyrifos, drinking water exposure by oxon-only exposure, currently registered non-occupational use, and worker exposure.

What is different in this current analysis, in the 2016 analysis, we did not use the PD model. We only used the PBPK model to simulate chlorpyrifos concentration in blood. The model is not being used to derive point of departure. It is just predicting blood concentration compared with exposure in the scenario we look at, food, water exposure, and worker exposure in our case studies, which we will present later this afternoon.

Here is a graphical representation of the chlorpyrifos PBPK-PD model. Since this model has been reviewed in the earlier SAP, I'm not going to talk about the detail of the structure. But mainly just to show you that this model predicts blood and

tissue concentration of chlorpyrifos and oxon, also the urine concentration of TCPy. In addition, there is a PD model that predicts the binding of oxon and cholinesterase in different tissue highlighted in blue there.

The chlorpyrifos PBPK-PD model was originally developed in 2002 and has been refined over the years as more data has become available. The latest version of the model includes multi-route exposure, oral, dermal, inhalation, and is published in the 2014 paper listed here. This model was reviewed by the SAP in 2011, and the Agency has continued to evaluate the model as it is being refined.

And here is to show you the chlorpyrifos model is one of the very few models that has had a lot of in vitro data for model calibration and evaluation. The grey highlighted boxes show what kind of data exists. And then there are data in both rat and human, in oral, inhalation, and dermal routes. The blood concentrations of chlorpyrifos-oxon TCPy as well as cholinesterase inhibition in different tissue and plasma, and also RBC. Also, I want to highlight that in blue here, we also have human data available

for both oral and dermal exposure. And then the data that is available are chlorpyrifos concentrations in blood.

So earlier I mentioned that we will be talking about the pregnant versus non-pregnant difference. So the biomarker measured in the Columbia cohorts were chlorpyrifos in cord blood. And we already showed you earlier that we believe that there is a strong correlation between the maternal blood and cord blood.

In our modeling analysis, we are using a 75 kg female as a surrogate for a pregnant woman. There is a version of the PBPK model that is available to describe the physiological changes and biochemical changes during pregnancy. During pregnancy, a lot of things are changing. For example, the fat to block partition lowers, but the fat mass increases, same as the other tissues. And there is this rapid increase in body weight and increase in blood volume; increase in urinary clearance; and also some changes of metabolism.

And then these changes are dynamic and complicated, and we are really lucky to have a model that can describe those changes.

This model is not peer-reviewed or published, and there are no time course data available to evaluate this version of the model. So we decided not to use the pregnant model in our analysis. But this model was built based on the best knowledge available of these changes during pregnancy.

Some preliminary results from comparing the pregnancy model and the average adult model suggested that because these combined effects of all these changes during pregnancy, the women in the third trimester has slightly lower chlorpyrifos concentration than non-pregnant women: slightly lower, not a lot. So we think it is reasonable to use a 75 kg female as a surrogate for a pregnant woman.

And now for the rest of my presentation, I'm going to focus on the two uncertainties when linking biomarker to exposure.

The first one is exposure scenario. The Agency has evaluated different scenarios likely to have occurred in the Columbia cohort and whether these scenarios could have resulted in the observed cord blood concentration found in this study. The scenarios that we looked at include food, drinking water, and residential indoor application use. The

detail of this evaluation will be presented later this afternoon.

What we found is that the most likely exposure scenario for these women in the Columbia cohort was dermal exposure from this once-a-month application of the pesticide. Again, the detail will be provided later this afternoon.

In this figure, I'm showing the time course of chlorpyrifos concentration, predicted chlorpyrifos concentration in blood, which has a unit of pg/g over a time period of about 33 days. What we are simulating here is daily dermal exposure for eight hours per day for 30 days to mimic the once-a-month application. It has an initial dermal dose of around 65 µg per kilogram, and the dose drops 10 percent per day. This exposure assumption, again, will come up later this afternoon.

The second source of uncertainty, as I mentioned earlier, is the time between exposure and sampling. For a lot of biomarker studies, we really don't know when the sample was taken in relation to the exposure. But for this specific cohort, it is a very unique condition because chlorpyrifos was measured in cord blood during delivery, and the time

between exposure and sampling is likely to be the time when these women leave their apartment, that's the end of exposure, and the time they deliver the baby.

Now, reported time for labor and delivery for the first pregnancy ranged from 8 to 20 hours. It may become faster for subsequent pregnancies.

You may say an average of 8 to 20 hours is still a really wide time range. But what I'm going to show you here is that because of the unique physical chemical properties of chlorpyrifos, and because of this unique labor and delivery condition, we can bind that biomarker concentration.

So what I'm showing you here is the last 140 hours from the figure, this figure I showed you earlier. So I'm looking at the end of exposure.

For chlorpyrifos, the clearance of chlorpyrifos is through the distribution to different tissues and also by metabolism and excretion of chlorpyrifos. Immediately after the exposure, chlorpyrifos is distributed to different tissues quickly and gets metabolized and binds with cholinesterase and excreted from the body. The half-life in this first phase is around three to four

hours, and this biphasic clearance is true for most of the chemicals.

About 8 to 10 hours after exposure, the clearance phase entered into this, we call the terminal half-life stage. The half-life during this stage for chlorpyrifos is about 120 hours, or five days. The reason it takes that long is because during the second phase, the chlorpyrifos is not being distributed to the tissues any more. It is only available for metabolism and excretion if it is available in blood. And because chlorpyrifos has a LogP of around five, it is sequestered in fat, and then it is slowly released into the blood. So it is slowly being cleared.

To give you some context when it means are rapidly cleared and slowly cleared, let's start at a peak. There some numbers here that you can look at.

The peak concentration is around 63 pg/g, and four hours after the peak, it is already at one-third of that concentration. Really fast. And around eight hours after the peak, the concentration is at around 14. Between eight and 20 hours, it only drops about 3 pg/g. And even two days after the peak, or 28 hours after the 11 pg/g level, it only drops to

9.6.

So for chlorpyrifos, we know that it's specific, this rapid clearance and the slow clearance in the second phase. Also, the time between labor and delivery is not going to be, I don't know, one hour immediately after exposure. There is a range. And during this range, chlorpyrifos concentration in blood is pretty stable. So we think the biomarker data that was measured is a reasonable surrogate for exposure, even though there is a lot of uncertainty.

Here's a summary. The PBPK model for chlorpyrifos has been evaluated using the human data, including chlorpyrifos concentration in blood, which is the biomarker measured in the Columbia cohort studies. We think using the PBPK model and our exposure assumptions and then also the survey data, all this information put together, we can address the two major uncertainties in interpreting biomarker data, which are exposure scenarios and time between exposure and biomarker sampling.

The likely exposure scenario, again, you will hear more this afternoon, is residential indoor use. And then the time between exposure and biomarker sampling, again, because of this unique

labor and delivery condition, it is about four hours and even up to two days that biomarkers that we are predicting is pretty stable.

Questions? Maybe I don't want any questions.

DR. JAMES MCMANAMAN: Thank you very much. So what we're going to do is we're going to break for lunch at 12:15.

So what I would like to do is maybe ask some immediate questions right now, and then I have some questions to be read into the record related to the analytical question. Dr. Hayton.

DR. WILLIAM HAYTON: Thank you. Very quickly, was that cord blood simulated or mother's blood?

DR. CECILIA TAN: It's mother's blood, and we are using non-pregnant women as a surrogate for pregnant women.

DR. WILLIAM HAYTON: Okay. And do you ever simulate cord blood?

DR. CECILIA TAN: No, because the model does not have that. We decided not to use the pregnant model.

DR. JAMES MCMANAMAN: Dr. Sweeney.

DR. LISA SWEENEY: Can you back up to slide number 73, the one that has the full 720-hour time course -- that one.

As I understand it from looking at the slide, you basically started with zero, whereas, if you had basically two months back-to-back, that your trough wouldn't be so low at the bottom. If you look at the bottom, you're sort of building up your trough. Is that because basically you're building up the fat stores, and so it's dropping more as a percentage in the early days? I guess a more realistic version of the Columbia scenario would be sort of two of those back-to-back and then do the analysis from the first?

Because if you look at that, the decline from the peak the same day to the delivery is going to be more if you happen to be at the beginning of the month. So that's actually sort of an artifact from -- okay. I wanted to be clear on that.

So if you go back to slide 75, two down from that, it shows the last peak. So that's really probably more representative of the decrease from peak to four to eight hours. Okay.

I spent a lot of time reading Dale Haddis's comments, and it seems he has data that you

have not incorporated or did not have access to. For example, in his analysis, he has specific information on the time from hospital admission to delivery. So it has the length of time for each -- and it's correlated to a blood sample concentration because he correlates the time from entering the hospital to the blood concentration. So it seems like for every individual in the study, he has the amount of time for the delivery. So it seems like for each point, you could back it up to a previous peak, that you don't have to just assume number of hours for labor.

DR. JAMES MCMANAMAN: This is for clarification not for -- when we get to the charge question, we can --

DR. LISA SWEENEY: Yeah. Okay. I was just, you know, pointing out that you made assumptions here where maybe if you had access to all of the data -- there's evidence of this data being available within the last couple of years. So it's not going back a decade.

DR. JAMES MCMANAMAN: We can discuss that during deliberations.

DR. LISA SWEENEY: Okay. I just wanted to clarify whether you had the data or not.

DR. ANNA LOWIT: One point of clarification for Dr. Sweeney: Dr. Haddis has collaborated with the Columbia investigators for a few years, and he has access to information that other people outside their group has not had access to.

DR. LISA SWEENEY: Okay. That clarifies that. Thank you very much.

Also on this figure, did you specifically do a sensitivity analysis of the predicted blood concentrations, say, at 720 hours, or something like that, to verify that it is specifically sensitive to the fat plasma partition coefficient or any other model parameters? Did you do an analytical and not just sort of a, yeah, I think this is why it is, but actually mathematically say, yes, if the fat partition coefficient were three times as high, it would be different?

DR. CECILIA TAN: Dr. Sweeney, we did not do a sensitivity analysis with the output of blood concentration of chlorpyrifos. That is an excellent idea. We do, however, look at a range of exposures and also compare that with -- just to predict blood concentration from a range of exposures, sort of like a variability analysis. And what we found is that the

scenarios that we look at kind of bound the data that was found in the Columbia studies. But we did not do a sensitivity analysis.

DR. LISA SWEENEY: Thank you.

DR. JAMES MCMANAMAN: Okay. So I think we'll hold questions until after the lunch break, further questions. And let me read these questions. You're going to transcribe these in, but we will also print them out and make them available.

So the questions are related to the analytical -- specifically related to the analytical question and the apparent discrepancy with that. This is related to the Barr et al. (2002) paper which gives the limit of detection for chlorpyrifos at 1 pg/g. But 0.5 to 1 pg/g were used as the limit of detection in the epidemiological studies and referred to in a number of subsequent papers. So there is a difference between limited detection and what was used in the papers.

And in another paper by Perez et al. (2010), it gives chlorpyrifos a limit of detection as 21 pg/ml with a linear range in the microgram per milliliter range of 21 to 6700. So it's got a limit of detection of parts per trillion, but the linear

range was in parts per billion. So there's another discrepancy there.

DR. ANNA LOWIT: Is it possible to get a Xeroxed copy of what you're reading from?

DR. JAMES MCMANAMAN: Yes. Would that make it easier?

DR. ANNA LOWIT: Yeah. You're going pretty fast.

DR. JAMES MCMANAMAN: Okay. So we'll just Xerox this. But let me read the questions in just so they are in the record.

The questions are, how can quantitation be done outside the limits of the linear range?

What was the signal to noise ratio on the limit of detection?

And in Table 1 of the issues document, which is on page 14, it gives the results as 2500 pg/g, which is 2500 ppt. And it looks like the 2500 pg/g was below the limit of quantitation. How does that convert to the cutoff data in pg/g of 6.17? So the 6.17 looks like it's really below the 2500 pg/g that was used in that issues document.

So those are the questions.

DR. ANNA LOWIT: Well, the last one we

can help. We can cover the last one. We apologize for the quality of the table. That's the way it was provided to us by the Columbia investigators. You have to look very closely. It's actually .25, not 2500. There's a 0.2500, is actually what the values are. That is below the LOD. That was the indication that was sent to us.

DR. JAMES MCMANAMAN: My glasses aren't good enough to read that table.

DR. EHRICH: They say pg/g, and then they gave 2500 below it? Is that 2.5?

DR. ANNA LOWIT: Are you looking at the --

DR. EHRICH: I'm looking at page 14.

DR. ANNA LOWIT: It's a .25.

DR. EHRICH: But then 2.5 would have been below the limit of detection. See, there's a mess with limit of detection --

DR. ANNA LOWIT: That's the way it was sent to us. They did that indication of the .25 to signify all the samples as below the LOD. If you look at the footnote to the table, it should say that.

DR. EHRICH: What footnote? We don't have a footnote.

DR. ANNA LOWIT: There's no footnote? There should be a footnote.

DR. JAMES MCMANAMAN: This is the white paper that was distributed for this particular panel meeting on page 14.

DR. ANNA LOWIT: Yes. So I have it open in front of me, also. Again, we apologize for the quality of the appearance. But it's .2500. So if you start at the top, it's .2500 and then again and again and again. And then -- should be point five-something. And then I think that's a three -- three point-something, and nine point-something. I'll have to blow it up to read it more closely.

DR. EHRICH: But if it's .25 pg/g, which is what they have on the top, that's below what they've given as a limit of detection. How can you --

DR. ANNA LOWIT: It's not intended to be quantified. It's intended to indicate that all the values are below the LOD. It's probably indicated as half the LOD at the point five.

DR. EHRICH: We had no information to let us know that.

DR. JAMES MCMANAMAN: Okay. So we have, again, this will be Xeroxed and give it to you.

Marion, did you have another question?

DR. EHRICH: No, that was --

DR. JAMES MCMANAMAN: So then the other questions the panel would like clarification on from the Agency is were there instrument differences between the early 1998/'99 and later analytical measures?

I thought that you answered that, but could you just clarify whether there were or not?

Number 2 is cross-validation -- were there cross-validation of early samples with later methods of instrumentation?

And then there is a question about the chain of custody.

So those are the questions if they're available and can get access to them, we would like to have answers to, and we will make copies of these and provide them.

DR. ANNA LOWIT: So the plan is you will give us those Xeroxed copies, we will type them in over lunch, email them to Dana Barr, and she is standing by to respond. So as soon as we get those --

DR. JAMES MCMANAMAN: And the Agency will respond with some clarification.

DR. ANNA LOWIT: Right.

DR. JAMES MCMANAMAN: Okay. So we're going to take an hour lunch break. So be back at 1:17.

(Whereupon, at 12:15 p.m., a luncheon recess was taken.)

DR. JAMES MCMANAMAN: Who's up next? Oh, that's right. I'm sorry. Yes?

DR. WILLIAM POPENDORF: I had a question, if I find your slides here. On your slide, you are talking -- there was a slide that had the information on duration of active labor, I believe it was, or something related to labor. Yes. And in the issues paper, Neil 2010 was referenced, and that it was like six-hours average with a standard deviation of three-and-a-half. Your numbers here are different from Neil's, and what I thought was in the issues paper. So why is there a difference?

DR. CECILIA TAN: There are many different sources that report the time for labor and delivery. You're right; in that issue paper we have that number from a specific reference. And this number, I also found it on other medical references.

But our point is to show that even if

considering a very short -- short labor time, say, four hours or less, three hours, and up to, say, two days. What I show here is that the concentration within the time range is pretty stable.

DR. WILLIAM POPENDORF: So there is a difference. We can discuss the meaning of it later, but there is a difference in what you're showing here. But you do have references for those numbers. So, okay.

DR. CECILIA TAN: Right. There are discrepancies, everyone reporting different things, different studies. They should have different results.

DR. WILLIAM POPENDORF: Okay.

DR. JAMES MCMANAMAN: Other questions?

(Whereupon, there was no response.)

DR. JAMES MCMANAMAN: Okay. So, the next session is by Wade Britton, Rochelle Bohaty, and Danette Drew, and I don’t know who goes first.

Was there another question? Sorry. Absolutely. I didn't see your hand up.

DR. JEFFREY FISHER: Yes, it's me.

You didn't go into details, but in the document, it talks about problems with axle

(phonetic). I don't know if it's memory problems. And I couldn't understand how you dealt with integrating the exposure routes with a PBPK model drinking water relative to the problem that was apparent with the software. I don't know what those sentences mean. I could look them up. I don't mean to put you on the spot.

DR. WILLIAM POPENDORF: It had to do with the duration of the runs that exceeded the capacity of the computer software.

DR. CECILIA TAN: Dr. Fisher, to respond to that question, I'm referring to the runs that -- results that we'll show in the next presentation. So for drinking water scenarios, we have data for a full year, water concentrations for a full year. But the software is not able for me to run hourly to integrate. So the model is run in units of hours. So you can imagine 365 days, that's how many hours. The software is not capable to -- the memory problem. It cannot retain all the numbers.

And it didn't matter in our case because we could run simulations in segments. But what we did is, we choose the maximum concentrations within that year. If you see the concentration in the

next presentation, you'll see that it's pretty flat throughout the year, and then there were some few peaks; and we focus on those high exposure to predict blood concentrations.

DR. ANNA LOWIT: Just for clarity, the issue we're talking about will actually come in the afternoon at the 3 o'clock presentation. But we're talking about what is Figure 9 in the document. We can talk about it later, but that's the run that we're talking about.

DR. JAMES MCMANAMAN: Okay. So we're asking if there are any follow-up questions to the presentation that came before the break. Those members that just came in, if they have questions, feel free to ask them now. If not, we will move on to the next presentation.

(Whereupon, there was no response.)

DR. JAMES MCMANAMAN: Seeing none, I'll turn it back to the Agency for the next presentation.

DR. WADE BRITTON: Good afternoon. My name is Wade Britton. I'm an environmental health scientist with the Health Effects Division of the Office of Pesticide Programs. Today I will be joined by Dr. Rochelle Bohaty, Environmental Effects Division

of the Office of Pesticide Programs, as well as Danette Drew, chemist with the Health Effects Division.

Today we will be presenting the evaluation of Columbia blood data and predicted exposures.

I'll just begin stepping through an outline of the presentation today. We begin our presentation with an introduction of the evaluation of the likely exposures to the women in the cohort.

We will then present the methods used and the results of our evaluation for these likely exposures. These exposures include drinking water, food, and residential.

Finally, we will present the conclusions of our evaluation.

The report from the 2012 SAP urged the Agency to find new ways to use the epidemiology studies from the three major children's cohort studies to inform the chlorpyrifos assessment, in particular, the Columbia study. The report stated that assuming these data reflect exposure levels during critical period of prenatal development, then these data will be ideal to derive a point of departure for

chlorpyrifos.

For use of the epidemiology studies, the Agency was encouraged to apply the chlorpyrifos PBPK model to further characterize Columbia dose estimates through additional analyses in the event the Agency decided to move beyond the acetylcholinesterase inhibition endpoint.

We saw this slide earlier today, but I wanted to show it again just because it's afternoon and for a point of review. We are talking about the Mothers and Newborns Study of North Manhattan and South Bronx, which was conducted by Columbia University.

Columbia measured parent chlorpyrifos in the cord blood and other indicators including air sampling, as well as behavioral information.

The other two birth cohorts, the CHAMACOS and Mt. Sinai birth cohorts, generally measured non-specific urinary metabolites of chlorpyrifos and other OPs, including TCPy and DAPs. For this reason, EPA has focused its exposure analysis on the Columbia study data as it is the most relevant to the chlorpyrifos Human Health Risk Assessment.

We're becoming more familiar with this

slide; you'll see this many times today. This is the distribution of the Columbia blood data. Again, as presented, we see '98/'99 blood levels compared to the 2001 blood levels for both cord blood and the maternal blood.

The point to make here is that we are using this data for basis of comparison to PBPK-predicted chlorpyrifos blood levels resulting from the likely exposures to the women in the cohort.

Just to give some history for chlorpyrifos, and also we've heard some of this earlier, but I will reiterate some points. Chlorpyrifos was one of the most widely used insecticides during the time of the Columbia cohort, and we believe these exposures were likely to have occurred. It was used on a variety of food and feed crops at the time of the Columbia study, and these uses continue today.

For the cohort, dietary exposures, including both drinking water and food, are likely given these uses.

In 2000, nearly all the residential uses of chlorpyrifos were voluntarily canceled. Until that time, they remained one of the most widely used

residential insecticides on the market.

In accordance with the 2012 SAP report, EPA has evaluated the exposures likely to have occurred to the Columbia cohort, and with use of the PBPK model, whether these exposures could have resulted in this study of chlorpyrifos blood levels. The following steps were taken to conduct these evaluations.

We first had to define the exposures likely to have occurred to the women in the Columbia cohort, these being, again, the drinking water, food, and residential exposures.

Next, these exposures were estimated using standard EPA methodologies.

Finally, these exposures were estimated for each route of exposure, were inputted into the PBPK model, and the resulting chlorpyrifos blood level predictions were compared to the Columbia study blood levels.

At this time, I will direct your attention to Dr. Rochelle Bohaty who will discuss the drinking water exposure evaluation.

DR. ROCHELLE BOHATY: Hi everyone. I'm Rochelle Bohaty in Environmental Fate and Effects

Division. I'm a chemist and an exposure scientist here. I want to share with you the analysis that I did to determine the potential exposure of the cohort to chlorpyrifos via drinking water.

Surface water is the primary route of exposure for chlorpyrifos as 99 percent of New York City's water is supplied through sourced surface water. I have identified the watersheds shown on this map of where the source drinking comes for New York City.

One thing that's interesting or important to note is that New York City watershed, they have a protection plan that many believe to eliminate the potential contamination of the drinking water. However, after careful examination of that watershed protection plan, I cannot simply rule out the potential exposure to chlorpyrifos. The protection plan primarily relies on best management practices that likely reduce the potential exposure but cannot completely eliminate it.

As an example to this, I have a second map showing down here the same watersheds that you see on this map are like underneath an agricultural use site layer where you can see there is an overlap of

agricultural use sites within the watershed. It also doesn't highlight potential for urban exposure as well within some of those watersheds. So as such, this analysis doesn't completely eliminate the potential for chlorpyrifos exposure or exposure to chlorpyrifos-oxon transformation product of chlorpyrifos.

Just to quickly mention, chlorpyrifos is converted to chlorpyrifos-oxon during drinking water treatment processes, typically chlorination. However, not under all drinking water conditions is it converted. But this is an important thing to consider when trying to evaluate potential exposure to chlorpyrifos or chlorpyrifos-oxon when considering finished drinking water. And it becomes important on my next slide.

First, once we knew the watersheds, I went to other water-monitoring data that we have available for chlorpyrifos, and I looked at the data available for the years of the cohort. And you can see from the figure or the table on this slide that the exposures would have been relatively low based on this water monitoring data. And actually, the only years with measured detection of chlorpyrifos in

surface water, and this isn't necessarily -- it's not drinking water or finished drinking water, is in 2000 and 2001. The other data that you see up there are one-half the detection limit. So this suggests that if exposure were to occur to chlorpyrifos, it would have happened at really low concentrations.

I also went to the New York City Community Water Systems reports for each one of these years and examined the different samplings that they did for chlorpyrifos as well as other compounds, and there was no detection of chlorpyrifos during these years. But in the process of doing that, I discovered that New York City relies heavily on -- or only on chlorination at least during the time period of the study for disinfection, and in this case, chlorpyrifos has been observed almost completely to chlorpyrifos-oxon. And I have a table showing that in the presence of chlorine, the reduction can be as low as 85 percent. And in some cases, it's much, much higher. So this suggests that potential exposure to chlorpyrifos was very low and as such -- or through drinking water would have been nonexistent and as such, couldn't have been measured in cord blood and correlated with the observed effects in the Columbia

study.

I'm going to turn it over to Danette Drew who will talk about food exposure.

DR. DANETTE DREW: Danette Drew, OPP Health Effects Division. I'm just going to speak very briefly about the food exposure. So as part of the 2014 Human Health Risk Assessment for chlorpyrifos, a dietary exposure analysis was performed. This analysis considered combined exposure from all food commodities, from crops or livestock with tolerances for chlorpyrifos. This analysis included chlorpyrifos as the residue of concern in food. As based on the results of food monitoring, crop metabolism and other field studies, the oxon metabolite is not expected to occur in food.

This analysis included the acute and repeated exposure durations and examined exposures for females of childbearing age, infants and young children.

Just a little background on the methods, the methods that were used have undergone previous multiple peer reviews by the FIFRA SAP, and I should also mention that these methods have also been presented and discussed at various forums in order to

get input from our stakeholder community.

The methods included the following models: The Dietary Exposure Evaluation Model, or DEEM, with the Food Commodity Intake Database; and the Calendex-FCID Model. Both these models incorporated the 2003-2008 consumption data from USDA's National Health and Nutrition Examination survey "What We Eat in America." This consumption information is combined in the models with the known residues in food in order to calculate exposure.

Okay, so how are we using these food exposure results today? The food exposure results are reflective of those which would be expected in the Columbia cohort. The food exposures have been used with the PBPK model in order to: 1) Predict chlorpyrifos blood levels that may occur from food exposure; and 2) To evaluate the contribution of food as a source of exposure of chlorpyrifos for women in the Columbia study.

The PBPK model was used to predict the chlorpyrifos blood concentrations from food for the following scenario: Females reflecting the NHANES body weight value of 72.9 kg following a single repeated daily exposure to chlorpyrifos in food. This was

performed using the food exposure results for a range of percentiles of exposure. The resulting PBPK predictions for the chlorpyrifos blood levels at 10 hours and 24 hours after the peak exposure through food are then compared to the blood levels measured in the Columbia cohort. These times were used to approximate the period which would be expected between labor and delivery, specifically between a meal and delivery when the blood samples would be collected. We may have more discussion on this case later today.

This table shows the comparison of the PBPK-predicted blood levels from food to the blood levels measured in the Columbia study after the cancellation and/or uses at several percentiles of exposure. So the second and third columns from the left are the predicted blood levels at 10 hours and 24 hours after the peak exposure from food. And the blood levels are less than the limited detection under most circumstances, the predicted levels. And the fourth column, I think you might have seen this before as well, that's the measured blood levels after the indoor use cancellation. These levels are less in the LOD at the 75th percentile of exposure and below.

We concluded from these results that

while food exposure to chlorpyrifos occurred before and after the cancellation of and/or use, food exposure is not contributing to the measured blood levels in the Columbia cohort across much of the distribution. That's all I have. We're back to Wade Britton.

MR. WADE BRITTON: All right. On residential exposures now. The analyses of residential exposures likely in the Columbia cohort have been conducted based on recommendations from the 2012 SAP. The recommendations identify the characterization of pre-cancellation exposure to the women in the cohort as a key uncertainty and using the epidemiology data for quantitative risk assessment. And the recommendations state that since the actual levels of exposure during critical windows of susceptibility are not known, it's necessary to establish a range of possible exposures to the women and whether acetylcholinesterase inhibition would have been elicited.

The agency has conducted two separate evaluations of the Columbia cohort residential exposures, the first in 2014, and the more present 2016 analysis. The first, termed The Dose

Reconstruction Analysis, was conducted in support of the 2014 Chlorpyrifos Human Health Risk Assessment. This analysis evaluated several indoor exposures likely at the time of the cohort and whether these exposures could have elicited 10 percent red blood cell acetylcholinesterase inhibition, the regulatory endpoint for chlorpyrifos. A second more recent biomarker analysis was conducted to make use of the PBPK model under a variety of exposure conditions to predict chlorpyrifos blood concentration for comparison to study blood levels.

In order to evaluate residential exposure to women in the Columbia cohort, it was first necessary to define the types of exposures expected. In 1997, all chlorpyrifos residential indoor broadcast and total release aerosol or fogger uses were voluntarily cancelled. However, the remaining or existing stock of these formulations were phased out until applied or depleted.

In 2000, the technical registrants agreed to phase out of nearly all the remaining residential uses including indoor crack and crevice and home lawn uses. While these product cancellations occurred during the time of the Columbia cohort, the

phase out implies that exposures could have continued to occur since these uses could have remained in the chain of trade and been legally used.

Again, chlorpyrifos is one of the most widely used insecticides during the time of the Columbia cohort and indoor residential exposures were likely to have occurred. In order to better understand residential exposure to women in the cohort, we made use of all available usage information from the Columbia study. In Whyatt et al. (2002) it was reported that pest control measures were used by 85 percent of the respondents either by treatment themselves, of by housing superintendent or by pest control operator or that would be a professional application. Whyatt et al. (2009) reported that of those who used pesticides, these were used once monthly.

EPA also reviewed all product and application types available at the time of the Columbia cohort. And those reported by the women to better understand whether these uses may have been used. Whyatt et al. (2002) the respondents recorded broadcast and crack and crevice or perimeter treatment

by a pest control operator or a professional occurring 39 percent of the time. They reported 26 percent of the time using an aerosol can spray, and that would be application by themselves. And 5 percent of the time, total release fogger or bombs were used, and again, this would be a user application. Products at the time in the residential market were registered as both 0.5 percent and 1 percent active ingredient formulations.

The 2014 Dose Reconstruction Analysis was conducted with use of the 2012 standard operating procedures for residential pesticide exposure assessment, hereafter termed the 2012 Residential SOPs. The 2012 Residential SOPs were subject to SAP review in 2009. For this analysis, any available chlorpyrifos specific exposure data were considered for use in conjunction with approaches outlined by the SOPs. Adult handler and children's post-application exposures were assessed, where a handler exposure would be the application of the product indoors by the women in the Columbia cohort themselves, and post-application exposures would be exposures following that application to adults on a treated surface, in this case, treated flooring.

The following SOP inputs were used to assess residential exposures. We used the maximum or the 1 percent active ingredient formulation available at the time. We assumed an exposure duration of 8 hours, and this would be 8-hours' activity on a treated carpeted floor daily and 2 hours on a treated hard floor daily. And as for the amount handled or the amount applied by the women in the cohort, we assumed one entire spray can for broadcast treatment or treatment of the entire flooring surface by the women in the cohort or a half a can for crack and crevice application.

Available exposure data includes registrant-submitted studies and data from the open literature. And although a number of studies, these are primarily related to indoor crack and crevice and broadcast treatments, which were the most prevalent uses at the time.

As previously described, the PBPK model was used to estimate red blood cell acetylcholinesterase inhibition from these estimated exposures. For adults, both dermal and inhalation exposures were assessed for handler and post-application activities, and for children, post-

application dermal, incidental oral, and inhalation exposures were assessed. For the PBPK modeling, we used specific inputs and the intention here to be a screening level assessment. So when you look at these inputs, that is the intent there. We assumed that the women spent 24 hours a day in their residences and were exposed through that exposure period. They did not leave the residences for 14 days as modeled, and there was no adjustment for bathing or showering during the 14-day period.

Based on evaluation of chemical-specific exposure residue data, a 10 percent daily residue dissipation input was used. Despite the use of these screening-level modeling inputs, all exposures assessed resulted in less than 10 percent peak red blood cell acetylcholinesterase inhibition for all the exposures assessed. And I'll note here that the highest of all the exposure scenarios resulted in the broadcast in the perimeter treatments being the highest and that we carried that forward into our 2016 analysis.

The 2016 biomarker analysis is conceptually similar to the 2014 analysis where both used the 2012 residential SOPs, and any available

chemical-specific exposure data was considered. However, whereas the 2014 residential analysis used the PBPK model to evaluate whether 10 percent red blood cell acetylcholinesterase inhibition could have occurred in the cohort, the 2016 analysis uses the PBPK model to evaluate chlorpyrifos blood concentration following exposure and compared these to the Columbia study blood levels. Further, the 2016 analysis focuses only on adult post-application exposures scenario. And for the 2016 analysis, the PBPK model was used under a variety of expanded exposure conditions, and these are specific to the model input; and I'll discuss these in greater length in several slides.

A total of six post-application exposure scenarios were developed to establish ranges of possible exposure to the women in the cohort and compare predicted chlorpyrifos blood levels reported by Columbia. The two post-application exposure scenarios shown here, these were conducted in order to mimic the highest exposure possible indoors.

The first scenario there is the broadcast treatment where the application of a liquid chlorpyrifos was sprayed by a professional to the

entire surface of a hard floor. Consistently in the 2014 and the 2016 assessments, this was the highest of all exposure scenarios.

The second scenario is a perimeter application of liquid chlorpyrifos by a professional in a band or strip around a carpeted room. We believe this based upon the cancellation in 2000 that this was likely the predominant type during the Columbia study.

Four additional post-application exposure scenarios were assessed using the highest reported Columbia study chlorpyrifos blood level as an anchor for analysis, 63 pg/g per day. We use this blood value as an upper and lower bound for PBPK modeling. So in this case, we're not assessing exposures prior; we're using this actual value as a point in our modeling and back calculating exposure.

Two of the four post-application exposure scenarios simulate what exposure that would have resulted in a peak 60 pg/g blood level on the final or the 30th day of modeled exposure. This was repeated assuming exposure to both hard flooding and to carpet flooring two and eight hours respectively.

From this 30th day, the 60 pg/g peak occurring on the 30th day, daily exposures were then

back calculated to the day of application. Two additional post-application exposure scenarios simulate what exposures would have resulted in 60 pg/g blood level on the first day of modeled exposure of the day of application. Again, these simulations were repeated for the hard floor and the carpeted floor, and in this case, the simulation occurring on the initial day was then simulated or modeled forward to the 30th day of modeled exposure.

As I said previously, some of the 2014 and the 2016 analysis PBPK exposure inputs differ, and the point being here -- or the purpose of this was to try to be more realistic in our assessment and our modeling of the women in the cohort in the 2016 analysis. We assumed that a daily shower occurred to the women and that they were exposed, as reported, once monthly, and then the exposure period carried out for 30 days following that just prior to the next pesticide application. We assumed that the women were exposed daily eight and two hours for the activity period on carpeted and hard flooring respectively. And in some cases, the inputs for the 2014 and the 2016 analysis were the same, and this that we assessed daily post-application indoor exposures. We assumed

that this was based on a single pesticide application, and again, based upon the evaluation of available data, we recommended a 10 percent daily residue dissipation input.

The results of the PBPK modeling of the six post-application exposure scenarios result in a consistent trend of exposures over the 30-day model period. All exposures modeled exhibited a saw-tooth pattern of daily, rapid increase in chlorpyrifos blood concentration during the exposure period and a rapid decline following the exposure period.

The rapid daily decline occurs just following the end of exposure and the showing event, and this decline continues until hour 24, just prior to the next day's exposure event. Once the next day's exposure event begins, the internal dose rapidly increased once again.

Peak internal dose for all exposure scenarios assessed occurred on the day of application, the first day, and then daily internal dose declines step-wise with each subsequent day due to the daily residue dissipation.

And finally, following peak on the final day of the exposure, the internal dose continues

to decline during terminal clearance phase.

I relayed these points just prior, and I will now step through the examples of the simulations that we conducted and describe how these trends play out in each post-application scenario. This slide presents example simulation resulting for the perimeter and the broadcast post-application scenarios. Again, these are our highest exposure scenarios intended to mimic exposures indoors. In both simulations, the saw-tooth pattern, or the daily peak blood concentrations during the exposure period and the decline immediately following exposure, can be observed. These peak concentrations decline daily in a step-wise fashion due to the residue dissipation input, and as you can see following the final day of modeled exposure, the 30th day in both cases, we see total clearance phase occurring. Please note the scale and the difference in the blood concentrations model for the perimeter and the broadcast exposure scenarios with the broadcast exposure scenario to the right being modeled at 7200 approximately pg/g on the initial day; and perimeter application to the carpeted flooring as scenario model is approximately 1100 on the initial day.

This slide presents two example simulations resulting from the use of the highest reported Columbia blood value, the 60 pg/g as the bounding estimate. Both examples provided in this case are for the two-hour or the hard flooding exposure scenario. On the left is the exposure scenario model to use the blood level as a bound on the initial day of exposure or the day of application. And to the right is the exposure scenario modeled to use the blood level as a bound on the final day of exposure. As you'll note, these simulations exhibit the same trends observed for the other modeled exposure scenario.

This table summarizes the results of all six post-application scenarios modeled. I'm not going to step through line-by-line, but I will follow this table with slides, which present the results as figures. But first, I'll introduce what we're looking at here, with the leftmost column being the post-application exposure scenarios assessed, and as we move to the right, we have the highest peak blood concentration. This is the blood concentration occurring again on that initial day of exposure, the day of application.

The next column over follows with the 24-hour blood concentration. This is the predicted blood measure at hour 24 on the day of application.

Next, we have blood concentration 10 hours following the peak on the 30th or the final day of modeled exposure. So we have our peak on the 30th day, and this would be 10 hours following that point. And the subsequent column to the right is the 24-hour time point following the peak on the final day of modeled exposure.

Presented on this slide are the results of chlorpyrifos blood concentration on the first day of modeled exposure. Beginning from the leftmost figure printed here, is the broadcast or the hard floor exposure scenario, and next to that to the right is the perimeter carpeted floor exposure scenario. These two scenarios here again -- these are our highest post-application exposure scenarios, the ones that were intended to mimic high-end use indoors.

The next four post-application exposure scenarios shown are the exposure scenarios which used the 60 pg/g or the highest Columbia blood level as the bound, the first two being the bound occurring on the 30th day of exposure, these two, and the final being

the day of application where the 60 pg/g was modeled to occur. I'll make a note here that the 60 pg/g on day 30, this would be the day of application. So 60 pg/g was modeled on day 30, but this is the back calculation. This is the point on the day of initial exposure, the day of application. If this were back calculated, this would be day 0, the highest value, and then the residues would decline to this point at 60 pg/g.

As you can see the high-end perimeter exposure scenario results in a modeled peak blood level very high. I'm sorry. Let me speak again, the broadcast hard floor exposure scenario is the highest of all exposure scenarios assessed, resulting in a level of 7200 on the day of application and then followed by the perimeter carpeted floor scenario, 1050. But what's important to note here is how similar those bounding or the modeled exposure scenarios with the 60 pg/g occurring on the final day of exposure, these are to the perimeter carpeted floor. They just so happen to model very similarly.

Presented on this slide are the results of chlorpyrifos blood concentrations at hour 24 on the first day of exposure of the day of application. So

what we saw previously was our peak on the initial day. What we see here is hour 24 following the rapid decline just prior to the next day's exposure event. The perimeter carpet and the 60 pg/g on the final day and the carpet exposure scenario modeled, again, very similarly, and the broadcast hard floor exposure scenario is the highest of all. It is most important to note, however, that due to the rapid decline of internal dose from the peak, all of the exposure scenarios modeled result in blood levels below the 60 pg/g pre-cancellation level. Therefore, these chlorpyrifos blood levels could have been reached as soon as the day of product application.

Presented on this slide are the resulting chlorpyrifos blood concentrations for all six post-application exposure scenarios 10 and 24 hours following the peak on the final day of exposure or the 30th day. So we've had our peak on the 30th days, and these measures are occurring as the rapid decline is happening, so 10 hours and at 24 hours with 10 hours being shown in blue, and in yellow, the 24-hour measure. In as little as 10 hours following the peak exposure on the final day, all post-application exposure scenarios result in blood levels below the 60

pg/g pre-cancellation blood level, and they drop even lower by hour 24 on this final day.

As shown many times before, now here is the distribution of Columbia blood concentration, but I'd like to direct your attention specifically on this slide to the maternal blood, specifically the upper percentile measures, the 75th, the 90th and the 95th. These upper percentile blood levels have been used as the basis for comparison to the modeled blood concentrations.

Shown on this slide are two views of the perimeter carpet exposure scenario which was modeled. And this is the most likely treatment type again for the Columbia cohort, we believe. On the left is the first day of simulated exposure, and to the right is the last day of simulated exposure, the 30th day. For both simulations, predicted blood concentrations are in the range of the 90th and the 95th percentile values within 24 hours of model exposure. And on the final day of exposure, blood levels in the range of 75th percentile value occurs shortly thereafter. These levels are achieved even with the peak value on the first day of exposure to the left of 1100 pg/g.

The figure presented here overlays the perimeter carpet exposure scenario and the 60 pg/g on the final day of exposure scenario. The ones that you saw previously that were very similar and, in fact, they overlay so closely that it's difficult to see the distinction between the two. As described, these exposure scenarios model very similarly, and we believe the similarity to support that the perimeter use was likely the predominant treatment type at the time of the Columbia cohort.

In summary, the approaches used by EPA for estimation of drinking water, food, and residential exposures have been supported by multiple SAPs and peer review. These exposure estimates make use of chemical-specific exposure and monitoring data where there's data available. Daily chlorpyrifos blood concentrations were simulated with use of the robust, highly refined PBPK model, and integration of all of these approaches has allowed for predictions related to the women in the Cohort.

In conclusion, chlorpyrifos blood concentrations predicted with the PBPK model are well within the range of those reported in the Columbia cohort. For drinking water exposure, the watershed

protection plan and water processing virtually eliminate all chlorpyrifos, and for food exposures, the resulting concentrations are consistent with the post-cancellation Columbia blood levels. Therefore, EPA believes that the higher levels of pre-cancellation blood concentrations reported by Columbia were likely the result of residential chlorpyrifos usage. At this time, we'll take questions. Thank you.

DR. JAMES MCMANAMAN: Okay, thank you. Questions for the agency, panel members?

DR. DAVID JETT: Dave Jett, NIH. Did you say that you guys measured or someone measured chlorpyrifos-oxon, or is that hard to measure? I know you said that you didn't think it was an issue because of the chlorination process and mixing, but was it ever directly measured?

DR. ROCHELLE BOHATY: Rochelle Bohaty, EPA. Are you asking if chlorpyrifos-oxon was actually measured in the drinking water? Yes. There is no sampling for chlorpyrifos-oxon, and generally the drinking water treatment processes references to that. They primarily focus on chlorpyrifos, the dissipation of it, but there are a few studies that look at the

dissipation of chlorpyrifos and the formation of chlorpyrifos-oxon.

DR. JAMES MCMANAMAN: Other questions?

MR. JEFF FISHER: Jeff Fisher, just to be clear that I understand, all the simulations that were done was using the female model as a surrogate for the pregnancy mom for the reasons you mentioned, and there's no infant modeling or pregnancy modeling that was completed by you for what you're showing us by the EPA?

DR. CECILIA TAN: Cecilia Tan, EPA. We did not use the pregnancy model for the reason that I described. It's not peer reviewed or published even though it is a great model and for the infants we are focusing on -- because the biomarker is core blood concentration, which we think is similar to the maternal blood concentration. So we did not predict infant exposure and blood level.

DR. ANNA LOWIT: This is Anna Lowit. Just to add on to what Cecilia said. So the simulations you've seen today were intended to try to understand the reported values from Columbia, so the focus has been on the females as representative of the mothers in a cohort. But in the case studies that

we'll talk about next as we move to doing a risk assessment that has to cover multiple life stages, we do have case studies for infants, for example, a bottle feeding infant drinking formula that's made from water that may have chlorpyrifos in it.

DR. WILLIAM HAYTON: You don't present them, but you must have brain concentration time data too. Does that track very closely to the blood concentration or the plasma concentration?

DR. CECILIA TAN: Cecilia Tan, EPA. The model is capable of predicting brain concentration, but we did not record it or compare that to blood concentration.

DR. WILLIAM HAYTON: Right, but you don't just have anything to say about whether there's a big lag between the peak in brain and the peak in blood or tracking. I mean, are they temporarily displaced; are the peaks similar or not?

DR. CECILIA TAN: I would say there shouldn't be a lag, but I can run the model now and then give you that answer.

DR. WILLIAM HAYTON: Thank you.

DR. ANNA LOWIT: The power of computers, we can do it right here. This is Anna

Lowit. We have not output -- our focus has been on the blood to match to the Columbia, so we have not -- none of the simulations you have, have tracked that. But there's a long history of evaluating the red blood cell inhibition cholinesterase to brain, and brain cholinesterase inhibition tends to be much less sensitive than the RBC does, suggesting a difference in tissue dosimetry, but we'll find out soon.

DR. JAMES MCMANAMAN: Marion had her hand up first.

DR. MARION EHRICH: Marion Ehrich. I'm looking at slide 88, and the concentrations there (inaudible) the levels of detection you'd think it would be lower at the later measurements because there are better equipment. 1997 is very, very low, and 2004 is 100 times higher.

DR. ROCHELLE BOHATY: Rochelle Bohaty, EPA. Yeah, we noticed that too. We went back to the source data to confirm the limits of detection that were reported, and that was what's available in the data. My thought is that they used different labs, different equipment, different labs.

DR. DAVID JETT: Dave Jett, NIH. The table on food exposure results, just some

clarification, these data were compared to the 2001 data. Why were they not compared to some of the other years before 2001?

DR. ANNA LOWIT: This is Anna Lowit again. That's a relatively easy comparison to do. We wanted to keep the slides not too busy for purposes of presentation. But keep in mind, or back to the issue of the pre-cancellation and the post-cancellation, so the pre-cancellation values are primarily above the LOD, and then the upper percentiles are above 10, reaching above 15. So we're matching here our predictions from food to the post-cancellation as we think about the experience the women in the cohort would have. So if you think about the women whose babies were born post-2000, they're primary exposure to chlorpyrifos would have been in food, not from residential and not from water. So what we're trying to show here is our predictions from our typical modeling approaches, the dietary exposure, pretty well matched the reported values from Columbia, post-cancellation. So the 2001 here is shown as a post-cancellation metric. So as we move from the lower percentiles upwards, there's a pretty good match of expected values below the LOD until we get to the

higher percentiles.

DR. JAMES MCMANAMAN: Dr. Carr.

DR. RUSSELL CARR: Could I get slide 110 please? It's the Residue 2016 Analysis PBPK Model. One more, there. All right, that was it. I'm sorry. Go back. Go back one. The first column is the highest peak right after exposure, correct? And the second column is 24 hours later.

MR. WAYNE BRITTON: This is Wayne Britton. That is correct.

DR. RUSSELL CARR: All right. Then the third column is 30 days later?

MR. WAYNE BRITTON: Yes.

DR. RUSSELL CARR: But the half -- that's what we call terminal half-life. The terminal half-life still is like 120 hours, and so every five days, that number between that second column and that third column should decrease by half. And there's like 5 -- 30 days is 106 times -- you should get some decrease between those two points just based on what I read in the document if the terminal half-life is 120 hours.

DR. ANNA LOWIT: This is Anna Lowit again. I'll try, and others can help me out. So if

we can go -- is it forward or backward? Show one of those spikey things. Here we go. So look on the right side. The first column in the table you're talking about represents that first peak of right above, the 0 day one, right? The first 24 hours is that initial first drop to the bottom. The next column over represents the other end, the far right side. So the first one is the first day; the other column is the 30th day. So go back to the table. Okay, so the second column is the 24 hours, so that's the 24-hour post-application. The next column, if you look at it closely, after the peak on day 30. So every day, there's a peak and a drop.

DR. RUSSELL CARR: Okay, so terminal half-life is basically the same; it's not dependent on the initial level of exposure. So you'll always go back to the same value regardless of the level of exposure.

DR. CECILIA TAN: Cecilia Tan, EPA. Regardless of the dose level, you always have the same half-life, which is 120 hours, the terminal half-life, but the level will be different depending on the peak.

DR. RUSSELL CARR: That's what I thought. I just weighed two numbers were the same, or

else they increased.

DR. CECILIA TAN: Were so similar, yes. I see what you're saying, okay.

DR. RUSSELL CARR: All right, thank you.

DR. LISA SWEENEY: Lisa Sweeney. The way I read those columns, the 24-hour blood concentration is 24 hours after application, and in the case of broadcast, that's 22 hours after peak. And in case of perimeter, it would be 16 hours after peak. Whereas the last column, it's 24 hours after the peak, so they're not exactly comparable. In one case, it's 24 hours after application, and you have to include application time; whereas the last column, it's 24 hours after the peak.

DR. RUSSELL CARR: Yeah, the last column is 24 hours after day 30. I assume that was when they went to a clean environment.

DR. LISA SWEENEY: Right.

DR. RUSSELL CARR: But I was talking between two and three.

DR. WILLIAM POPENDORF: This is Will Popendorf. If you look at table three in the issues paper, there's a column missing in this table, which

is the lowest peak, which is the peak on day 30, and maybe that's where you're sort of missing. Because at 10 percent per day, you're talking the half-life for the DK of the residue. So that's how fast the peaks go down, which is a lot different from the terminal phase within the body. So there's two things going on. Part of it's missing here, which may be just a little confusing to me.

DR. JAMES MCMANAMAN: Dr. Carr, are you clear?

DR. RUSSELL CARR: Yes.

DR. JAMES MCMANAMAN: Okay. Other questions? Yes.

DR. WILLIAM POPENDORF: Will Popendorf again. Two questions, follow up a little on the background. I still have this interest in oxon we'll talk about later, but wondered about on the water side, is there any information on the use of bottled water within the cohort as an alternative to city water if oxon were in the city water?

DR. ROCHELLE BOHATY: We didn't look into the exposure potential from bottled water.

DR. WILLIAM POPENDORF: Right, okay. So as far as you know, you don't have information at

least about bottled water use, right?

DR. ROCHELLE BOHATY: No, there's no information available on that.

DR. WILLIAM POPENDORF: The other question, if you go to your slide 115, which is a little further on, I sort of saw this in a few other. Earlier I think you said the cycle time on the simulation, your PBPK simulation, was like an hour and the peak or the curve there looks pretty fine for -- it would be 10 points that make up that peak and part of it going down. I wonder is that -- you're pretty sure about the one-hour cycle time, or is that a variable that might be --

DR. CECILIA TAN: The one-hour time, what I meant is that that's the time unit for this model, but it is the DE server. The differential equation server is a stiff system, so it's much smaller time points when they calculate the equation when it is changing a lot. But when it is not changing a lot, the time set can be longer, so it is not every hour it runs; but it depends on how fast it's changing. When it's faster, it runs more time points, so that's why you can -- you see that peak looks more refined.

DR. WILLIAM POPENDORF: Okay great, thank you.

DR. JAMES MCMANAMAN: Questions? Yes, Dr. Fisher.

DR. JEFF FISHER: Bill, in Axel, this software, there's a communication interval. You can make it very small and click simulated digitized data points per communication. So you can have massive data sets of simulated data to such an extent that you can run out of memory during the simulation, but these simulations are very smooth. They have enough resolve to show the shape of the expected behavior.

DR. JAMES MCMANAMAN: Questions for the panel? Okay, so before the next presentation, I think we'll take a break. The next one's by Dr. Lowit, and we'll have the answers to questions that we addressed by the end of the day or by tomorrow. So 15 minutes, all right, thank you.

(Brief recess.)

DR. JAMES MCMANAMAN: Okay. I think we'll get started. So at last we have an answer to our analysis question, so we'll start with that. That's was supposed to be funny, but I guess not. Anna Lowit is going to read into the record the

response from principal investigators related to the question about analysis levels.

DR. ANNA LOWIT: Okay. These will end up in the docket as well. I'll make sure that we put the email records back and forth from Dr. Barr and myself just, for full transparency on what transpired. So there's quite a bit and so I'm just going to read it verbatim.

The first are those questions I believe from Dr. Ehrich, although I'm not certain. So the notes read from the panel, Barr et al. (2002), give limits of detection for chlorpyrifos at 1 pg/g (part per trillion) with 0.5 to 1.0 pg/g used as a limited detection in the epidemiology studies and referred to in a number of subsequent papers.

Dr. Barr's response: Limits of detection (LOD) are not static values but rather dynamic in the three citations here listed to support that statement. LODs can change from project-to-project, run-to-run, or even sample-to-sample based on a variety of factors, including individual sample matrix effects, sample volume analysis, instrument performance, column life, et cetera.

Typically, LODs are reported as an average LOD over

the course of a sample batch or study. For these studies, average LODs were determined for each batch of data reported. Similarly, an average LOD was reported in the Barr 2002 paper. The LODs were determined using the method of Taylor 1987, page 79 to 81, and represent the method LOD not the instrument LOD.

The LODs were verified visually, e.g., a spiked serum sample at the concentration was measured to ensure detectability, and the signal-to-noise ratio had to be greater than three; although it was typically greater than 10. The LOD of chlorpyrifos tended to range from about .5 to 1.0 pg/g.

All right. So moving on, the comment from the panel said yet Perez et al. (2010) gives chlorpyrifos limit of detection as 21 pg/mL, i.e., part per trillion, with a linear range in µg/mL ppb of 21 to 6400.

So the response from Dr. Barr: This method was developed primarily to measure pyrethroid insecticides, so the parameters, e.g., extraction mass spectral parameters, were set to optimize detectability of pyrethroid, not chlorpyrifos. As

with any multi-analyte method, it cannot be optimized for each individual chemical. We specifically chose to focus on the pyrethroids because with their increase in use after the voluntary elimination of chlorpyrifos in diazinon registrations. Therefore, this method was not optimized to detect chlorpyrifos. This method was not used for generating chlorpyrifos data for the Columbia study.

Okay, so same set of comments from the panel. There are a couple of questions. Question number 1, how can quantitation be done outside the linear range? Response from Dr. Barr: The upper cap of the linear range defined in the method was simply the highest standard used as a method possessed linearity at all concentrations used in a calibration plot. If concentrations were calculated outside the range of the highest standard, one of three scenarios was used for reporting data in priority order.

Number 1: If residual sample remained, the sample was re-prepared and reanalyzed using a smaller volume of serum to bring the concentration within the calibration range.

Number 2: Additional higher level standards were evaluated to ensure linearity at or

above the quantified value.

Number 3: The value was reported but was flagged as being above the highest standard, the subject to more error. In the study, the third scenario listed was never encountered.

Question number 2 from the panel: What was the signal-to-noise ratio at the limit of detection? The SN was a minimum of three but was usually in excess of 10. Although some define the LOD as the point at which the SN is three, we did not define it; this way, it was used as a quality assessment criteria and always had to exceed three.

Question number 3 was the one that we largely covered in the room about the table 1, the issues of the reporting on page 14. However, in addition to the explanation that we gave earlier about the difficulty in seeing the decimal point in front of the .25, Dr. Barr adds to our response: Values in the table range from .25 to 12 pg/g. Note that the two trailing zeros should not be construed as significant digits as we only reported out to 0.00 significant digits.

Okay, the second set of questions, there are three of those. Question 1 in the second

set, were there instrumentation differences between 1998 and 1999 and later analytical measures? The answer from Dr. Barr: No, the same instrument was used for all analyses. Obviously as the instrument aged, its performance diminished somewhat, but the LODs remain relatively steady.

Question number 2, cross validation of early samples with later methods in instrumentation. Dr. Barr's response, all methods were cross validated against each other for common analytes. The chlorpyrifos measured in the Perez 2010 method were cross validated against the Barr 2002 method. To be considered cross validated, the measured value using the Perez 2010 method was within 20 percent of the measured value of the Barr 2002 method. The measurements were highly correlated, are greater than .97, and the absolute standard deviation from the mean measure value was less than standard deviations. Bland-Altman plot demonstrated no systematic bias between the methods; however, better agreement was observed at higher concentrations. In addition, as part of the CLIA certification requirements, all analysts were cross validated as well such that analyst A was compared to analyst B, and their

measurement disagreement was less than 10 percent. The same instrument was used for both methods.

Question 3 chain of custody, standard operating procedures, SOPs, for collection of maternal and umbilical cord blood were provided to Columbia University by the CDC Sample Logistic Group (SLG) as per CDC's requirement. The SLG is a part of the CDC NCEH DLS Laboratory that is comprised of chemists and medical technologists with experience in sample collection and handling. The detailed SOPs also included flow chart diagrams for collection in post-collection aliquoting, post-allocation handling procedures such as, processing of plasma; aliquoting of samples of plasma; creation of a shipping manifest; storage; and dry ice shipment instructions. Samples were shipped in batches, typically 50 to 100 samples. They were stored at Columbia University at minus 80 degrees Celsius until shipment. Upon arrival at CDC, the SLG inventoried the samples; created CDC CISPIR identification codes for each sample (required of each independent sample received at CDC for sample tracking purposes); assigned a study number, if the first batch from the study; and transferred samples to the appropriate laboratory, in this case, the pesticide

laboratory. After analysis, samples were returned to the SLG who either disposed of the samples at the PI's request or shipped them back to the PI. Tubes with no residual samples were autoclaved and discarded as hazardous waste.

And then there are several citations here supporting the comments. There are six citations here.

DR. JAMES MCMANAMAN: Thank you. Are there clarification questions that need to be asked at this point? Or would the time be better spent entering the deliberations following the agency's presentation? Okay, hearing no additional questions are needed, we'll go on to the next presentation.

DR. ANNA LOWIT: Dr. McManaman, there's a natural break about halfway in the slides. I can just go all the way through, or I can take the natural break and take questions. Or would you like me to just go?

DR. JAMES MCMANAMAN: Why don't you just go?

DR. ANNA LOWIT: Just go, okay.

DR. JAMES MCMANAMAN: We took the break early.

DR. ANNA LOWIT: I'm just asking. Okay. So I'm going to cover a number of issues. So what we've heard about today, as you heard from Dana Vogel this morning, we've been looking into these chlorpyrifos issues since around 2007, 2008 with multiple trips for SAP including two focused on epidemiology and another focused on the PBPK model. So then you've heard throughout the day about -- as we are honest about our uncertainties with respect to the biomonitoring data and the things that we've done in our simulations that we think help to address many of those uncertainties. So what I'm going to do for the next bit is go through a series of slides that talk about how we would, in practice, use the information form the Columbia studies to put into a risk assessment, so deriving a point of departure, looking at intra-species extrapolation, the FQPA 10X safety factor, and then show a few case studies of how we would put this into practice.

The first half of my presentation will be on the point of departure, the intra-species extrapolation and the FQPA 10X. The second half will be on the case studies looking at contemporary current exposures of food, water, and also occupational

exposure.

So since you've seen that slide several times today, just to remind all of you, at the 2012 SAP, at that point in time, the PBPK model was not at the point where the agency was comfortable using it in a regulatory decision making process. And SAP concurred with us that, in that state of science, that we were better off to maintain the point of departure with acetylcholinesterase inhibition. However, the panel encouraged us, once the PBPK model was mature for our use, that we use it to characterize the dose-response data from the Columbia studies, which we've largely talked about over the last couple of hours. So the analysis that you've seen today is largely in response to the 2012 SAP.

I'm going to take just a couple minutes and talk about some risk assessment principles and jargon, just to make sure we're all on the same page about the risk assessment side of things. So the plot there on the right side is actually taken from an EPA guidance document called the Data-Derived Extrapolation Factor Guidance. And what you see here, if you can look where the green arrow is toward the center that's on a round dot that sits on a solid

black line, over to the right is a dark dot on a dotted line. In the overwhelming majority of risk assessments done at EPA including the Pesticide Office we use animal data to derive our points of departure. And when the animal data is used we do like a two-step extrapolation.

The first one is extrapolation from animals to humans, and then the second extrapolation is across human population. So those are the delineations of those two arrows, the black arrows with the UF. Going from right to left would be UFA, so extrapolation animal to human and the other one is within human variability. However, in the case of chlorpyrifos for our proposal for the new assessment, we would be using the human data from the biomonitoring, directly which would avoid the animal extrapolation step. So hence my green arrow on that open dot on the dark line, the dark line being the human dose-response. What the agency typically does from a point of departure is do an additional extrapolation step from that human point of departure to account for human variability to account for susceptible populations that may not have been included in the study.

So how would we use this information in practice? The pesticide program, we tend to use two different metrics. The first one is a typical RfD approach which many other offices use which takes the point of departure and divides it by the uncertainty factors to achieve a reference dose. Alternatively, in our occupational exposure assessments, and also residential exposure assessments where we have to combine different routes whether it's oral, dermal or inhalation, we do what's called a margin of exposure approach, or what we call an MOE. In that case, the math uses those exact same numbers. We just use the ratio a little bit differently. So the point of departure is compared to the exposure, and then that in turn, is compared against the total uncertainty factors. So basically, use the same three pieces of information, but just two different ratios.

From the 2014 Risk Assessment, as discussed earlier, the points of departure were based on 10 percent acetylcholinesterase inhibition. In that assessment from 2014, we used the PBPK model to actually predict a human derived point of departure to achieve 10 percent cholinesterase inhibition, and that was done in a very sophisticated way. We did that

very explicitly across each age group, across each duration, and across each route. So for example, for a dermal exposure to a female worker to achieve 10 percent cholinesterase inhibition, we used the same kind of assumptions used in our occupational assessment where an individual that works eight hours a day, five days a week and we did that for a three-week simulation. So just, for example, to achieve 10 percent cholinesterase, the blood concentration peaked over 120,000 pg/g, and even 32 days after the exposure, it still exceeds 100. So keep in mind the reference of that compared to the values we were talking about in the previous presentation, all certainly in the order of 10 and lower, and six and lower.

Food exposure, for example, for an adult female exposed once a day to achieve 10 percent cholinesterase inhibition, you get approximately 7,000 pg/g at the daily peaks, and across the 21-day exposure simulation, the values never go below 100. Just for comparison, there's a recent publication by Arnold et al. supported by Dow that comes up with very similar values. They looked at the full distribution, so from the 5th to the 95th percentile, their values

for 10 percent oral exposure ranged from 6,000 upwards to 64,000. So our estimates are in line with theirs.

So once we transitioned from using acetylcholinesterase inhibition to neurodevelopmental effects, we feel there are two fundamental options. The first one is the Rauh et al. (2006) paper that we discussed quite a bit this morning that uses that dichotomous greater than or less than the 6.17 pg/g cord blood from that paper. In that paper, there are over 250 children followed at age three using that dichotomous approach with the high and the low. And there are a number of findings in that paper that we discussed at length this morning, including the PDI, the psychomotor delay, along with a number of other things including attention disorders, ADHD and the PDD. And of note, particularly for these three outcomes, the odds ratios are fairly large, ranging from 11 and 6 and 5, albeit the confidence bounds are also quite large.

If we were to follow option 1 for the point of departure, our PoD would be the 6.17 pg/g cord blood. Option 2, and the one that we're proposing, is to derive benchmark dose estimates from linear regression reported by the Rauh et al. (2011)

paper looking at Working Memory. If you remember from Beth's presentation this morning, Working Memory in particular has been observed in all three of the U.S. cohorts associated with OP exposure, so there's a strength in the combined from all three cohorts for this outcome.

In the Rauh paper again, there's over 250 children, and at this point, the children have reached age 7. And those in this study had a complete set of data. Rauh reported a linear regression that's largely there, and in their abstract, talked about for each standard deviation and increase in chlorpyrifos exposure, there is a 1.4 reduction in Full-Scale IQ and a 2.8 reduction in Working Memory.

To my left is James Nguyen, who has taken these results from Rauh and calculated benchmark dose levels and also lower limits on those benchmark dose levels, the one-sided lower limits. We did this analysis in combination with Woody Setzer, who is a statistician who works for the Office of Research and Development in the Cox Tox Center and has for many years supported our program in benchmark dose-response modeling.

The table on the right is directly out

of the paper. These are the estimated concentrations in different reductions in Working Memory and then the lower limit, the one-sided lower limit, to those values. As a matter of science policy, EPA uses the lower limit as a point of departure and not the central estimate. So we're talking about using the values on the far right column as the possible points of departure. We ran the values for the 1 percent ranging up to 5 percent reduction Working Memory, the values are listed there. And as we look at the values at the 1 percent change, we see that the BMDL value of basically 1, just above 1, is very close if not equal to the reported LODs from the analytical lab. In our mind, that gives them more uncertainty as they approach or even equal to the LOD.

At the higher percent that we tried, from the 3 percent to the 5 percent, the BMDs and the BMDLs begin to approach, if not exceed, the 6.17 value that represents that top tier tile from the original paper and to us suggest that the 3 to 5 percent changes in Working Memory would not provide a health protective endpoint. So as a middle ground, it leaves us with the 2 percent Working Memory reduction that corresponds to an internal dose of 2.16 pg/g such that

the values are within the detectible levels of the analytical method but also below those that are associated with neurodevelopmental outcome.

Can someone advance the slide for me? Laura or Steve, can you advance the slide for me? I tried turning it off and on a couple times; that's not helping. And the little light's off too, so, here we go, magic.

Okay, so I'll move on from the point of departure evaluation to the intra-species extrapolation. Just to repeat where we are, so in a typical assessment, we would use animal data, but in this assessment, we're proposing to use the human biomonitoring, in which case we just need to think about the intra-species uncertainty factor. And this is intended to account for variations in susceptibility across the human population and the potential that the database is not representative of the dose-response relationship in groups outside of those assessed. And the agency typically often looks at pharmacodynamics and pharmacokinetics in separate evaluation.

There's this same graph I talked you through a minute ago with the open dot towards the

bottom, which represents the point of departure for humans, and then we're talking about this extrapolation where the green arrow is pointing.

From the pharmacodynamics side, something we haven't talked about really much of any today is the adverse outcome pathways and what is or isn't known about the pathways for neurodevelopmental outcomes. I'm very lucky to sit near Ginger Moser who sits at the table with us, who's been a long-time, almost a decade if not more, member of our OPP Chlorpyrifos team. For the 2014 risk assessment, Ginger developed systematic review of available literature on chlorpyrifos with respect to studies in laboratory animals exposed to chlorpyrifos either during gestation of early postnatal, and then those animals are evaluated later in life.

What we also haven't talked about much today is all the mechanistic information that underlies the biological plausibility of the outcomes reported by the epi studies. There are multiple hypotheses out there including some of you at the table have been working on these for many years. There are multiple hypotheses that groups have and of today in our view, there is not one developed adverse

outcome pathway for neurodevelopmental effects, and it seems likely that that's years away; that kind of knowledge is probably years away.

The Columbia cohort, as Beth talked about earlier self-identified as primarily African-American and Dominican, fairly young 18-35, who live in specific neighborhoods in New York, Northern Manhattan, Central Harlem or Western Heights/Inwood, South Bronx, have lived there for a year or more before they got pregnant, they're generally low SES and generally at the time had incomes less than $30,000. We do not have information that allows us to assess the relative sensitivity of the women in that cohort with other groups, whether it's ethnic groups or socioeconomic groups across the country. We cannot compare their sensitivity to anyone else. So given this state of knowledge around the adverse outcome pathways or the lack of a defined set of key events leading to an outcome and lack of our understanding of ability to understand how the Columbia cohort compares to other groups, the default 3X for pharmacodynamics for intra-species extrapolation has to be retained.

With respect to pharmacokinetics for within human variability, there is a robust PBPK model

that we're taking advantage of. Once piece that we haven't talked about today is the ability of that model to look at variation across the population. That model is able to look at variations in pharmacokinetics across most life stages but cannot do so for pregnant women and because it cannot do that for pregnant women we believe we have to retain the PK variation as 3X which at EPA 3 times 3 is 10 so we're proposing to retain the 10X intra-species extrapolation factor. And it is worth noting that this decision logic is very consistent with that used for methyl mercury by the Office of Water and reviewed by the NRC. In one of our appendices to the document. we actually did a side-by-side evaluation of the NRC's review of the uncertainties in the methyl mercury epidemiology studies and use of cord blood and points of departure, and our evaluation is very much in line with what the NRC and our Office of Water colleagues and our IRIS colleagues for methyl mercury.

One of the unique aspects of regulating pesticides here in the U.S. is a mandate under the Food Quality Protection Act to add an additional 10X safety factor to protect for infants and children. And I have the exact wording out of the statute here

because the wording is important. So if I start about halfway through the quote, "take into account potential pre- and postnatal toxicity and completeness of data with respect to exposure and toxicity to infants and children." And we infer that fetuses are included within that. So what I'm going to do, and what we did in the paper, is explicitly walk through what we know about pre- and postnatal toxicity and think about the completeness of the data that we have.

The statute goes further to say that the Administrator or their delegate may use a different margin of safety only if based on reliable data that such margin is safe. As stated in the paper, and I'll say again in few minutes, our belief is that at this moment in time, we have to continue to retain the FQPA factor. I do want to let you know that the FQPA Safety Factor is a policy decision made by the agency that has multiple components. And although we're not asking you about the factor and the magnitude of the factor, we are in question 6b and 6c asking you to input on the science we have underlying that policy choice.

I'll systematically, very quickly walk through what we know about pre- and postnatal

toxicity. Starting with laboratory animals, and we haven't talked about laboratory animals much today, but in the 2008 and 2012 meetings, we went through these data extensively. And Ginger Moser has done a systematic review for our 2014 risk assessment, and, in fact, she's actually updated that review in our 2015 paper that Beth talked about at length this morning that expands our analysis of neurodevelopment effects from just chlorpyrifos to all of the OPs. So our evaluation on these issues we believe to be quite up to date.

There are numerous animal studies in rats and mice in the literature that report changes in aspects of neurobehavioral function from adolescence to adulthood following developmental exposure. And these include multiple domains, cognitive, anxiety and emotion, social interactions, neuromotor function. But there are extensive differences in study design across the numerous studies which makes direct comparability across the studies difficult. For example, there are multiple species; different ages are tested. Some report findings in males; some report findings in females. The exposure level is different; the timing of the dosage but also when the

animals are evaluated later in life are different. The route of exposure in the test method differ quite a bit along with a number of other things. But among these studies, they involve both early and late gestation or early and postnatal dosing. Keep in mind that the timing of the development of the nervous system is not directly comparable across rodents and humans. So, for example, generally, not exact, generally, early postnatal periods in rodents tend to correspond to last trimester in human development. However, on the other side the later postnatal studies we believe generally correspond more closely to a human infant. So it's important with the studies to try to match them as close as possible. And it's our view that these studies showed no clear evidence of a single critical period of exposure. There are some behavior outcomes that are observed across the all the windows of exposure and for others, there are not. There are systematic comparisons, although it's difficult given all the differences in those studies to really make those systematic comparisons.

As Beth talked about at length this morning, the epidemiology database with respect to prenatal or gestational exposure is fairly robust.

There are numerous investigations across the three U.S. cohorts looking at biomonitors taken during pregnancy and looked at those associations to neurodevelopmental effects in children later on, largely up to age 7 and to a lesser degree, up to age 11. And I won't repeat all that data, but just for example, she talked about things related to autism spectrum, intelligence decrements, attentional problems, ADHD, etc. But we do note the results are not always consistent with the magnitude in the ages across the studies.

With respect to the epidemiology, the postnatal is not as robust. A smaller number of studies have assessed postnatal exposure to OPs, primarily measured as the DAPs. So these are the non-specific metabolites. But we do acknowledge that postnatal exposure was assessed in the CHAMACOS cohort, and the citations are listed there, and three cross-sectional studies including one from Canada and one from China.

Postnatal exposure to chlorpyrifos were not assessed in Columbia or the Mt. Sinai, but it's important to remember that in the Columbia study, as the indoor cancellation occurred partway through the

study, just that fact alone limits the Columbia study to inform the postnatal question because chlorpyrifos was removed from the environment as the children were young.

There is a Bouchard et al. study which looked at U.S. kids' urinary metabolites 8 to 15 and did show a positive association between attention and behavior problems and DAPs. But besides that, there are no other developmental associations found between the postnatal biomarkers.

So in sum, if we think about the extensive experimental animal database and integrate that with the information available from the epidemiology cohorts, it seems that the lack of postnatal exposure assessment in Columbia and Mt. Sinai is a source of uncertainty in the epidemiology database as the animals do not identify a specific critical period but, in fact, show that the entire time of neurodevelopment may be susceptible. If I go back to the quote from the statute, it talks about the dose-response curve and uncertainties associated with the dose-response curve.

A couple more quotes from the 2012 SAP who looked extensively at the Columbia studies and

provide a very nice list of uncertainties associated with those studies. Two of the ones that were identified in 2012 had to do with the sample size. The first quote being, "Relatively modest sample sizes limited the statistical power to classify some meaningful differences as significant." And the second one being, "Relatively moderate to large exposure differences are needed to see significant effects largely due to the modest sample sizes."

So in sum, the modest sample size in the Columbia study makes it difficult to say the dose-response relationship between chlorpyrifos and neurodevelopmental effects across the U.S. population has been fully characterized. This was particularly true at the lower end of dose-response curve where many of the values are below the LOD. The magnitude of the point of departure that we calculated and proposed a few slides ago may, in fact, be higher or even lower than that estimated by the Columbia study.

So as we think about the science that underlies the policy's decision for the FQPA 10X, there are some remaining uncertainties associated with lack of information on postnatal exposure and evaluation in the Columbia and the Mt. Sinai and the

modest sample sizes that limit the statistical power.

So the agency has concluded there is sufficient uncertainty that prevents the agency from reducing or removing the factor. But just remember that that's a policy decision, and we're looking for your input on the science, not the policy.

Just quickly, the information I went through now covers a whole bunch of charge questions, subsections 5 and 6. And I think that moves me into the case studies.

DR. JAMES MCMANAMAN: We lost our webcasting abilities, so we will take a short break. It looks like this is the ideal place to do that so we can get back online. Five-minute break.

(Brief recess.)

DR. JAMES MCMANAMAN: We lost the webcast ability because, for some reason, we've gone longer than eight hours. I can't imagine how that could have occurred, but it certainly did. Too many questions, O think. Too much deliberation. I think we'll get started with the last part of the presentation.

DR. ANNA LOWIT: Okay, the last part of the presentation has to do with the case studies that

are in the last section of the issue paper. So as we move forward with a new assessment in the coming few months, we'll need to reassess exposure in food, water and occupational scenarios using the new point of departure. In order to facilitate that, we have developed some case studies to illustrate how we would use the PBPK model to predict internal blood concentration from exposure to current uses of chlorpyrifos. Remember that our exposure approaches have been extensively reviewed by previous SAPs along with the models and the assumptions that goes into them.

Just to reiterate, we're proposing an internal concentration point of departure of 2.16 pg/g, which is adjusted by two values, the first one being the intra-species factor of 10X and the second one being the FQPA Safety Factor, which yields us to an internal concentration RfD of .022 pg/g. For residential, occupational exposure where we use the margin of exposure risk metric, what that means is our point of departure is 2.6 and would be using a target margin of exposure of 100.

Just to remind you what Dr. Tan talked about earlier, the pharmacokinetic profile of

chlorpyrifos in blood is characterized by rapid increases and decreases during the exposure period and immediately after followed by slower decrease during the terminal clearance phase. We believe the cord blood and maternal blood report by Columbia likely represent data from the lower points of the PK curve and more likely in the terminal phase. In order to do, you know, what I would call an apples-to-apples comparison, we're proposing to compare our exposure assessment at 10 and 24 hours after the last peak of each simulation to do as close as we can as an apples comparison to the Columbia data. Water is a little bit more complicated as I'll show.

So you've seen this slide before. It's the same one that Cecilia used. This is an example of one of our simulations. The last peak, so there's a rapid decrease with a half-life in the order of three to four hours so it's very quick. And then followed by a much slower, gradual decrease with a half-life of about 120 hours. This is another representation of the same kind of information. We have a peak there at hour 1098 representing a peak internal concentration of almost 400. But only four hours later, the internal concentration has already dropped to a value

of roughly 100, and just a few hours later, we're down to 51. But from hour around 700 upwards to 730, the values are very stable between 30 and 50.

And so this is all in the context of an exposure scenario of a woman going into labor. Keep in mind that the assumption here in this plot would be that she is in her apartment doing high activity, so on the floor doing activity, and then she decides it's time to go. She leaves her apartment, and a number of hours later, her cord blood and her maternal blood are taken.

The Neil paper does show an average of about six hours, and we thank Dr. Sweeney for pointing out to us Dr. Hattis's data that we had just gotten -- we had just gotten it yesterday. It hadn't been through the paper yet, but it looks like the Columbia cohort the average time reported by Dr. Hattis is also about six hours between the time of admittance into the hospital and the time of the cord blood taken, which is in line with what we had found in the literature thinking about active phase between at four and eight hours and the Neil value of about six hours, so I think all of those match extremely well.

Our first set of case studies is the

food exposure. This is a different representation of the same thing that Danette showed earlier in the day. What I have is a set of percentile of exposure across the distribution, ranging from the 10th to the 99.9 across the distribution. These are adult females. We have the percentile of the food exposure from our exposure model at that percentile and then values for our simulation. So the maximum blood level, the 10 hour after the peak, and then what's reported is 24 hours, but it's probably really, I think, 22 or so because of the same issue Dr. Sweeney brought up earlier about subtracting out the time to achieve the peak.

What I'm going to show in the case study is the two ends of that spectrum. I'll start with the values at the 99.9, and then I'll show the 10th percentile. So on the left side, this is the food exposure scenario to an adult female at the 99.9th percentile where this individual was exposed at the level for 40 consecutive days. So you see 40 consecutive spikes and drops and spikes and drops. What I have on the right side is the last day of that simulation. So you see a spike just above 7 and a quick drop down. And everything here is reported as

pg/g.

On the other end of the distribution is the same kind of simulation, but in this case, the adult female is assumed to be exposed at the 10th percentile for 40 consecutive days. And here you see the peak come up to just under .3, but even at 10 and 24 hours, we're at or around .02, if not a little bit higher.

We did in the issue paper show some example worker scenarios, and I'll just show one here; but there may be some questions coming on some of those. In the 2014 Human Health Risk Assessment, we've assessed somewhere in the order of over 200 different scenarios, and those scenarios range in their exposure value over a pretty broad range of the continuum of exposure levels. We've only showed a very small subset of that over 200 in the case studies but eventually we'll need to do all of those for risk assessment purposes. We selected a subset of what we would call the lower scenarios, and those are also representative of the most often used application rates, so what we do have to show you is really representative across many of the uses.

The same kind of format, the left side

is a full simulation. So what we have here is two consecutive work weeks. That's five days of work, two days off, five days' work, two days off. This is for workers who handle, mix, and load liquids for cole crops. And you're thinking what is a cole crop? It's broccoli and kale and vegetables like that. If we take the last day of that simulation and blow it up on the right side, we see the peak of that simulation exceeds 300 pg/g. and even at 10 hours. we're still, I believe, above 10.

So thinking about drinking water exposure potential, as Rochelle talked about earlier, there are a variety of drinking water treatment methods that are used across the country depending on the different locality. And depending on the treatment will also depend on how much chlorpyrifos may be converted to its oxon, and so you see across there, a range from a very low percent of conversion to nearly 100 percent of reduction.

We have a few drinking water exposure scenarios. They have a similar format shown here. The left side will be our simulations of our modeled estimated values. So on the left side, what we have here is a simulation for a use on onions at one pound

per acre, and this is a 30-year estimate of drinking water exposure across a variety of weather. The red circle represents 120-day subset of that 30 years. As it's been talked about a couple times, there is some memory limitations with axels that we can only do a subset of the 30 years at one time. So we've selected that highest peak shown in the red, but as you see in the arrows on the right side, it's not a 1-in-30-year event; there are actually other years that spike fairly high.

On the right side of all the drinking water slides is data that comes from Orestimba Creek, which is actually measured concentrations. So each of these will have one simulation for an estimated model value and another one for a measured source, and these are two different locations, two different kinds of scenarios.

We've done some scenarios looking at females of childbearing age as we've talked about all day. So the left side is that 120-day subset from the bulb onion scenario. You can see across the peak in there is 6.24, but the values never go below 1 across the entire 120 days. If you look on the right side to the measured values, the peak here is lower at 1.97

and in between the two peaks comes down pretty quickly. Our assumptions here is that an adult female consumes water four times a day for a total of 1.7 liters.

We've also done some infant scenarios for infants who are fed with formula constituted with water. So these infants would have water exposure from these bottle feeding events. With infants, we make an assumption of 6 times per day with a total consumption of about 2.7 liters. On the left side is that estimated bulb onion scenario, and you can see the peak from the infant in our scenario exceeds 20 pg/g, and even on the lower days, it's still above 5. On the right side is the Orestimba Creek measure values in the infant, and you see the peak is around 6 and also drops fairly low in between those peaks.

We do have a charge question, the last one of all the charge questions on how we're doing this linkage. Keeping in mind that we will need to assess all the current uses and you only have a subset in the case studies.

The last section of the issue paper explicitly goes through some of the uncertainties identified by the 2012 SAP. We're keenly aware that

transitioning from using acetylcholinesterase as the point of departure to using the biomonitoring data from the Columbia comes with associated uncertainties. And in many ways, we feel like our analysis and the work that we've been doing largely addresses those. These are rows directly out of the table that's in the last section of the main part of the issue paper. The SAP in 2012 as I mentioned about a half hour ago, the relatively modest sample sizes and how those modest sample sizes mean that moderate to large exposure differences are need for significant affects. Moreover there's uncertainty identified that the cord blood data represent a single point in time and there are no other additional information on postnatal exposures. All of these we think are part of our explanation of why we're retaining the FQPA 10X with respect to the sample size and the uncertainty in the dose-response curve that supports retention of that factor.

The next one raised by the SAP in 2012 is the lack of clarity regarding the linear dose-response curve instead of a potential threshold. The Rauh 2011 paper, as we noted earlier, reported a linear regression, and we're actually using that

linear regression to derive a point of departure in the BMDL we're proposing for the point of departure.

Next set of uncertainties is the use of a single or average sample exposure, and the representativeness of that single point exposure is still unclear in that we know that there are going to be time-varying exposures. And then second, that there's really a lack of understanding around the critical window of potential susceptibility. And as we've shown in our own simulations that we do admit that there's time-varying exposures, and those exposures actually can vary quite rapidly on a fairly short time frame. But what we believe is that the reported values by Columbia actually are less likely to represent the times when the values are going up and down very quickly and more likely at the bottom of those curves if not near the terminal half-life where the values become more stable.

Also the lack of the critical window, it's likely that chlorpyrifos was applied nearly monthly across the women's apartments whether it was by themselves or by individuals, professionals or somebody with the apartments. So we've done these 30-day simulations that represent that monthly

evaluation.

The SAP in 2012 commented on the lack of clarity about the external generalizability of the cohorts or what I noted earlier as the unknown information about how the Columbia cohort differs or is similar to susceptible other groups across the U.S. population. And because of that lack of information is part of why we're retaining the 10X intra-species factor. So in 2012, there were questions about the biological plausibility in the lack of mechanisms and adverse outcome pathways and the mixed results found in the animal studies. We have not really fully talked about these issues today, but they were discussed at length in 2012. And we have included for all of you to look at in Appendix 3 summaries of our review of these issues, and also it's included in the 2014 risk assessment.

There are multiple hypotheses looking at the adverse outcome pathways, but those are likely years away. And I think one of the things -- it's important to remember that lead and methyl mercury, the agency has been using epidemiology data for lead and methyl mercury for a very long time, and neither of those have defined adverse outcome pathways during

developmental effect. So the lack of an understanding of adverse outcome pathway does not prevent the agency from using the epi data.

In sum, you've heard a lot of detailed analysis today. We believe we have pretty well characterized our predictions of exposure to women in the Columbia cohort prior to the time of their giving birth. We're proposing an approach for using the cord blood data from Columbia to derive a point of departure for use in quantitative risk assessment. And as part of this, it proposes an innovative approach to use the PBPK model to integrate external and internal dose from food, water, and occupational exposure. And that's it.

DR. JAMES MCMANAMAN: Thank you. Any questions for Dr. Lowit and the agency? Dr. Fisher.

DR. JEFF FISHER: So in the case of the infant model, where does that come from?

DR. CECILIA TAN: The infant model is part -- there is a life-stage model for chlorpyrifos, and I believe it's also part of the 2014 publication. That model includes the entire life stage, just not including the gestational period. So it has an infant.

DR. JEFF FISHER: It's the life-stage model that you talk about in the report?

DR. CECILIA TAN: Yes.

DR. JEFF FISHER: Okay.

DR. JAMES MCMANAMAN: Yes.

DR. STELLA KOUTROS: I have a question for you, Anna, which I hope I can articulate, but I'm not familiar with the risk assessment approaches. But I'm just trying to wrap my mind around some of the questions that I'm supposed to weigh in on here.

One part of the question that I've been asked to comment on is the impact of the sample size on the Columbia sample size or the uncertainty surrounding the sample size. I didn't understand -- I saw that you provided the language about the pre- and postnatal exposure, and then something you said about dose-response, and I didn't understand why this particular issue, just the sample size, would be linked with the uncertainty around the dose-response issue rather than other uncertainties than dose-response. So are we to comment specifically on the sample size? And I didn't know if that was or was not also related to the option where you're showing using the linear regression and the standard error estimate,

which I think account for the sample size issue, if that's a separate thing altogether or if those two things are related in any way?

Sorry, I know it was kind of a lot. Again, forgive my lack of understanding of the risk assessment process, but I'm trying to link these two thoughts about the language that requires this pre- and postnatal exposure consideration and the impact of the sample size.

DR. ANNA LOWIT: Let me see if I can find it in and then we can -- that way we're talking about the same thing. Okay, so on the left side, those are the direct quotes out of the SAP report.

DR. STELLA KOUTROS: Yes, so actually it was more about in the first part of your talk. I saw that there are several more uncertainties here, and I didn't understand how they've been separated across various parts for our consideration.

DR. ANNA LOWIT: Okay, I'm following now. Let me see if I can find the -- I understand that it may feel awkward, although that might be an incorrect description, to parse out the uncertainties. I think that's kind of what you're getting at. So what we've done --

DR. STELLA KOUTROS: Like, if you go back to -- yes, this language. Originally when you showed the language that said why you were required to consider pre- and postnatal parts, which I get, but then the next thing that follows, you said something about the dose-response.

DR. ANNA LOWIT: So there's the statement out of the statute, the pre- and postnatal toxicity and completeness of the data with respect to exposure and toxicity. This phrasing anchors how we can start parsing out the uncertainty so that within human variability, we would parse out thinking about susceptibility across the population and a lack of -- for the intra-species, we'd think about the adverse outcome pathways and what is known about that and the integration of the animal studies with the epi, thinking about that plausibility issue. So for the FQPA factor, it's parsed out. The pre- and the postnatal I think is probably fairly self-explanatory. The completeness of data with respect to exposure and toxicity I think is where we're thinking about the sample size issue and the modest sample size requiring the fairly large risk ratios to get a statistical change as it relates to the Rauh 2011. So they've

done that linear regression, but remember 30 or 40 percent of the cohort is below the 1 picogram, so those values are all imputed. So although they've reported linear regression, there's an uncertainty about the shape of that curve, of the truth of the linearity below the measured values. I don't know if someone else would want to weigh in.

DR. STELLA KOUTROS: I guess I thought that -- maybe I'm not understanding this correctly, that the truth is bound by the 95 percent confidence or one way that we use to bind what to put bounds on, the true values around that factor. And it sounded like you were proposing an option to use that information already.

DR. ANNA LOWIT: And we are, and that's a matter of science policy. So if it is your belief that those are already covered and it would be sort of a pseudo double counting, then we would welcome that in your comments when you answer the question.

DR. STELLA KOUTROS: Thank you.

DR. JAMES MCMANAMAN: Others? Yes, Dr. Popendorf.

DR. WILLIAM POPENDORF: I've got three questions really, one going back to, I guess, slide

130. Well, I can explain it without having to go back there, but the Rauh et al. (2011) provided a slope that you're proposing to use. Do you know how that slope was actually generated? That is to say it sounds like regression, and if it was like linear, it's sort of logged on your regression because they've got all the score. But was the intercept fixed or was it variable?

MR. JIM NGUYEN: My name is Jim Nguyen from U.S. EPA. In the Rauh study, they do the log of Working Memory equal the intercept in the model. Why is the Working Memory -- why equal intercept, plus slope, times exposure? So when you have the exposure equal 0, that become a typical Working Memory of children, they have no exposure. And when you have exposure increase the Working Memory reduction by the slope times the exposure level.

DR. WILLIAM POPENDORF: I'm not sure that I followed all of that, but they didn't report the intercept, which suggests to me that maybe they fixed it rather than -- in fact, the cube exploring regressions that they did show on their plots all converge toward zero exposure suggesting that there wasn't much variance there, and yet the data at zero

exposure is very wide, which suggests that it was a fixed value and not an unknown.

DR: SHARON SAGIV: That's pretty standard to have fixed intercept in many regression for epi studies. I don't think that's unusual.

DR. WILLIAM POPENDORF: Well, we can talk about the rationale for that, but I'm just trying to establish that it was, in fact, fixed.

DR. JAMES MCMANAMAN: That was an interjection by Dr. Sagiv.

MR. JIM NGUYEN: So when you have a regression intercept -- the intercept is one value but if the exposure equal zero so we have the Working Memory, it's a variation. So the standard deviation of Working Memory is about 15, so there is a lot of (inaudible) intercept.

DR. WILLIAM POPENDORF: Yes.

MR. JIM NGUYEN: And in the model we have only one intercept that's the mean of the Working Memory at no exposure. So when we do the BMDL after we put into the model the exposure level -- subtract the new exposure level of Working Memory, the intercept cancels out. So only left over is the mean times the exposure level.

DR. WILLIAM POPENDORF: Well, what I'm concerned is -- a couple of concerns, but one is that you would get a different confidence interval particularly around no zero exposure level if you fix that intercept or if you left it a variable. And you're proposing to use that confidence interval in the calculations as I understand it. You're going to go, what, 95 percent or something, the diagram. That was sort of my other question, but I'm trying to get a handle on, you know, what did they use to determine that confidence interval that, Jim, you're using, which may or may not be the appropriate thing they should have done. I think in this case they didn't say if they fixed it. I presume if they did, they fixed it to a value of 100 which LN of 4.605 I think would be on that diagram, but they didn't say that. So I'm just trying to get a handle on it.

Oh, so then as I understand your diagrams there and the process, what you would be doing is taking the confidence interval -- well basically, using the regression of dose against Working Memory index to derive the slope, confidence interval, and then trying to use that same -- you're going to go the other way taking the 1 percent of

change in Working Memory and trying to use the confidence interval based on the other regression, right? If you're following, I mean, you know you're basically X against Y to begin with, and then Y against X is the way you're going to use it. But you probably didn't regress it the other way, did you? Or did they? You're just using their data, right? You don't have the data, so you didn't run your own regression. So basically, if we're looking at Rauh 2011, we're seeing what you're seeing and whatever is there is what you're using.

MR. JIM NGUYEN: So when we have an intercept plus the model is log Working Memory index equal the intercept plus slope times the exposure level. So when we have an exposure level increase the percent reduction, delta Y equal beta times log and slope times the exposure. So given the delta Y, we can calculate the exposure level by delta Y divided by slope beta. And by definition, the 95 percent lower limit of the slope, that's 95 percent confidence of the beta L that's in the lower limit will be less than the true value and then if you have the inverse of that one reciprocal then we have a 95 percent confidence that the one over beta L will be greater

than one over beta 2, two slope. And then when you have multiplied both sides by the delta Y, delta Y is negative so the (inaudible) of inequality will (inaudible) again so 95 percent confident that delta Y over the beta L will be less than delta Y over the beta 2. Beta 2 is a two slope, and delta Y divided by beta 2 is actually the true value of the exposure level. Ninety-five percent exposure level would be less than the true value exposure level. and that is BMDL. By the combination the intercept will not evolve into the BMDL at all. So even that we don't have the intercept they involve intercept value, we're still able to cover the BMDL.

DR. WILLIAM POPENDORF: It doesn't come into your calculations, but the 1 percent, is it 1 percent of the population which may or may not, you know, no exposure for this population may be more than 100 percent. It could be less than 100 percent. That wasn't calculated. It apparently wasn't a variable. We'll talk about that later, but I'm just -- let me come back to my third question if you don't mind.

DR. JAMES MCMANAMAN: Okay, sure. Dr. Terry.

DR. ALVIN TERRY: I have a couple of

questions related to the biologic plausibility and this idea that you moved from using animal data to make decisions about points of departure to human data. And I do understand there are a lot of differences in the various basic research studies. However, I was perusing a number of review articles during the break looking at animal data, cell culture data and the whole gamut, and I have yet to find a single case where a pg/g concentration correlates with anything, any neurodevelopmental deficits or anything else. And so doesn't that give you cause for concern?

I mean, you're jumping to, you know, making a really big jump, and you're sort of discounting reams of animal data where there is absolutely no evidence I could find that this low concentration does much of anything.

DR. GINGER MOSER: This is Ginger Moser with EPA, and you're entirely correct. There are no studies that used doses that low. The problem is, for the most part, the studies used doses that inhibit cholinesterase, and we know that cholinesterase was not inhibited in these women. These concentrations were orders of magnitude lower than anything that would inhibit cholinesterase. So you're not comparing

apples and apples. In the animal studies, you're looking at doses high enough to inhibit cholinesterase and may also be acting on other systems. But what we don't know is if you go down lower in dose, are we still getting effects on other systems? And there is a lot of basic research looking a lot of the different kinds of pathways that they may be affecting. You know, there's the serotonergic systems, the dopaminergic system, endocannabinoid system, the different kinds of things that could be affected that are not a result of cholinesterase inhibition. So we just don't know, and that's the uncertainty. There are very few studies out there now that are looking at lower doses, but the database is very small. That's the problem. What you just said is the problem. That's why there's uncertainty, and we just don't know how to make that extrapolation.

DR. ALVIN TERRY: Can I ask a follow up?

DR. JAMES MCMANAMAN: Yes.

DR. ALVIN TERRY: I guess, at least with cholinesterase, it's a real biochemical measurement, you know. It's a tangible number you can reproduce. And one of the things I don't know; I'm

not a human researcher, but I do a lot of animal research where Working Memory is one of our outcome measures. And I can tell you that 2, 4, 6 percent change is easily within the day-to-day variance in performance. So I don't know if there's a human researcher that does Wechsler in the group, but are those numbers really meaningful, I guess, is my question.

DR. GINGER MOSER: Yes, that is definitely within the range that you would get in animal studies. Because there's more variability in those types of animal studies. I don't do those measurements in humans, and I think that there might be some people here that could address that more. But I think that the variability in those human results is very different from what you get in animal studies, but we're just using very crude behaviors to measure what we think are cognitive functions Working Memory.

DR. JAMES MCMANAMAN: Dr. Sagiv.

DR. SHARON SAGIV: I wanted to address the last comment. Sharon Sagiv from UC Berkeley. As Ginger mentioned, the animal studies and the human studies are really different, and one of the big difference is the human studies tend to be a lot

larger. So you have a much bigger sample size, and you might not see the variability you would see with a much smaller sample size; that's one thing. The second thing is that you may only see a couple of points on a Wechsler Scale difference per unit increase in your exposure, whatever it may be. But I think there are a lot of studies that have talked about how even those small increments or small effect size can mean a lot in a population level. So I just wanted to bring that up, and I know everyone's familiar with small changes in the mean can mean profound changes in the tails of the distribution or outcome.

DR. JAMES MCMANAMAN: Yes, Dr. Pessah.

DR. ISAAC PESSAH: Just wanted to point out I did a rough back-of-the-envelope calculation. I mean, you're talking about somewhere between 5 and 25 picomolar activity at a target. That's rarely achieved even with the highest affinity drugs, so chlorpyrifos must be pretty special to be able to target a molecule at that low of concentration.

DR. JAMES MCMANAMAN: Dr. Jett. I'm sorry, Marion.

DR. MARION EHRICH: Mine follows that

last one because I'm looking at slide 146. Are you proposing to actually measure point of departure at 2 pg/g and dietary food/water at .02 pg/g, the numbers that are on slide 146?

DR. ANNA LOWIT: Okay, so those values on slide 146 to remind, the point of departure was derived from the slide we had up a minute ago from the 2 percent change in Working Memory from the Rauh 2011. And so the RfD on the next bullet down is our proposal of that point of departure adjusted by 2 factors of 10, one for the human variability and the other one for the statutory required FQPA 10X. That would be well below the limit of detection within the Columbia study.

DR. MARION EHRICH: How can you regulate on that one? It's something that you can't measure.

DR. ANNA LOWIT: Well, I think what's measurable and what level you define as the line in the sand is what's safe for the entire U.S. population, it may not necessarily be the same thing. So the measurable levels that come from Columbia derive the point of departure, but the Agency, as a matter of policy, does low-dose extrapolation to

ensure that that point of departure and the line in sand is protected for the entire U.S. population.

DR. JAMES MCMANAMAN: Yes, Dr. Sweeney.

DR. LISA SWEENEY: I have a question about mode of action. In terms of thinking of mode of action as a sequence of events, I understand that you don't have one theorized for chlorpyrifos, but by making the reference dose basically based on something that appears to be basically a one-time peak concentration, are you implying that the mode of action is based on an achieved peak concentration of chlorpyrifos as opposed to any consideration of multiple peaks throughout a period of time or even a daily time weighted average blood concentration? I'm just saying are you sort of implying something about how it acts in terms of peak versus average even if you're not talking specifically about biological events?

DR. ANNA LOWIT: So I'll get it started, and I may pass to Cecilia next to me.

DR. JAMES MCMANAMAN: Anna Lowit.

DR. ANNA LOWIT: Yes, sorry Anna Lowit. So Cecilia and I both used the same slide a couple times today that I'm going to try and find really

quick. There's a lot of slides to go backwards. Did I go the wrong way? Can you find that peak slide? So Cecilia will find the slide. Okay, so your question, you asked if we're assuming that this is the peak value. Actually, we don't think these are the peak values. We think that as we've shown a couple of times today, that the pattern of the internal concentration we think rises and drops fairly quickly because of that three-to-four half-life. And so during the time of exposure, whether it's a food eating event or an occupational event, someone in the field picking apples or someone in their apartment sitting on the floor for a while, that those exposure events lead to rapid changes in those internal concentrations. But when those events are in that, there is a fairly rapid drop within the matter of a few hours. And then once that drop occurs, the reported -- that the values within the terminal half-life are stable within the few days. In fact, we don't think it's the peak. We think it's the lower point values on the curve, and if you go back to Wade and Danette's presentations, our estimates, our predictions to the women at somewhere in the order of 8 to 24 hours post-exposure actually match pretty well

the Columbia data at the higher percentiles.

DR. LISA SWEENEY: I understand you're saying that the Columbia measurements are not a peak concentration, that they're a post-peak concentration, but are the concentrations of concern because a particular peak was achieved. And does it only matter if that peak is achieved once, or does it matter if it's achieved every day of pregnancy? Does it matter if it peaks for two weeks as an applicator? That's what I'm asking about mode of action.

DR. ANNA LOWIT: We're not making any statement on the number and the frequency of the how often those may have occurred and, in fact, the exposure pattern to the women in the cohort is not a knowable event. The Columbia investigators did not collect information on how the frequency of the applications, the timing of those applications, the kind of application. This was why we embarked on the scenarios that Wade discussed earlier. Our goal with those was to try to characterized the continuum of what those exposures could have been theoretically from the highest exposure scenario, which would have been that broadcast down to something far lower, even orders of magnitude lower, and to characterize that

continuum. Because that pattern across the nine months of her pregnancy is unknowable, and on top of that, since the adverse outcome pathway or pathways are not known, we can't match the critical window susceptibility to when those applications occurred. But what we do know is that the women were exposed, and we do know they were exposed close enough to the time of the delivery that a large number of them before the cancellation had measurable levels and levels that we've been actually pretty well able to reproduce here.

DR. CECILIA TAN: Cecelia Tan, EPA. Dr. Sweeney, let me try to understand your question first. So you're saying that we really don't know given that there are unknown AOPs. That it could be C max that's causing the effect. It could be average concentration that's causing the effect, or it could be I don't know some average AUC above some threshold. We don't know that. And our assumptions here first of all, from the epi studies -- let's say that the association is true that biomarkers associated with the outcome, the next assumption that we're making if you remember the slide that I presented that you have to find exposure time course, it can end up with the

same biomarker concentration. But what we're saying is we have a pretty good estimate of what the real exposure scenario is. On top of that, we have a pretty good bound on what is the time between exposure and biomarkers samples. So in a way, we are using that biomarker concentration as a surrogate of the entire exposure scenario, the patterns, so it may be the peak that's causing the effect. It may be the average that's causing the effect. But what we're saying is this one measurement is a good representation of whether the peak or the average concentration, the entire time course.

DR. LISA SWEENEY: I guess I'm just saying that if you're going to compare the 10-hour value after a particular scenario for all sorts of different worker, residential, various uses, what happens before that last day can be very different in the study population as opposed to the potentially exposed populations that you're looking at. I'm saying that it could be very different. It could be similar, but they could be very different.

DR. ANNA LOWIT: And we fully acknowledge that. I mean, we've got a variety of these simulations that have these spikey appearances,

and the magnitude of their peaks ranges across orders of magnitudes. I think to some degree, because of that, there's a benefit to sticking to the 10- and the 24-hour post-exposure because the values at that point are far more stable across a several day time frame and becomes a much more apples-to-apples comparison to that from the Columbia data.

DR. JAMES MCMANAMAN: Dr. Pessah.

DR. ISAAC PESSAH: Isaac Pessah, UC Davis. I was just wondering could this -- we do know that organophosphates covalently modify at least one target, esterase and estro cholinesterase. Do you account for the accumulative nature of the biological effects where it's not the peaks and the troughs where you're going to phosphorylate/dephosphorylate, but you're going to systematically reduce -- and I realize these women didn't have reduction in cholinesterase, but there could be another target that's covalently modified which don't follow the PK. They actually add accumulative. Is that possible? Did you consider that in your model?

DR. CECILIA TAN: Cecelia Tan, EPA. I will -- maybe I don't completely understand your question, but earlier when we did the 2014 risk

assessment, we did look at the blood concentration and cholinesterase inhibition, and they do have different patterns. So for blood concentration, there is this rapid increase and decrease as Anna had shown in her slides, the worker exposure if you remember that, but for cholinesterase inhibition, you do see that accumulative effect. So it doesn't go all the way back. It doesn't have that rapid change as the blood concentration.

DR. ISAAC PESSAH: So I guess is your calculation -- if there is some other target with picomolar affinity, could it be cumulative, and could your 10X underestimate? I'm going the other direction.

DR. ANNA LOWIT: On the pharmacodynamics side, the only marker within the model is the acetylcholinesterase protein. So other markers, I'll defer to Ginger to say what some of those are so I don't misspeak, are not implicit in the calculations. So I think the answer is no.

DR. JAMES MCMANAMAN: Yes. Dr. Fisher.

DR. JEFF FISHER: So now one of my questions I've been thinking about until now to talk about it, is your selection of the dose metric of peak

is looking at the stable time versus other options, and it was just discussed. Why did you not use area under the curve to capture the complex exposure scenarios for the duration of whatever unit time you want?

DR. ANNA LOWIT: I'm not sure this is going to answer you or not, and we can try again. With the drinking water scenarios, we don't have -- because there is drinking events through the day, you don't see this up and down, up and down, up and down kind of event you do with those other scenarios. It smooths out quite a bit because it never achieves that drop. So if an adult is assumed to drink three or four times a day and an infant six, I believe it's six times a day that we're assuming, you don't see these spikes. This is one of our infant case study, on the left side is the predicted values from our modeling, the right side being the measured values from Orestimba Creek. Certainly on the left side from the predicted values because the concentrations are remaining fairly high through that 120 days, you don't see any quick drop like you do on the right side where the times of measured values are more distinct and separated. But even within that, because there's

these four to six times per day even on the right side, you can see that within those days of measured values, nothing is dropping. Are you following?

DR. JEFF FISHER: So because of the disagreement between the model and the measured data, is that why? No? Maybe I'm not getting it.

DR. CECILIA TAN: Cecelia Tan, EPA. For the drinking scenarios, we are using the average concentration, right, for comparison, because there's no – oh, it's to measure the concentration --

DR. ANNA LOWIT: So the right side are actually values from an actual measurement from a creek. But since the drinking events are within a few hours, if the half-life is three hours, you have a drinking event equal to that half-life, so you don't see the up and down once a day thing. It's a little more bumpy because of the frequency of the drinking compared to the half-life. And so during these events of water exposure, you don't actually enter into the terminal phase. The values stay fairly high, but you do see it between those two measured peaks. Whereas on the left side is the predicted values from the bulb onion which are predicting fairly, you know, descent levels of chlorpyrifos consecutively across many days,

so you never see that drop because there's a drinking event every few hours.

DR. CECILIA TAN: Cecelia Tan, EPA. Dr. Fisher, maybe we didn't understand your question correctly. For these case studies, the PBPK model is now used to simulate different exposure scenarios, not the biomarker scenario any more. But what we think is the drinking water scenario, food scenario and worker scenarios to predict the internal blood concentration and that prediction is compared with -- what is that level, the point of departure to see if any of the predicted concentration exceed that point of departure.

DR. JEFF FISHER: That helped because the concentration is your anchor, the measured concentration. You're always going back to that.

DR. CECILIA TAN: Yes.

DR. ANNA LOWIT: We could, on any of these plots put a line, you know, a colored line that would represent either the point of departure or the extrapolated to the reference dose. So if we did the point of departure, it would, if you look on the left side at the two, it would basically start from that two and go across meaning that the internal

concentration in the infant for this bulb water onion scenario basically equals the point of departure for the bulk of the 120 days and actually exceed it some days. We could do the same thing on the right side, but the scale is different so that the two is much higher and so that would be the point of departure and you would then compare that to a value 10 or 100 times lower which would be at the .02, which is pretty far which would be essentially how we would do on a risk assessment. We could do that for any of the scenarios. So if I pull up the worker ones, it would be the same deal that the point of departure is around two and so the scale here, it's hard to see the two because the values are much higher, you can draw that same line at two across to see how they match. And you could do the exact same thing on the food.

DR. JEFF FISHER: Thank you, I have one more question. The within person variability that translates to an uncertainty factor, would Monte Carlo simulation help with that factor instead of, I think you had 10X.

DR. ANNA LOWIT: For the 2014 risk assessment, we actually did those Monte Carlo simulations for the acetylcholinesterase endpoint. We

did that for life stages except for women who could become pregnant. Because the pregnancy model hasn't been published or doesn't have chlorpyrifos data within it, we didn't feel like that model was robust enough to develop that factor. But for other life stages, theoretically, yes, you could do it; from a pharmacokinetic point of view, not for the dynamic point of view, and we have done it. For example, you could do the infants that way.

DR. JAMES MCMANAMAN: Yes Dr. Rohlman.

DR. DIANE ROHLMAN: I want to go back to Isaac's point when he was talking about the cumulative effect of exposure over time, and maybe you could talk a little bit more about that to make sure I'm clear on it. What we see and what you're modeling here is the chlorpyrifos in the blood. You can see the peaks, and then there's troughs; and I see, you know, when it was up before, we do see a lower level, which shows a slight cumulative effect because the bottom of the trough increases there. But if we look at something like cholinesterase inhibition or urinary biomarkers, we see cumulative effect where the lab would stay up until exposure has ended. How is that captured in your model? I don't think it is, or

should it be?

DR. CECILIA TAN: Cecelia Tan, EPA. For the chlorpyrifos model, there are two parts. There's the PBPK part, which predicts the concentration in tissue and blood. There's also the PD model, which I showed earlier and then that PD model describes the binding between the chlorpyrifos and cholinesterase; and there is an accumulation because in that model, it describes the binding as irreversible. So it binds and then the only way for it to go away is for the enzyme to die, if that's the word, and then that is captured in the model.

DR. DIANE ROHLMAN: In which model?

DR. CECILIA TAN: In the PBPK-PD model, the chlorpyrifos model.

DR. DIANE ROHLMAN: Okay.

DR. CECILIA TAN: So the accumulative effect is captured in the model, but we did not talk about it in this analysis because we focused on the blood concentration rather than the cholinesterase.

DR. JAMES MCMANAMAN: Dr. Pessah.

DR. ISAAC PESSAH: In the PD model, are you modeling on red blood cell cholinesterase or on brain cholinesterase?

DR. CECILIA TAN: Various red blood cell cholinesterase. There is brain cholinesterase, and then I believe there is diaphragm cholinesterase; and I believe there is one more, lungs. I'll go back to the slide, but it's really a far way. So I'll show the structure of the PBPK-PD model. I don't know if you can see it, and then the tissue that has cholinesterase described -- are highlighted in blue. So lungs, diaphragm, blood, and brain.

DR. ISAAC PESSAH: In the brain compartment, are you modeling the massive culling of neurons during the perinatal period? Because those cells are not dividing. You're actually losing millions of cells.

DR. ANNA LOWIT: No the PD component of the model is simply just the calculations for acetylcholinesterase inhibition. None of the neurodevelopmental targets or any of the cellular changes are included and because of that we're only using the kinetic portion of the model here.

DR. JAMES MCMANAMAN: That was Dr. Lowit. Dr. Rohlman.

DR. DIANE ROHLMAN: So just to follow up again about -- I keep, seem to be fixated on this

cumulative exposure, and you know you've done this for 30 days with anticipation that there's one application of pesticide in the home, 30-day period we have a -- but then there's another pesticide application period, another 30 days. So you could presume that throughout the whole nine months, the child has had exposures; have you looked at longer periods than 30 days? Have you put that out? And would the effects that we see in the bottom of the trough accumulate over those --

DR. CECILIA TAN: I think we've heard a similar question earlier. I think Dr. Sweeney has mentioned that but if you look at two months, there's this accumulation. To answer your question, we did not look beyond 30 days. If you remember Wade's presentation, he showed that the peak of the first day and then also the concentration at the 24 hours, not 24 hours after, but the concentration at 24 hours, you can see that it's very low already. Again, I can run the model. It will take a long time, but I'm guessing even if there is cumulative -- even if it's building up, I do not think that the number is dramatically different.

DR. DIANE ROHLMAN: So the number may not be different, but then if we extrapolate that to

say what are the effects other, you know, cholinesterase inhibition -- these are our load levels, but, you know, are we seeing these effects that are chronic continuing? And so I guess I'm going back to Isaac's point of being maybe more protected.

DR. JAMES MCMANAMAN: Dr. Jett.

DR. DAVID JETT: Real quick question, a follow up. Do we know what the recommended frequency of application of chlorpyrifos is?

MR. JEFF DAWSON: Hello, my name's Jeff Dawson. I'm in the Health Effect Division. So within the simulations that were run in the residential environment when in the period of time where chlorpyrifos was the preferred indoor insecticide, the once a month application frequency is a pretty reasonable approximation of the actual practices that were going on at that point in time. For other settings like agricultural settings and so forth, it kind of varies by crop and pest pressure. For most of the uses, if you look at total pounds of chlorpyrifos and my colleagues correct me if I'm mistaken, but most of the times, it's just on average about one application per crop cycle per year where most of the pounds are used, and that's on field crops like soy

and corn and so forth. There are other pest complexes in crops where it's higher frequency. I think some of the trees for instance and stuff like that where you might have more than, you know, one or two applications a year, but they would be much more limited in the big universe of how chlorpyrifos could be used.

DR. DAVID JETT: And during the Columbia study, was chlorpyrifos available off the shelf where you could apply it as needed? A homeowner?

MR. JEFF DAWSON: Yes, you could go and purchase and use chlorpyrifos and then was also because of the nature of the housing within the cohort there were also, as we understand it, institutional uses where it would be scheduled for once a month.

DR. DAVID JETT: But it is possible that you could actually use it more than once a month.

MR. JEFF DAWSON: It is possible. Part of the way that we inferred doing our simulations was also based on the reporting of the participants in the cohort as well.

DR. JAMES MCMANAMAN: Dr. Hayden.

DR. WILLIAM HAYDEN: Just to respond to

Dr. Rohlman's question about the rising bottoms. Those should expeditiously approach a limiting value that's driving by the long half-life, the five-day half-life. So after, you know, say four half-lives, after 20 days, those bottoms are going to stop going up.

DR. DIANE ROHLMAN: But if they continue to have exposure every month, won't that continue that process?

DR. WILLIAM HAYDEN: No, because it is reflecting kind of the pseudo equilibrium between all the tissues in the blood and once that gets established that's what drives that long elimination half-life too, if you stop the input. That's the way I'd understand that.

DR. SHARON SWEENEY: I suggest you look at slide 151 because in that simulation you have the same exposure every day for 40 days, and so you can see that the peaks -- the increase in the peaks slows down and the troughs also stabilize so that illustrates that pretty well. Yes, hypothetically they are getting a wee bit higher, but by 40 days, you can't really see the difference.

DR. JAMES MCMANAMAN: Other questions?

Dr. Popendorf.

DR. WILIAM POPENDORF: Question on another topic a bit. The FQPA issue, it makes sense to protect people like the law says, but I'm wondering in a case like this since you're using the sensitive base of basically the fetus to determine the effect and applying it essentially back to that same group, is there any other example of point of departure set based on fetal effects -- or fetal exposure shall we say actually?

DR. ANNA LOWIT: So there's kind of a lot in that question. Across EPA, if you look across the entire EPA, I think methyl mercury is a good example of a chemical evaluated based on epidemiologic data from cord blood used primarily by the Office of Water and reviewed by the NRC a number of years ago. The Office of Water is not regulated under the Food Quality Protection Act as we are in the Pesticide Office. So in the Pesticide Office this will be the first example of using a cord blood measure to evaluate a pesticide under the Food Quality Protection Act.

I think that answers your question although routinely in all of our assessments we by

statute have to assess all life stages. So we get large amounts of animal data including reproductive toxicology studies and developmental toxicology studies in rabbit along with for OPs we get a number of special cholinesterase studies. We routinely assess fetal and early life exposure in animals in all our assessments but this is the first one to do what we're proposing here which is use cord blood from an epidemiologic study under the Food Quality Protection Act.

DR. JAMES MCMANAMAN: Dr. Fisher.

DR. JEFF FISHER: I'm drawing on my memory banks concerning that question. I was on the Dioxin Science Advisory Panel and for non-cancer I remember cord blood and changes in serum TSH and extrapolation, empirical extrapolations, time extrapolations, so that's an example -- a human pregnancy if I recall correctly it's fetal cord blood measures of TCDD as it relates to the thyroid the HPT axis perturbations, TSH specifically.

UNIDENTIFIED: You have a glossary for that statement?

DR. JAMES MCMANAMAN: Okay, Dave.

DR. DAVID JETT: My quick question, one

as a practical question to help with the charge question, but I also wanted to take advantage of my long-time colleague Ginger here and ask her if you know of any animal studies that have empowered well enough to find a one-to-five percent change in any memory test, water maze, Working Memory, what have you? I don't think so, but I just wondered while you're here if you thought of anything?

DR. GINGER MOSER: I would say no. Typically, these types of animal studies will look at maybe 10 to 12 animals -- litters, per treatment and in the chlorpyrifos literature that's good. There is many of them that are as low as five and six which are just totally underpowered. But to pick up -- for example with the Morris Water Maze, you know, you're going to have to have more than 10 to 12 to pick up a 5 percent change in something. And for many reasons, resource types of reasons, people just don't use that many animals in a study. But then if the data are really tight, you can possibly get close to that. You can get statistical significance close to that, but I haven't gone through all of them and looked at the percent change in these affects, in these changes.

DR. DAVID JETT: I'm getting at the

extrapolation issue, but I think I wanted to ask a more practical question about -- one of the questions I'm charged with is, I guess it's questions 4, and I heard something earlier about that the exposure approaches have already been reviewed extensively and to not really concern ourselves with that but I'm looking at this question and it says please comment on the agency's conclusion that these scenarios adequately capture the range of exposure and I guess you mean in comparison with the Columbia study data. That's what you're talking about when you ask --

DR. GINGER MOSER: I was pulling up the charge questions quickly.

DR. DAVID JETT: Okay, question number 4.

DR. GINGER MOSER: But I believe that's the case that we're talking about human exposure as it would have bene related to the cohort.

DR. DAVID JETT: Please comment on the Agency's conclusion that these scenarios adequately capture the range of exposure based on the human data that we're now looking at or just in general do these make sense. Because if that's the case it seems to be that that's already been covered based on your earlier

comment. I'm just trying to see where to focus on this question.

DR. GINGER MOSER: Yes so Charge Question 4 is largely aimed at the presentation you heard from our exposure team, Dr. Bohaty, Danette and Wade earlier with respect to our efforts to look at the different pathways of exposures; food, water and the residential. And within the residential to look at a variety of scenarios that capture the range of what those possibilities could have been to help us understand the reported values in Columbia. Yes this is a question about the human exposure in the scenarios.

DR. JAMES MCMANAMAN: Dr. Popendorf.

DR. WILIAM POPENDORF: Just to follow up on Dr. Jett's question, going back to lead. I'm haven't look at lead exposure, lead standard in a long time, but was there any effect on learning or IQ or Working Memory as part of that standard when it was set for children?

DR. ANNA LOWIT: Ginger, go ahead.

DR. GINGER MOSER: This is what I think, at least for the secondary lead standards, that yes, it is based on IQ changes. The lead standards

are based on IQ changes based on the human data. Animal studies have confirmed this, but the human data were obviously much stronger. They had much larger samples in those human studies.

DR. WILIAM POPENDORF: Was there a quantitative threshold that they used to say this is the exposure?

DR. GINGER MOSER: When they first started, they did regressions on IQ and lead levels, blood lead levels, and as studies have progressed, they've looked lower -- at lower and lower lead levels, and now it's looking like the line is not completely linear between the lowest and the highest exposures so actually as you go lower with blood lead levels the change in IQ has a steeper slope than when you get higher. So it's almost like a biphasic kind of line and that's causing some issues too which is causing some people to believe, and I believe agencies are starting to think there may not be a threshold for lead, that you just keep going lower and lower more like a one-hit cancer theory. The data in terms of those kinds of regressions is much, much better than anything we have with chlorpyrifos.

DR. WILIAM POPENDORF: But did they

pick an IQ, you know a change in IQ level to say this is where we're going to set that lead number? I mean, if we don't know we should probably, you know.

DR. DANELLE LOBDELL: At this point in time, I don't know. They're in the process of actually reevaluating that right now and so to really comment -- I don't know what they're doing. I have not been involved in any of that but we can't go there.

DR. WILLIAM POPENDORF: Well yeah, we shouldn't go there, but look to what the last, you know, the current standard is, the criteria, and that would be worth comparison I suppose.

DR. GINGER MOSER: Just to point out that I believe it was the lead studies a long time ago when they started looking at these small IQ shifts. When they started looking at how that affects the normal distribution and the decrease in the high end and how much more you get in the lower end. With just a very small shift in the average IQs you greatly increase the number of people at the lower IQs which increases, you know just a lot resource values, economic kinds of things that they can get into and I think it was the lead data where they first started

looking at just like a one percent change can really make a big change in the population and the consequences of having just that slight shift in IQ change.

DR. JAMES MCMANAMAN: Okay Dr. Funk.

DR. WILLIAM FUNK: I just wanted to know with lead, the new standards for lead from the CDC are based not on health affects but rather with the assumption that there is there is no safe level. The new level for the CDC is set just to protect the most highly exposed children so it's based off of the 95 percentile NHANES data. So it's based off of exposure not based on health affect.

DR. JAMES MCMANAMAN: I have a question for Dr. Moser or maybe for the entire agency. We were looking at the modeling data for levels. Maybe I missed this, but has anyone actually done an experiment to show experimentally how the levels of chlorpyrifos change over time with multiple injections in animals?

DR. GINGER MOSER: As they've been developing the PBPK model they have been using, they mostly meaning Chuck Timchalk's (phonetic) group, they have used animal data to help validate their model and

they've used animal data from sub-chronic feeding studies, year-long feeding studies, and it worked very well to predict those levels. They've also -- I know that because they used my data. They've also used data looking at the different life stages. So they've used data from animals at PND 10, 17, 21 to see how the model predicts the cholinesterase inhibition at different ages. So yes it has been looked at, all the different kinds of aspect that you want to look. But again it's the cholinesterase inhibition that it's modeling and that's been used to validate it.

DR. JAMES MCMANAMAN: But in the PBPK and the animal studies they were actually measuring chlorpyrifos over our metabolite right? Or were they just looking at cholinesterase inhibition?

DR. GINGER MOSER: Cholinesterase inhibition. Well, mostly in the dietary study we did, we did look at chlorpyrifos and oxon, and I would imagine they probably used those data too.

DR. JAMES MCMANAMAN: Okay, another follow-up question on this. Has anyone measured the levels in the brain?

DR. GINGER MOSER: Yes. Cholinesterase in the brain --

DR. JAMES MCMANAMAN: No, chlorpyrifos in the brain.

DR. GINGER MOSER: -- and in the oxon -- in the levels of chlorpyrifos and chlorpyrifos-oxon, we looked at it in the blood and the brain and then fetal tissue. Part of the problem is that the oxon is very reactive, and it's very difficult to measure because it just clumps onto everything.

DR. JAMES MCMANAMAN: I guess where I was heading with this is that there was statement made that it likes to go into fats, so does it like to go into the fat in the brain? And is it more stable there? And would the levels come to the point where it could become a mode of action? You know, we're not talking about picomolar now we're up to nanomolar because of accumulation in the brain.

DR. GINGER MOSER: I'm not sure if he looked at that, but we can maybe go back and pull up some of those papers and find out if he's published it, which I assume he has. I'm not sure exactly. I was doing some checking, to get back to the issue of the concentrations and how low that really is. The 6 pg/g turns out to be 17 picomolar, which is extremely low, yes. But there are in vitro studies that have

looked at chlorpyrifos and the oxon, and some of them have used very, very low concentrations. And there is one that I remember right off-hand and happens to be coauthored by someone sitting right next to you; they used --

DR. JAMES MCMANAMAN: Don't trust it then.

DR. GINGER MOSER: They used a concentration as low as .001 nanomolar. So you're talking 1000 picomolar, and they were getting effects on axonal length grown in cell culture. You don't know how that's going to extrapolate exactly to in vivo, but we are still talking about some fairly low concentrations. They did not even get a concentration that was not affective because they didn't go any lower than that.

UNIDENTIFIED: Thanks for bringing that up, but I can comment on that because I actually have -- so there's two -- I was going to save this for my written comments, but there's two issues I was thinking about when you brought that up. And one is we are talking about potential events during the developing nervous system that could have not necessarily accumulative effects but sequelae from

that event that could alter the development of the nervous system that could end up in some aberrant phenotype.

Now, the other issue is that for more acute interactions you were talking about, and I think we've talked about this before, we've shown and published that we had interactions with transcription factors and the EC50s were in the femtomolar range. So it's not unheard of, but it's, you know, it certainly isn't a sure thing that those kinds of levels would have significant effects.

DR. JAMES MCMANAMAN: All right, other questions about this presentation? Okay, well, then we had a response related to the question about the analytical – the quantitation questions, and those were nice, very well-thought answers. Unfortunately, it didn't address the question. So we're going to go back with some clarification questions. I'll read these in. We've handed out Xerox copies of these. They will be made available in the public docket so that every will have them. But for the time being, I'm just going to read them in so that it's on this record.

Question was what was the relationship

between LOD and LOQ? So lowest level of detection versus lowest level of quantitation.

Number two is were recoveries always as low as only 18 percent? The Perez paper has recoveries at 77 percent. Ninety or 70?

UNIDENTIFIED: Seventy percent. The recoveries in that other paper were 70 percent. That makes a difference on your level detection. If your level of detection is one, it would go up to four if your recovery was four-fold higher.

DR. JAMES MCMANAMAN: The third question is how were samples quantified when only LOD was provided and no calibration was given?

And number four, samples below the LOQ, were they further concentrated? It appears that they were concentrated by about 400 fold in the Barr 2002 paper.

So those are the additional questions that we'd like to get responses to.

DR. ANNA LOWIT: Thank you for those, and we're in the process of having someone upstairs type them out in the way we did over lunch; and we have already alerted Dr. Barr that more questions were coming. So as soon as we get the typed-up versions,

we'll send them to her. Obviously, we won't have responses by the end of today.

DR. JAMES MCMANAMAN: So what we'll do is that once we get those responses, we'll take some time tomorrow morning to hear those responses and get any further clarification questions to the agency before we move to the public comments. So with that, we'll call it a day today and reconvene tomorrow at nine.

MR. JENKINS: I got a quick note. So tomorrow, we'll go into the comment period. Important points for the public commenters tomorrow: First, it's very important that all the public commenters are here during the public comment period. Once the public comment period closes, there will be no more opportunity to provide your public comments, so we want you to get an opportunity to provide your public comments. We ask that all public commenters please remain to your agreed-upon time frame. It's very important that we stick to the schedule for this meeting to get accomplished all that we need to get accomplished. There is a list outside of this door on that desk outside for all those who have made arrangements to give oral public comments tomorrow.

Please take a look at that list just to make sure that you're on it. If you're not on the list and you think you should be on it, please let me know or someone else on the SAP staff. Also, if you want to provide public comments or public comments for tomorrow, please let me know as soon as possible or someone else on our staff. And as a reminder, you'll be limited to a five-minute time frame since you didn't make prior arrangements to provide your public comments. Thank you all for a very productive day, and see you all in the morning. Have a great evening.

(Whereupon, the meeting was adjourned for the day)

DAY 2 - April 20, 2016

DR. JAMES MCMANAMAN: Good morning everyone and welcome back. We'll have everyone introduce themselves for this day's event. I'm Jim McManaman, I am the session chair. I'm a professor at the University of Colorado.

DR. DAVID JETT: And I'm Dave Jett. I am the Director of Countermeasures Against Chemical Threats at the National Institutes of Health.

DR. MARION EHRICH: Marion Ehrich, Improvement Panel Member from Virginia Tech, College of Veterinary Medicine, Toxicology Diagnostic Laboratory.

DR. SONYA SOBRIAN: Good morning. I'm Sonya Sobrian from the Howard University College of Medicine, Department of Pharmacology.

DR. ALVIN TERRY: Alvin Terry. I'm the Chair of Pharmacology and Toxicology at Augusta University.

DR. LISA SWEENEY: Lisa Sweeney, Henry Mt. Jackson Foundation at Detail at the Naval Medical Research Unit, Dayton, ad hoc member.

DR. SHARON SAGIV: I'm Sharon Sagiv, Division of Epidemiology at U.C. Berkeley.

DR. DIANE ROHLMAN: Diane Rohlman, Department of Occupational and Environmental Health, University of Iowa.

DR. WILLIAM POPENDORF: Will Popendorf, Emeritus Professor of Industrial Hygiene, Utah State University.

DR. ISAAC PESSAH: Isaac Pessah, a Professor of Toxicology, University of California, Davis.

DR. STELLA KOUTROS: Stella Koutros, the Division of Cancer Epidemiology and Genetics of the National Cancer Institute.

DR. WILLIAM HAYTON: William Hayton, Emeritus Professor of Pharmacy, Ohio State University, ad hoc member.

DR. WILLIAM FUNK: Bill Funk, Northwestern University, Department of Preventive Medicine.

DR. JEFFREY FISHER: Jeff Fisher, FDA, NCTR Division of Biochemical Toxicology.

DR. RUSSELL CARR: Russell Carr, Center for Environmental Health Sciences, College of Veterinary Medicine, Mississippi State University.

DR. JAMES MCMANAMAN: Okay. Thank you. So I've been reminded to ask everyone to speak a little closer to the microphones, because they're having a hard time picking up our voices for the recordings. Usually, these microphones are quite good. But I think we still have to get a little closer. So we left -- yes?

DR. PANOS GEORGOPOULOS: Yes. Professor Panos Georgopoulos also on the call.

DR. JAMES MCMANAMAN: Okay. So that was what I was just reminded to say is that Dr. Georgopoulos was going to be calling in and he is here. Thank you. Welcome, Dr. Georgopoulos.

So we left yesterday with -- the agency was going to get back with the principal investigator about the analytical question. They did, and she responded. And that information has been entered into the docket and provided to the panel members.

So at this point, I think what I'll do is ask the panel if they have any further questions for the agency related to yesterday's presentation. And if not, we will then go on to the public commenters. Okay. Hearing none then, thank you for your presentations, and we'll move on to their public

commenters.

So, first up is Dow AgroSciences. Welcome, and please introduce yourselves.

DR. DALAND JUBERG: Yes. Can you hear me? This is Daland Juberg with Dow AgroSciences.

DR. CAROL BURNS: Carol Burns, The Dow Chemical Company.

DR. JEFFREY DRIVER: Good morning, Jeffrey Driver with Risk Sciences.

DR. WILLIAM BANNER: Hi. I'm Bill Banner from INTEGRIS Baptist Medical Center, Oklahoma.

DR. DALAND JUBERG: And while Dr. Jenkins is loading that, let me say on behalf of Dow AgroSciences, I'd like to thank Dr. Jenkins, Dr. McManaman, members of the Scientific Advisory Panel for giving us the opportunity to speak before you today.

The booklet that you have in front of you contains two important sets of documents: One, all the oral presentations that you'll be seeing; and secondly, written submitted comments from Dow AgroSciences and from external scientists that are in attendance here today.

In particular, for those of you that

are addressing charge questions, I would note that the Dow AgroSciences comments in response contains responses to numerous questions, and that is in Tab 6. For anyone looking at Question 2, Dr. Driver will be addressing some of those questions in Tab 7. And Dr. Goodman, excuse me, she addressed Questions 2A, 5A and 5B in Tab 10.

The order of the presenters today will be as follows: I'll offer some opening comments. I'm a global leader, Human Health Assessment for Dow AgroSciences and also been the chief toxicologist for chlorpyrifos for Dow AgroSciences for the past 10 years; followed by Dr. Jeffrey Driver, a principal with Risk Sciences; Dr. Carol Burns, Senior Epidemiologist with The Dow Chemical Company; followed by Dr. William Banner, who's the medical director for the Oklahoma Poison Control Center and also attending physician for Baptist INTEGRIS Medical Center.

Just a bit of personal background, let me move into my presentation. I have a Master's of Science Degree in Environmental Health Sciences and a Ph.D. in toxicology, both from the University of Michigan. I'm a fellow of the Academy of Toxicological Sciences, and I have 24 years of

applied, regulatory toxicology experience with a number of different firms.

So today, there are some important concepts that we'll discuss. One, the EPA proposal to change the point of departure assumes that the Columbia data are the best available data. Yet, this could trigger elimination of chlorpyrifos, and I don't know if that's been clearly articulated in yesterday's discussion.

As Dr. Jack Housenger said, "This is a very important insecticide," and I quote him. I would, again, articulate the decision and the actions before this panel could trigger the elimination of this insecticide.

This is both an unprecedented, and I would say precedent-setting process that jeopardizes the established science-based regulatory process. Again, Dr. Housenger yesterday quoted and said, "This is a groundbreaking approach."

The impact goes beyond the discussion of chlorpyrifos before this SAP. In fact, 40 major agricultural organizations have joined together to express their concern. And before the SAP Charge Questions are addressed, there are some basic

assumptions and, I would point out, reliability of data, that need to be vetted.

In a recent communication back from EPA leadership, two registrants, it was noted that this SAP can consider reliability of relevant data. And we consider this to be an integral part of the SAP's assessment.

So I have four points I'd like to cover today: One, the current point of departure involving red blood cell cholinesterase inhibition. I'd like to raise to the panel's attention, Dow AgroSciences studies and some of our past reviews over the past eight years that I don't think are well recognized.

In addition, I'd like to bring forward some independent reviews that have been published in the peer review literature that address many and have formed many of the questions before the panel, and currently speak briefly on the current PoD proposal.

So just two quick quotes from the 2012 Scientific Advisory Panel Conclusions on RBC ChEI as a PoD: "AChE data," that is acetylcholinesterase, "continued to be the strongest resource of data for deriving points of departure for chlorpyrifos."

Secondly, "this panel advises that the

Agency continue to use acetylcholinesterase data at the most sensitive life stages for dose-response analysis and for deriving points of departure."

I'd like to augment those 2012 panel reviews with a more than 45-year history involving global regulatory bodies involving such as the World Health Organization; Canadian authorities, beginning in 1969; Australia authorities; and the European Food Safety Authority, just recently in 2014. I will not read these. But you'll notice in a couple of the middle quotes, they talk about being the most sensitive indicator of toxicity, the most sensitive toxicological endpoint for chlorpyrifos.

So I think this demonstrates that globally, all other regulatory bodies are still adhering to RBC ChEI as a point of departure. And I would remind the panel that red blood cell cholinesterase inhibition is not the biological target. It would be brain cholinesterase inhibition.

But to augment that last statement, the EFSA Review in 2014 did, in fact, look at some of the epidemiological evidence and concluded that the epidemiology data are not sufficiently robust to support the hypothesis that chlorpyrifos is a causal

factor for neurodevelopmental effects.

Let me move on now to some of Dow AgroSciences', the acronym being DAS, Science and Registration Review. We are the primary registrant that has supported EPA re-registration and registration review. And all of our raw data are submitted to the EPA, both over the last eight years of the registration review and over the course of history of this molecule.

We take extra efforts and sometimes go beyond required agency requests for scientific rigor and clarification. And I would point out three facets to this: We sometimes do studies that are not required. We very frequently augment study designs as we did in the 2010 Comparative Cholinesterase Assay in which we employ various dosing regimens. We often tax both the high and the low-dose regimen. We are required by law to define a no-observed adverse effect level. So we do exploit and explore the low end of the dose range. We did this in the CCH study. Conversely, we did this recently with some inhalation studies in which we saturated atmospheres with both chlorpyrifos and oxones. So I'd like to point out that we do take our science seriously and employ

rigorous methods when we do that science.

When we don't have the internal expertise or when we want to get external guidance, we often go out to external panels, and bullet three here speaks to that. We have consistently, over the years, engaged external panels.

Beginning in 1991, the Clegg and van Gemert panel specifically brought together both Dow AgroSciences and EPA to look at neurobehavioral effects. We followed those with some sentinel and serious reviews, and you can see those up there. So we're not opposed to looking and getting eternal advice when we need to.

Finally, 40 years plus of science continues to support red blood cell cholinesterase as the biologically-relevant and protective point of departure.

What this slide demonstrates and what I'd like to point out is that all of these are submissions from DAS to the U.S. EPA over the last eight years. And the significance of these is that they contain a number of pieces of information that I think would inform questions before the panel today.

We would note on the bottom that,

somewhat discouragingly, the EPA has not responded to these or other stakeholder comments. So we take time and effort to put together thoughtful comments. And I would like, you know, the panel to understand that these are available for this panel's review.

In addition, what's before you on this slide are what I would consider expert reviews on animal/human data and neurodevelopment. These are not insignificant. These are robust reviews, starting with Eaton et al. in 2008, an independent review done on -- basically, a scientific advisory panel of its own, looking at chlorpyrifos and neurodevelopment. You can see these have all been published in various scientific journals involving very different author sets.

So importantly, I think my point of this slide is that these inform specifically on two things: One, whether red blood cell cholinesterase inhibition has protected the neurodevelopmental effects; and secondly, the use of epidemiology and risk assessment. And all of these reports do weigh in on those two questions.

To bring just one conclusion of one of these reviews, Prueitt et al. concluded that a causal

association between chlorpyrifos exposure and neurodevelopmental effects in the absence of acetylcholinesterase inhibition in the brain is not plausible in humans.

So what we have before us today is a proposed paradigm shift, one being from 40-plus years of data to one involving a single-point measurement from one study. DAS is not aware of any significant new data that supports abruptly moving away from the red blood cell cholinesterase point of departure.

In fact, we've been on an eight-year journey with the EPA refining this point of departure and specifically looking at cholinesterase inhibition in tissues such as the lung, such as the GI tract. And now we have an abrupt shift. So that's a bit disconcerting.

And my point three would follow that a shift of this magnitude should be accompanied by a reliability in all contributing scientific information -- animal, human, and exposure. We believe that the FQPA, Food Quality Protection Act, requires a high standard, that being reliable data, when proposing to revoke tolerances, such as the EPA is asking for, before you today.

Point four, studies for regulatory decision-making should have a common standard, including the need for the agency to have access to underlying raw data. We would note that the Columbia data have not been made available to the EPA, that is our understanding, nor to other stakeholder requests.

Finally, DAS is very concerned about the process and lack of time. And you'll see in parenthesis, we've had 11 business days to do this work, transparency and scientific rigor that must underpin objective risk assessment.

We would encourage the agency and panel to deliberate carefully and, if needed, notify the Ninth Circuit Court that its deadline is impractical to meet. This is an option to the agency. I don't know if that's been made aware to the panel. But by June 30th, that can be made. That can be extended. So we would ask that seriously be considered.

I'd like to quote, in closing, before I turn it over to Dr. Driver, two former quotes -- no, current quotes from two former OPP or U.S. EPA leaders, the first from Dr. Debra Edwards, in 2013; and I would note that her full report is in Tab 11. I would encourage you to look at this. She quotes, "The

totality of problems relating to the reliability of the reported findings on the Columbia cohort renders the study inappropriate for risk assessment."

Secondly, and a contemporary quote; and this is in Tab 9, Dr. Rita Schoeny, "It is my opinion that it is not the best approach for EPA to use as a PoD for chlorpyrifos a benchmark dose calculated from the published summary data rather than from the underlying raw data. I submit this is a major vulnerability for the agency. I have experienced first-hand the intense scrutiny to which EPA's risk-assessment process is subject, even after many years after its publication. I caution EPA against moving forward without the benefit of the raw data."

I would specifically note that Dr. Schoeny comments fairly extensively on methylmercury in Tab 9. She had a lot of experience with this in her former role. And so she contrasts the specificity and use of data for setting a PoD for chlorpyrifos with methylmercury, and I encourage you to look at that.

Finally, these are references. I doubt anyone's had the time to look at these, but a lot of submitted comments just over the last two weeks.

These are included in the books before you today. And again, we would hope that some of this material would be considered.

Finally, in summary, four points: In our view, it is premature to consider a new point of departure for chlorpyrifos until all issues regarding the Columbia epidemiology raw data are resolved and a thorough, transparent and weight of evidence review is conducted.

We believe that 40-plus years of science continue to support red blood cell cholinesterase inhibition as the relevant and protected point of departure, including protection against neurodevelopmental effects. No identifiable and replicated mode of action in either animals or humans has been demonstrated to support a relationship between exposure to chlorpyrifos and neurodevelopmental outcomes at the current regulatory standard.

And finally, numerous, independent reviews on global regulatory agencies continue to consistently support RBC cholinesterase inhibition as a protective point of departure, including protection against all toxicities, including neurodevelopmental.

So with that, I'll conclude and if there are questions, I'd take those. If not, I would turn it to Dr. Driver at this point.

DR. JAMES MCMANAMAN: Thank you. Any questions from the panel? Dr. Popendorf.

DR. WILLIAM POPENDORF: Yes. Two questions and clarification. On your references, page 16 or Slide 16, perhaps, page 16 in the book. Since I haven't looked at any of those, was Dow involved in any of those studies financially or in any other way?

DR. DALAND JUBERG: Dr. Popendorf, yes, we supported the reviews of all of these.

DR. WILLIAM POPENDORF: Second question, on a few slides later, that your statement about studies to regulatory decision-making, the Agency should have access to the underlying data. Is that an opinion or...

DR. DALAND JUBERG: Well, in fact, under FIFRA and under GLP and guideline studies, we have to do studies. We submit all the data to the U.S. EPA. These are guideline toxicological studies. We have no -- we can, with the agency's concurrence, maybe modify a design, but we can't do that on our own accord. So yes, everything is submitted. So my point

is I think human data, if they're going to be considered in this relevance, we ought to set an approach under your common standard for submission of data.

DR. WILLIAM POPENDORF: Okay.

DR. JAMES MCMANAMAN: Other questions? Does Dow not recognize that there may be other modes of action of chlorpyrifos than through cholinesterase inhibition or is -- that's the only mode of action?

DR. DALAND JUBERG: There have been many purported non-cholinergic modes of action. We're well aware of those. In fact, the Lee et al. review looked at some of those. The 2012 SAP reviewed some of those. The agency concurred that there's no identifiable current mode of action. There are many, many, hundreds, if not thousands, of in vitro, in vivo studies that have looked at those. Importantly, many of them conclude that if you're protecting against cholinesterase inhibition, you're also protecting against effects that are purported and show in some of those studies. So that's why the realign and consistent return to RBC ChEI as a protective point of departure. But no, we're well aware that there are many. And you know, we support the agency and former

SAP panels in encouraging investigators to keep looking. Let's build some of those in vitro data into an in vivo animal model, and let's try to build this up and see then if we can tease out and test some of this.

DR. JAMES MCMANAMAN: Okay. Thank you. The question was from Dr. McManaman. The answerer is Dr. Juberg.

DR. DALAN JUBERG: Thank you.

DR. JAMES MCMANAMAN: We have another question. Dr. Sagiv.

DR. SHARON SAGIV: Sharon Sagiv from U.C. Berkeley. Does Dow Chemical recognize epidemiologic studies as a way of looking at neurotoxic effects of these chemicals?

DR. DALAND JUBERG: Yes, Dr. Sagiv. And I think I'll let Dr. Burns, when that comes up, refer to that. But that's, in fact, why we had Dr. Mink, Dr. Prueitt look at some of the epidemiological evidence. I mean, we take these very seriously. So yes, we're firm believers that both animal and human data can inform and contribute. But it's a weight-of-evidence approach and we need to look at, at the end of the day, let's bring the data forward and see what

we can do to wrestle and tease out tough issues.

DR. JAMES MCMANAMAN: Dr. Juberg again. Other questions from the panel? Okay. Thank you very much. Please identify yourself before you begin.

DR. JEFFREY DRIVER: Good morning. Jeffrey Driver. I'm a consultant with Risk Sciences. I appreciate the opportunity to provide comments to the panel and to EPA colleagues. I'm a toxicologist by training, but have spent 20-plus years focusing on exposure monitoring and modeling as well as quantitative risk analyses. I've been involved in a number of research and development programs developing data specifically aimed at meeting data requirements on behalf of pesticide registrants, industry task forces, as well as public sector research programs.

I began my career at NIH, then EPA, and then became a consultant. I've also enjoyed some academic appointments, and I've submitted detailed comments, which are also in the folder in front of you. So we appreciate your opportunity to read those. I realize the panelists have to develop speed-reading skills to get through all the materials provided to you.

So just as a matter of preface to my

more specific comments about chlorpyrifos. As we all recognize, the use of reliable data that meet EPA requirements and quality criteria are fundamental to risk management decision-making under FIFRA. So given that preface, we also fully appreciate that research studies, discovery science and related publications, while important to hypothesis testing, supporting weight of evidence analyses, many different purposes, are very important, but not specifically or intentionally developed to satisfy those EPA requirements.

So before the panel, EPA is asking, and I'm speaking specifically to you, by the way of Charge Question Number 2, is asking the panel to really look at and certainly is associated with the blood data and their use in quantitative risk analysis. This is in the absence of having the underlying raw data or being able to evaluate that issue in the associated detail, which you could do, with those data being in your possession.

Basic assumptions, such as a slope of the dose-response curve, goodness of fit and other statistical inferences cannot be confirmed nor refuted in the absence of that information.

Let's explore this a little further. So this is the figure, of course, from Rauh et al., 2011 log, Working Memory composite score versus chlorpyrifos concentrations in pg/g. Just a visual inspection of the graph would suggest that, obviously, clusters of data spatially could influence the slope of the curve.

I noted at the top that data are not provided for concentrations greater than 23 pg/g. There is a letter from Dr. Whyatt explaining the rationale for this to the EPA. I don't know if the panel has seen that letter. Basically, the officers have admitted four subjects higher than 23 or 25 pg/g because of the influence they had on the slope and the corresponding statistical fit, goodness of fit that they were trying to achieve. So while that's not wrong, per se, the investigators do not provide this information in their methods or discussion.

I think it suggests the association of IQ and chlorpyrifos is somewhat tenuous, and the slope is not sufficiently robust, in my view, to support the derivation of a PoD. I'll talk more about that later. So I think that it's important to recognize that this just speaks to the need for more transparency and

careful deliberation.

Other examples, the top bullets, as we know, chlorpyrifos and cord blood appears to be highly variable. There's some inconsistencies within the publication itself. I'm sure the authors could provide some explanation. The mean standard deviations are listed, you know, differently on pages 1197 and 1198. The max values are also differently expressed. Could be explanations for this, but again, just speaks to the need for more clarification.

The bottom bullet, a significant concern that we've discussed is the recovery of the method. I know that Columbia is suggesting because they had isotopically labeled internal standards at a recovery of 21 percent is acceptable. But in general, that might be true, but the CV is very high at 67 percent and the recovery was at 32 pg/g, which is about 30 times the stated LOD.

Most importantly, no laboratory has independently validated recovery with spiked chlorpyrifos samples and the plasma matrix below 15. I'll talk more about that.

Another area of concern that really presents, in my view, a significant limitation. As

EPA noted, since informational frequency and magnitude of application of the actual pesticide application events in the residences of the cohort is unknown. So there's uncertainty to the degree to which the monthly application period assumption is accurate.

I've been involved in two national surveys where homes kept pesticide application records diligently for an entire year. Those data are available to EPA. They are certainly ways to infer the variability and application schemes for both consumer products and professional pesticide products.

The source of this uncertainty is important to our limitations, and it's important to consider because of the sensitivity of just the frequency itself. So these two figures will explore that.

So to illustrate the impact, the top figure is essentially what EPA did. If we assume, as they did, a simplistic monthly repeat application continues to happen with chlorpyrifos-based product, you would see a blood time, of course, as shown on the top figure.

Now just with one modification of the application schedule, which would be as shown on the

bottom figure, no application during the ninth month. So you would have the results that are shown. So you don't really see a significant difference in the predicted blood levels across the nine-month period, the average, 130 versus 145. However, the single-blood spot concentration measurements had collected 24 hours after hospital administration are vastly different from these two scenarios -- 10 versus 0.3.

So what's the impact of this? Well, this very possible scenario, of a single missed pesticide application would really create a 30-fold difference in these measured levels and a result in a different categorization of low versus high exposure. So this could have a significant misclassification impact. So the exploration of this sensitivity to this variable is something that certainly can be accomplished and should be explored for that.

The analytical methods used for chlorpyrifos determination was insufficiently validated, in my view. There are beyond the plasma spikes at concentrations below 15, there are a number of reasons here as mentioned. Verification that samples were not contaminated during collection, transport, storage, so no field travel spikes to my

knowledge, no data verifying stability in plasma during storage. That needs to be further, at least, provided. No data on method accuracy at the stated level of the LOQ in plasma. No independent validation of the analytical method at another laboratory.

I appreciate Dr. Barr's efforts, of course, in the last couple of days to providing explanations, but I'm not sure we still have enough information to establish the reliability of the data.

So to further explore this, this shows a comparison of the reported blood concentrations from the cohort by tertile. And I wanted to point out that each -- there are mixed birth years in these categories, versus the validated limit of quantitation.

The validated analytical method, as published in Whyatt 2004/2006, actually the lowest validated value is 15 pg/g. The method, of course, is at 1. So you can see that, in fact, most of the tertile data are below, of course, the currently validated value of 15.

Impact of this, you can see with the blue bar and then to the left of the graph, anything basically below 15 would be questionable, were less

than the LOQ or non-detect and as far as we can tell from validated methods at this point. The impact on the slope then would be unknown. We're dealing with largely a censored dataset. I think this is important for the panel to seriously consider.

Application of EPA's guidelines with respect to review of these data, let's just be clear about this: If a registrant or an industry task force were to submit data with the characteristics that I just described, it would be deemed unacceptable.

EPA typically does not allow the use of summary data. There needs to be very compelling reasons to do so. It might be useful for guidance or confirmatory confirmation, comparisons. But to establish a data requirement under 40CFR, that would not be acceptable. Preference, of course, would be for good laboratory practice based data or minimally, GLP-like conditions. And there's documentation that, of course, that needs to provide that categorization.

The analytical method does not meet EPA's criteria in terms of reproducibility, accuracy, or reporting. Independent laboratory validation is an issue, as I've pointed out. Requirements for data reporting have not been met. You know, several

publications, we're trying to piece together the picture. But without the raw data and other related information, it's difficult to really verify and confirm. And I think this is an important enough decision that EPA is facing, and that needs to be taken care of. It certainly can be remedied or it should be.

Okay, just to recap with a few conclusions, EPA is proposing, as you know, to make a fundamental change to the PoD, and this is based on extrapolation from summary data in a single publication.

EPA cannot provide the actual data on individual blood levels or response data.

The summary data, as presented in the publication, has some inconsistencies that need to be resolved.

The analytical method has not yet, to my knowledge, been validated for serum samples at the concentrations relevant to the Columbia cohort measurements by an independent laboratory, and that needs to happen. Even if the raw data become available, the analytical results are not reliable, in my view.

As a result of these deficiencies, the Columbia cohort should not be the basis for the PoD as of yet. The purpose of the proposed PoD process really is a very -- that metric, in and of itself, the PoD, really has to have a lot of data to underlay. It's been carefully peer reviewed by EPA and external stakeholders. So this represents a fundamental change, and I think this is important for the panel to appreciate that. Thank you very much. Any questions?

DR. JAMES MCMANAMAN: Thank you, Dr. Driver. Questions? Yes? Dr. Sagiv.

DR. SHARON SAGIV: This is Sharon Sagiv from U.C. Berkeley. I just wanted to add one thing to your conclusion. If the PoD is based on one study, which is true, but there is a number of studies that are from this cohort that are shown. And so, I just wanted to add that.

DR. JEFFREY DRIVER: That's just for clarification. Yes, thank you.

DR. DAVID JETT: This is Dave Jett, NIH. You were talking about validation of those lower levels. What do you mean by validation?

DR. JEFFREY DRIVER: Spiked plasma samples, you know, at those lower levels. I'm not

aware of any data below 15 where those have been demonstrated in terms of recovery.

DR. DAVID JETT: And so, you're talking about within the Columbia study, those study spike samples?

DR. JAMES MCMANAMAN: Yes, Dr. Rohlman.

DR. DIANE ROHLMAN: Diane Rohlman. So you talk about misclassification with exposure, and you showed a figure where you modeled different exposures. It's on Page 7 in my panel.

DR. JEFFREY DRIVER: Yes.

DR. DIANE ROHLMAN: So your assumption here is that the misclassification that there was no application in the ninth month would lead to a lower level than what we see. But conversely, that could also increase, depending on when the application was and whether there was over application --

DR. JEFFREY DRIVER: Correct.

DR. DIANE ROHLMAN: -- by personal use.

DR. JEFFREY DRIVER: Absolutely correct. So I thank you for clarifying. And I think that it really speaks to the opportunity to explore the sensitivity of different application patterns, which we know occur. And there's empirical data

available to demonstrate that with both consumers, as well as professionals.

DR. JAMES MCMANAMAN: Other questions? Thank you, Dr. Driver. Oh, sorry. Dr. Popendorf.

DR. WILLIAM POPENDORF: Yeah, just to follow up on that question on the same slide, Slide 7. It's a log scale, and it looks like you're starting at a high level, so this was -- like, you started from some equilibrium condition and -- so that's one question, right?

DR. JEFFREY DRIVER: Correct. Yeah.

DR. WILLIAM POPENDORF: And then are these ranges similar to the ranges that --

DR. JEFFREY DRIVER: Yes. Yes. In fact --

DR. WILLIAM POPENDORF: -- whatever is used by the agency?

DR. JEFFREY DRIVER: -- yes, correct. Thanks for that clarification, as well, Dr. Popendorf. So that the top figure, which was basically EPA simulation, it's the same as you'd see in Figure 6A of the issues paper. So we're sort of starting with their baseline simulation --

DR. WILLIAM POPENDORF: Okay.

DR. JEFFREY DRIVER: -- of 30-day interval. So yeah.

DR. WILLIAM POPENDORF: And a second question, just to clarify again on that grid of -- on number 11, you say the "EPA does not allow the use of summary data," and you reference a CFR. So again is that -- what are you really saying here?

DR. JEFFREY DRIVER: Well, I think my intent was that --

DR. WILLIAM POPENDORF: Does the CFR say you can't do that? Is that policy of the agency or is that an opinion?

DR. JEFFREY DRIVER: That's a good clarifying question. Yeah. Again, Jeffrey Driver speaking. I think I was speaking to specific data requirements as they are articulated in 40CFR and the related documentation.

So publications are not -- published research is typically not used to satisfy data requirements. Now, can it be used for a variety of other purposes? Certainly. To inform exposure factors, as you well know, or for other aspects. But I was speaking specifically to the data requirements toxicology studies, for example.

DR. JAMES MCMANAMAN: Dr. Sagiv.

DR. SHARON SAGIV: Sharon Sagiv, U.C. Berkeley. I just wanted to make a note. You mentioned a few sources of exposure misclassification that occur. And it seems like most of them are non-differential or random. And often, those kinds of exposure misclassification lead to a null effect, rather than an effect, so I wanted to make a note of that in light of the findings.

DR. JEFFREY DRIVER: Very good. Yeah, I concur.

DR. JAMES MCMANAMAN: Other questions, comments? Dr. Pessah.

DR. ISAAC PESSAH: Isaac Pessah, U.C. Davis. In terms of the profile that you show on Slide 7, does Dow recognize that chlorpyrifos, once it's on its bioactive -- it's converted to its bioactive, is irreversible and could lead to summation of effects?

DR. JEFFREY DRIVER: Yeah. I'm not really speaking to the biological target. Correct. This is more about just trying to follow blood levels, relative to sampling time for the blood samples.

DR. JAMES MCMANAMAN: No questions? Thank you very much

DR. DALAND JUBERG: Dr. Jenkins, if we could have, I think, number three up? Thank you.

DR. JAMES MCMANAMAN: Dr. Burns, before you begin, could you identify yourself and -- just so it's on the record?

DR. CAROL BURNS: Yes. Absolutely. This is -- my name is Carol Burns. I'm an epidemiologist with The Dow Chemical Company. Today I want to talk about making epidemiology more consequential. And in the 2015 --

DR. JAMES MCMANAMAN: Could you move your microphone just a little bit closer?

DR. CAROL BURNS: Yes. In the 2015 American College of Epidemiology, this was the theme of the meeting. And I think it resonates well with today's meeting. And in that meeting, we discussed -- it's not about criticizing epidemiology data, but it's how can epidemiologists provide better data so that we can make better decisions for public health and human health risk assessment.

So as a point of background, I have degrees in epidemiology from the University of Michigan and Tulane University School of Public Health. I've worked at The Dow Chemical Company in

that capacity for two decades, and I'm active in the American College of Epidemiology.

In its full disclosure, we grow corn, soybeans and alfalfa in Hubbardston, Michigan and have done so since the late 1800s.

Today my concept, I'd like to bring up the concepts, and I've labeled these by the charge questions so that you can follow along with my logic. And really, it's these concepts that directly impact the use of the Columbia study and epidemiology data in general.

So first off, with Charge Question 1, that maternal blood does not adequately predict fetal exposure.

Neurodevelopment effects reported by the Columbia study are not sufficiently established as casually linked to chlorpyrifos.

There are limitations and certain biases in the epidemiology studies that can be better characterized and quantified.

Publication bias of negative results impedes the use of epidemiology data. And I'd like to propose some additional charge questions for discussion.

So before we launch into charge questions, I think it's relevant to talk about where we are today with exposure. And to explain briefly, on the y-axis is the cholinesterase activity. And because cholinesterase can -- not just be inhibited, but can go up, if you -- it's a little bit backwards, if you think about 10 percent inhibition. On this graph would be at 90 percent.

And we know that the animal studies are at the far right of the continuum of the research. On the y-axis is the urinary TCPy or trichloropyridinol metabolite. So you toxicologists that want to see a dose, this is -- we're talking about a urinary level.

And as you can see the brain cholinesterase is to the far right and the red blood cell acetocholinesterase is in the middle. And this is where we look for effects in occupational studies and applicators. But this is not the focus of our talk today. We are really focusing at the far left of the continuum where we see exposures in women and children in the Huen study from residues of TCPy in food. And the point of discussion, as well, is other sources of exposure.

A point of context is that the plasma

BuChE inhibition has been used successfully for decades to evaluate exposure, particularly in occupational settings. And at Dow, we use that as our point of action to remove people from exposure.

Now the point of departure, as we're talking about, is at 10 percent RBC inhibition. And as you see, this line was calculated by the group from Arnold et al. to calculate a biomonitoring guidance value, and this translates to about 2100 µg/L of what you would see in a human biomonitoring study. This comparably equates to about 6100 ng/L in blood. So as you were discussing yesterday, the proposed point of departure would move this line to the y-axis.

Well, let's talk about some of the charge questions. And this gets to the -- it is our position that maternal blood does not adequately predict fetal exposure. Some examples from the Columbia study are that they did collect personal air samples during pregnancy, but these did not correlate with either maternal or cord blood.

Furthermore, maternal cord blood did not correlate with urinary TCPy. And there's quite a bit of missing data in the maternal newborn pairs, and we see this pretty strikingly in Fig1 where you can

see the numbers for each.

I would remind the panel that the CHAMACOS study from the University of California at Berkeley did collect blood in the infants, as reflected in the Huen 2012 paper. And in that paper, neither the maternal or the cord blood were correlated. Furthermore, their outliers were not in the mother/newborn pairs.

Talking about the degree of a causal inference from neural development effects as reported by Columbia, the EPA has recognized that consistency of observations is important, both within and across studies. And we heard yesterday them talking about the reason why we're not talking about fetal outcomes today is because of this very reason.

So I'd like to talk further about consistency. And in this example, I'd like to talk just about the Columbia study and internal consistency about whether we're seeing the same results in the same study.

And this shows you -- this is a short list of the important risk factors that were presented in the Columbia study. And you can see that they're looking at exposure such as chlorpyrifos, but also

PAH, phthalates, and environmental tobacco smoke. They have a range of factors to estimate socioeconomic status such as income, maternal intelligence, education, and so forth.

In the 2011 Rauh paper, which we've been discussing at length for this panel meeting, just some brief explanations. So in the written comments, the full P values and confidence intervals are provided. But here, "YES" is to indicate statistically significant. And so, yes, indeed, the higher levels of chlorpyrifos were statistically associated with lower Full-Scale IQ scores.

Also statistically significant in this multi-linear regression model were income, child gender, and maternal education. "NO" indicates that other factors were included in the model, but were not associated with IQ, and these include tobacco smoke, race, and maternal education -- excuse me -- intelligence.

The designation "Not in Model" means that the investigators looked at the correlations, but determined that they were not sufficiently significant to be included in the final model. And these examples are lead and birth weight.

But importantly, as we discussed the role of chlorpyrifos with IQ, it's important to look at other publications of the same children in the Columbia study, but other topics, and these include the poly aromatic hydrocarbon paper of 2009 and the phthalates paper in 2014.

In both of these studies, interestingly, chlorpyrifos was considered early on, but was not sufficiently significant to be included in the final model. So this is an example of poor internal consistency where chlorpyrifos is not significant across the other publications.

Next we look at consistency across publications. And again, you have this information in your packet. So going across, again, we start with the Rauh 2011 paper. And the outcome, of course, is chlorpyrifos in blood. And you might think of this as a hypothesis generation. The question is, do the other studies -- are they sufficient to accept or reject that hypothesis? And we've talked at length yesterday about the CHAMACOS and the Mt. Sinai studies. And here we see that they analyze their results with urinary dialkyl phosphates.

And I'd like to pause quickly because

yesterday you were explained the difference between the metabolites. So DEPs, or the dialkyl phosphate, is a nonspecific metabolite of all the OPs.

DEP is a metabolite of 10 organophosphates, which includes chlorpyrifos. And we see that using DEP, the analysis is not statistically significant. So logically, you might think that if the analysis were positive for DEP, you would not be able to detect the role of chlorpyrifos. But being negative, you can then think, well, it can't be chlorpyrifos.

I think it's further important to note that the CHAMACOS and the Mt. Sinai study have data on urinary TCPy which is much more specific to chlorpyrifos. But neither of these studies reported on their TCPy data and IQ.

Lastly, I introduced a third study, the PELAGIE study from France, which also evaluated DEPs in their children and found no statistically significant correlations.

Moving on to talk about publication bias, and this falls within sample size. And I think it's important to note that sample size drives statistical significance. But statistical

significance drives publication. And it's a reality that statistically significant results are more likely to be published, and vice versa.

We'd like to believe that if we just had more study subjects, that we would then have statistical significance. But that's not necessarily the case, because you don't know what those additional subjects will show. And there are few guidelines on publishing epidemiology data.

Now in industry, if I get an adverse result, I have 30 days to submit my results to the Agency under TSCA. I understood that in genetics research, you have two years to publish your data, whether it was positive or negative. For longitudinal cohort studies such as the Columbia study and others, as I understand it, there are no guidelines. You can publish as the investigators wish. And this is important from a weight of evidence that you need to know all the evidence in order to make valid decisions.

And my kids, it drives them crazy when I say, "You don't know what you don't know." And here we have some examples where we have indications that are additional data that would be relevant for this

discussion. For example, we know that the CHAMACOS and Mt. Sinai study have more specific exposure data using urinary TCPy, but that has not been published on the IQ data.

The HOME study is another prospective cohort study that they published early on fetal outcome. We had no idea that they had collected more data until the study appeared in a pooled analysis. Similarly, we had no idea that the Columbia study had collected DEP data on their children until those data appeared in that pool of analysis. So these are just some examples of transparency crosses the publication bias.

Talking about uncertainty, and this has a different connotation in epidemiology than it does in risk assessment. And we can describe the uncertainty, as opposed to just default. In industry, we're often criticized for generating doubt. And I want to be clear today that that's not what we're trying to do. We're trying to improve the status quo and generate more information.

And in this case, I direct your attention to the written comments by Goodman and Loftus, and they really speak to the data that are

currently available and new analyses could be done and published by the investigators themselves, EPA, or a third party. And this is important for a transparent weight of evidence evaluation.

Some of the activities that could be done would evaluate the impact of the number of non-detects, and I think this speaks to Dr. Carr's comments yesterday about if we're concerned about the limited detection or the biological number, per se, a counter approach would be to go by birth year. That doesn't mean that it's sufficient and the best way to go, but it's an example of other analyses that you could do to compare and contrast your conclusions.

We've talked about correlations between maternal and cord blood. Similarly, you could do additional analyses about how the outcomes change, whether you're using continuous and categorical.

There's been some talk about the direction of the bias. Often, we are trained that if the classification is incorrect, it's considered to be non-differential. That's absolutely true, and the effect can be to dilute your interpretation of your odds ratio.

However, that isn't always the case,

especially if you're moving away from categorical analyses, and you include additional covariates in a linear regression. Statistically, then your direction of your bias or your true value could be bigger or smaller. So this is just an example of additional analyses could and maybe should be done before we consider using epidemiology in risk assessment.

In 2000 -- I bring this up as a point of discussion that in 2012, ILSI/HESI, which is the Health Environmental Safety Sciences Institute -- excuse me -- how the workshop with 30 epidemiologists and other scientists talk about not how to integrate epidemiology into risk assessment, but how do we reduce that uncertainty. How do we make it better and stronger?

And three points resonated with this group that I think are important today is that we should be characterizing uncertainty in our papers and not just saying it exists; work to improve the exposure assessment; and use the available analytical tools to better distinguish associations from causes.

So I'd like to propose maybe some additional charge questions to discuss. First of all, we've talked a lot about raw data. But I think it's

important to not just demand it, but say, well, how can it be shared? How can we maintain confidentiality of our study subjects? How do we protect the ability of the investigators to publish their data and other concepts such as that, and who has the ability and the capacity to evaluate those complex data?

There are real barriers for epidemiologists to doing improved exposure assessment and data analysis. These take time. They're costly, and that requires money. And so how can those barriers be removed and solved, so that epidemiology data are more consequential for discussions like this?

And Dr. Juberg mentioned this briefly is that when we start with a known mode of action and we want to change that, what are the minimum criteria for using new data? This includes both human and animal data.

So in conclusion, the epi data for chlorpyrifos, in particular, the Columbia study, are not sufficiently robust to be consequential for use in risk assessment.

Two points, although there are others to discuss, the Columbia study is not internally consistent. The associations of chlorpyrifos are not

significant in the other Columbia publications. And the Columbia study results are not replicated in other studies. I'd be happy to entertain questions.

DR. JAMES MCMANAMAN: Thank you, Dr. Burns. Questions? We'll go with Marion first.

DR. MARION EHRICH: Okay. Slide 7. I think I just missed what you said. Your workers are using the plasma -- I think I heard you, the measure of chlorpyrifos in workers? But I think that this has to do with your Slide 4? What are you measuring for your workers when you take them out? I think I just heard wrong.

DR. CAROL BURNS: We take monthly cholinesterase. We measure blood monthly in our workers. And if it's below -- I think it's below 40 percent BuChE, we have a conversation.

DR. MARION EHRICH: Okay. So it's the BuChE?

DR. CAROL BURNS: Yes.

DR. MARION EHRICH: Okay. Thank you.

DR. JAMES MCMANAMAN: Sharon Sagiv.

DR. SHARON SAGIV: I'm Sharon Sagiv from U.C. Berkeley. Can we go to Slide 10, please? Slide 10, please. Forward. Yes, that's fine. So there are

a few criteria for putting a covariate in a model. One is that they be statistically associated with the outcome, which we know we see that in column one. The chlorpyrifos is associated with IQ or Working Memory.

The other for the other two columns is that they be associated with the exposure of interest. So they would -- so chlorpyrifos would have had to have been associated with PAHs and phthalates.

If they were not associated with the exposure interest, they would not meet the criterion to be a confounder and may not be included for that reason. That doesn't indicate that there's no association with chlorpyrifos, but rather that it may not have made the criteria to be a confounder in those models.

DR. CAROL BURNS: Okay. Good point.

DR. JAMES MCMANAMAN: Other -- Dr. Popendorf?

DR. WILLIAM POPENDORF: I was just going to add another comment. Just, I think the question about BuChE monitoring, just to clarify, when you say your workers, you're talking production workers, right? These aren't agricultural applicators --

DR. CAROL BURNS: This is true. This is manufacturers and formulators.

DR. WILLIAM POPENDORF: Just to be clear, yeah.

DR. JAMES MCMANAMAN: Other questions? Yes. Dr. Rohlman.

DR. DIANE ROHLMAN: First of all, I agree with Sharon on her comments about -- this is Diane Rohlman -- about the -- including covariates in the model. Although, once they are added into the model, they are, you know, we look at the contribution each variable makes to the outcome. And so, based on that, we do see that they do contribute in some cases, but also we see the effect of the exposure of interest as well.

A second comment is, you make a strong point about the need for more rigorous epidemiological research and criterion. I think that certainly is an important conversation. There are reasons why publications may not have happened, and that could be due to a multitude of reasons.

So speculating on why a study has or has not published something without the authors there to offer explanations, I think, is not appropriate.

And those reasons can range from null findings, which certainly would be a concern, and we hope that those would be published. But also things like a delay in the lab for analysis, you know, concern about new data that's coming out and other issues as well. So I think that's an important consideration.

DR. CAROL BURNS: This is Carol Burns. Yeah, I don't disagree, and I don't mean to have that be a criticism of authors at all. But I do think if we want to have epidemiology used in a conversation like this, it's something that we should be talking about is availability of data in a timely fashion so that we can make the best decisions. I didn't mean it as a criticism of those authors in any way.

DR. JAMES MCMANAMAN: Other questions? Okay. Thank you very much. Dr. Banner.

DR. WILLIAM BANNER: Thank you.

DR. JAMES MCMANAMAN: Okay. Just introduce yourself for the record, please.

DR. WILLIAM BANNER: Hi. I'm Dr. Bill Banner, and I applaud the group here. I think I have a little too much productive ADHD to sit this long in meetings, because you guys are amazing to sit here.

You know, I was invited by Dow

AgroSciences to review some of these studies, particularly the Columbia studies and to provide a clinical sort of prospective on things. So I always told them I was glad to do that. I've been very interested in these areas, particularly the impact on public health on some of the decisions we make.

I have been a practicing pediatric physician and a medical toxicologist for about three decades now. My background was I was first trained in pediatrics and then did an NIH-sponsored fellowship in clinical pharmacology and then did a Ph.D. in pharmacology at the University of Arizona. Then I undertook -- again, that ADHD kicked, in and I did critical care medicine and became board certified in both pediatrics, medical toxicology, and critical care medicine.

I'm currently the medical director for the Oklahoma Poison Control Center and an attending physician in the Pediatric Intensive Care Unit at Baptist INTEGRIS Medical Center.

I'm also -- have been president of the American College of Medical Toxicology and the president of the American Academy of Clinical Toxicology, so very interested in toxicology.

But day-to-day, I treat children. And I treat children with a lot of life-threatening diseases. Nutrition is incredibly important to me, in terms of its impact and where we go, how we do that. I also treat children with a variety of very interesting infectious diseases that we may talk more about.

But you know, I've treated bubonic plague; I've treated ehrlichiosis; I've treated tularemia, all vector-driven diseases. We see a lot of vector-driven encephalitis in Oklahoma, West Nile. And I'll tell you, on our radar, there are a number of vector-driven diseases because we are, frankly, losing the game.

I hate to see us rely on a series of studies, unless they are extremely sound scientifically because they can drive us to different directions. And I think, looking at the raw data, it is absolutely critical to understanding how it was done in some cases. And if we're going to make decisions, you know, unlike something like methylmercury, which I've heard mentioned a number of times. I've treated methylmercury poisoning. Without the raw data, I think you really need to be careful.

We're making decisions here that are more important than that. We're regulating something. '

I think there are some very systemic deficiencies in the Columbia study group articles. And you know, I would urge you to consider the broader impact on this. We need nutritious foods. Poverty in Oklahoma is a real issue and around the country. And again, we're facing threats like Zika virus this next couple of summers that are going to really challenge us. And we don't want to take tools out of the tool shed, until we're sure that we know that the data is sound.

And I think looking at the raw data is critical for replicating and understanding the scientific studies themselves. I think it's an integral part of the scientific process. In many other disciplines, it is absolutely just an understood part that they share their data.

And especially critical in these kinds of things, I had a number of questions about the methods in these studies, as I've heard around the table, and very complex databases. And you need to understand how the data was analyzed to really understand where they were at.

When we talk about the Columbia -- I'll talk about the Columbia study and then the individual articles, the first thing that struck me clinically was there were a lot of handling of some of the key confounders that I know as a pediatrician to be very important to neurodevelopmental outcome.

For example, gestational age, I don't understand how they derive gestational age in the studies. We know that a difference of one week in gestational age in what we used to consider full term, 37 to 41 weeks, one-week difference, it has been linked to neurodevelopmental differences on things like Bayley scores. It's very critical that you accurately measure it.

ACOG, the American College of Obstetrics and Gynecology has guidelines, very specifically, for research on how to measure gestational age. I couldn't tell from the article how they did it. If they did it by LMP, it is known to be off by more than five days 40 percent of the time. So there is a key variable. Knowing how to measure it would be critically important, if you're understanding the study, if that's inaccurate.

They recommend first trimester

ultrasound, verification of LMP, Ballard scores, Dubowitz scores; they all have their own pros and cons. And you know, use them all, But I think you have to specify. So again, we don't know.

In these studies, here's the key critical confounding variable that we need to understand. In several of the studies, gestational age was listed as a strong covariate, as a matter of fact. In other ones, it doesn't seem to have been entered into the model. Is this because of the small numbers that we were dealing with?

One study, a 2011 Rauh study, they use babies down to gestational age of 30 weeks. These are 1200-gram babies. I don't know many of you are familiar with -- their lowest weight was 1295, I think. This is a baby I can hold in one hand. They're going to have neurodevelopmental problems.

So including them, most studies go down to 37 and don't do any kind of neurodevelopmental outcome studies on babies with that severe prematurity. They also went up to 43-weeks' gestation. We know that babies that get past 41 weeks, also have neurodevelopmental problems. It's a bell-shaped curve.

So including those babies, I think, really, you know, makes you wonder about the outlier problems and things like that, when you've got both ends of the spectrum, and they're not telling us. They say, well, it was a small number. They should not have been included in this study, in my opinion.

Other confounding factors that we know, as pediatricians, we look at maternal IQ. We'll talk about the number of missing values: Paternal IQ, not considered, not measured in these studies. Iron deficiency is one that goes back a long way. And we know that, as a nutritional part of the assessment, measurements of iron are critical to understanding neurodevelopmental outcome.

They assess the medical records, and they analyze them. But we're not really told what they did with this. Apgar scores are a crude measure; maternal medications, where did those play in, a number of things like that.

In the last decade, the Academy of Pediatrics has really come strong on the socioeconomic factors that affect our patients. We know and have known for a long time that alcohol use is a critical variable, and drug use, which is very hard to get a

handle on.

Now we recognize that violence, whether that is witnessing violence, witnessing domestic violence, being involved, the victim of child abuse, all of these things, just being around in a pervasive atmosphere of stress raises both maternal and child cortisol levels and affects neurodevelopmental outcome. How you control for those is, you know, something that's very difficult. But a lot of authors are trying to do that. There's a lot of literature on that nowadays. That's not very well addressed in the overall Columbia studies.

Other exposures. You know, lead's been mentioned. Basically, there was really no effort to look at lead in here. They've got a few cord blood lead levels, but we know for the later developmental studies, that would be associated with contemporaneous lead exposure. Other chemicals are out there, lots of them, and it's hard to know how those all fit together.

They handle their data from study-to-study very differently. And I'll try to sort of show that to you in a table in a minute. They utilize different models. They stratify the data from one

study to another differently. And there's findings where, at one age, there was nothing, and at the next stage, there was, where you would sort of expect a longitudinal effect. That causes me to wonder how strong the data was or what we're really measuring there.

Neurodevelopmental tests are used to try to draw clinical diagnoses and particularly when you get into things like pervasive developmental delay and Attention Deficit Disorders or Autistic Spectrum Disorders. You know, those are clinical diagnoses. And to do those -- try to infer that from isolated clinical scores on a developmental test, I think is very difficult. But I note the testers in the room probably disagree with me. But as a clinician, I fall back on how is the child functioning in the environment.

Now when I looked at the 2006 study, particularly from Rauh, I wondered, as I've heard, where did the 6.17 come from, and where did that number fall in. And what it appeared to me was that they initially divided their subjects into four groups, based on exposure level. There was a "no detection," and then they divided their detectable

levels into three groups, sort of a low, medium and high, which seemed reasonable.

Some of their earlier studies from the same group used a continuous variable. But in here, they divided it. In their method section, they say, and I quoted it, "most highly exposed group and the undetectable group," this was an analysis of variance study, "had lower mean PDI and MDI scores," than the two middle groups. In other words, there was no difference between the most highly exposed group and the undetectable group.

So as I understand it, they lumped together the nons, the low and the medium, and then separated that from the high scores and called those two groups. So there were about 80 percent of the patients were in the low-exposure group, which was actually the non-detectables, the lows and the mediums. And then cut off at 6.17 and compared that to about 20 percent of the patients, which were in that high-exposure group. And they said, well, you know, in their initial assessment, again, there was "no evidence of a linear or nonlinear dose-response relationship between chlorpyrifos levels and developmental outcomes." Of course, that clinical

pharmacology training dose-response is everything. But they couldn't find it, again, because the very low and the very high were the same.

Then, I didn't notice then, but in a later study, we found out that there was only one patient enrolled in the high-exposure group after January 1st of 2001, and that was because of the regulatory changes that occurred. So that sort of 1/1/01 became a critical time-point in their study.

So I would have said, looking at this study as a reviewer, I would have said, this is a negative study. Analysis of variance, they could not find any difference between the four groups that they originally had identified. And so, lumping it together into this 80/20 mix, to me, just a simple clinician, I would have said, this is a negative study, end of discussion. I know everybody's going to say, well, you could go back and do this and this. But since we're talking about, you know, important actions here, I think that is scientifically flawed, as a comparison, and I think to use that 6.17 is very concerning as its point of departure. It was a very artificially drawn point, and they already had data analysis pointing them away from that.

The other thing that bothered me in this study when I looked at it, they were -- for maternal IQ, 29 subjects, they did not have data for. And here's an important covariant, and we don't know whether they fell largely in the high exposure, low, exposure, or were they randomly distributed. But it's a lot for a smaller number of patients as they had.

When I looked at the Lovasi article in 2011, that's where they sort of identified that only one child was born into this high-exposure group, and after January 1st. And the first thing, as a clinician, I said, well, I know from 1995 to 2005, obstetrical practice was changing dramatically.

So I pulled up some birth statistics. Caesarean sections rates were increasing; vacuum extractions were decreasing. Through this time period, there were a number of changes going on. Vaginal deliveries after caesarian section, that was virtually disappearing from the scene. So there are all sorts of things particularly focusing on lengthening gestational stages for deliveries.

And now, I don't know the Northern Manhattan hospitals or the Bronx Hospitals, but when you have a study that suddenly is stratified over 10

years where the two groups were enrolled at very different time periods, I would say you've got to know what else was going on. Were practice standards changing? Were these guys early adopters and not doing -- you know, I know I had two children born in that time period. And it's like, "Well, when would you like to schedule your delivery? We're going to do the induction." And now it's like, "Oh, no, we let them go as far as we can." So standards have been changing. Everything is undergoing a lot of radical changes in that time period from '95 to 2005. And if you don't know that -- as far as I could tell, again, I would have said this is not well conceived, epidemiologically or otherwise, because they had this huge practice change over a time period. There's no more randomness over when the patients were exposed.

I think it's difficult to draw any conclusions when you stratify the patients in such a fashion to where the groups are separated in such a fashion over medical practice periods.

I've put this together; could be wrong in the way I've said things. But you know, when you look at the sequential studies from 2003, and this is all from the Columbia data, through 2015, first, the

data was treated as -- the chlorpyrifos data was treated as a continuous variable. Then in 2004, they divided it equally into four groups, no exposure, low, medium, high, and used more of analysis of variance type of model in that. Then it was 2006 when they did this 80/20 split at the 6.17. So again, it was not like that was the original design. This was something that was changed in midstream.

Then in 2011, they went back to using it as continuous variable. And then as far as I could tell in the 2015 study, they went back to dividing it into non-detectable, low, medium, and high for that particular study.

Alcohol use was another thing that caught my attention clinically. Perera, the original data that they had, 24 percent of their mothers admitted to using alcohol during pregnancy. I thought that was astonishing because, typically, they don't tell you the truth. You know, 24 percent is a strikingly high number because it usually well-underestimates the incidents.

I didn't see where they had done carbohydrate-deficient transferrin or ethyl glucuronide or gammaGTP to see if there were any

indications of chronic alcohol abuse, some of the objective things. So it doesn't appear that they verified that.

There were no drug screens done. And of course, this is a high-risk population. And again, you know, these moms are looking at losing custody of their children, if they're using drugs during pregnancy. So they're not going to tell anything. So drug abuse, to me, is something that you want to have some sort of objective verification of.

It doesn't -- in the next study by Whyatt, they said there were a few mothers that were drinkers, that was 25 percent, said they were consuming alcohol during the pregnancy. But only a few of them said they were drinking a lot during the pregnancy.

The Rauh in 2006, 2011 and 2015 don't seem to have included that, as far as I could tell, as part of their model or considered that as a strong variant or eliminated those patients or anything.

Gestational age, again, we kind of talked about that, something that we know is an important covariant in the development of children. It was significant in the Perera study. It was

significant and highly -- one of their most important covariates in the Whyatt study. But by 2006, it was not significant. And in 2011, I don't think they included it in their model at all. I couldn't find it on the appendix. So I'm not sure how they handled that. But we know they used babies that were less than 37-weeks' gestation -- in other words, extremely high-risk deliveries -- and they used babies that were greater than 41-week gestation which is also another high-risk group.

And maternal IQ, again, a lot of missing values certainly not included in the earlier studies, because they didn't measure it until later. But they had a lot of missing values.

In the 2011 study, it was a significant covariant and Full-Scale IQ, but in this Working Memory. Intuitively, I ask myself is that because of the small numbers or the missing data, that they just couldn't find important covariates. You guys are better at that than I am, but it raised questions in my mind. And then you get the 2015 study where it really wasn't part of the model, and that study was really about asthma medications, as far as I can tell, which were important, some of their other studies.

What I find most interesting about the gestational age study is that the same group did another study of 128,000 deliveries in the New York area, in their same area, and found that gestational age was one of the most important covariates in academic achievement at the same age as the 2011 study, but yet, they don't seem to have really included that as an important covariant or accurately measured it in their study. So I mean, it was Dr. Noble, I believe, is part of that group that looked at gestational age in their general population -- 128,000 birth records, I believe. So again, gestational age, maternal IQ, the things that, as a clinician, I look at to figure out how my kids are going to develop here.

So my conclusions without making you sit here much longer, the cutoff value of 6.17, I found no scientific basis for that. They were not able to find the dose-response curve. There seems to have been an arbitrary system to lump data together when, in fact, the two extremes, ends of the data, appeared to be the same in analysis of variants.

I would say that if you're going to get to the bottom of this, you're going to have to look at

the raw data to try to replicate this, to try to evaluate this study.

I think they did not do a good job with their confounders. And you know, I know you guys are better at that than I am. But the things that I think are important for child development were not handled very well or accurately measured. And I think that we really need to be cautious because this has the potential to negatively impact children.

You know, I know what I deal with is the food supply, poverty. You know, we have -- you know, one of my colleagues said they went on a mission trip. And I said, "Yes, I did, too; I went home." You know, we've got a very poor population in Oklahoma. Nutrition is critical. Anything that interferes with our ability to deliver that food supply is going to negatively impact our children.

I also, you know, up here, y'all don't, even though you're south of the Mason-Dixon line, you don't deal with -- -I could list the vector-driven diseases: Tularemia, ehrlichiosis, Rocky Mountain Spotted Fever, West Nile Virus.

And now, they're telling us, you know, I mean, the CDC is sending me alerts on Zika virus,

chikungunya virus. We know those are the things that are going to impact child development negatively. I don't want to lose any tools out of the tool shed. We're having trouble controlling our insect vectors in these very poor counties in Oklahoma. Don't take these things away, unless there's a good, sound scientific basis. Thank you. I'll try to answer questions.

DR. JAMES MCMANAMAN: Thank you, Dr. Banner. Questions for Dr. Banner?

DR. DALAND JUBERG: This is Daland Juberg. I'm just curious, is chlorpyrifos approved for mosquito control?

DR. WILLIAM BANNER: I don't think it is. You know, it's certainly the -- for other insects, it would be. And we see a lot of non-mosquito-driven disease, as well as mosquito-driven diseases.

DR. JAMES MCMANAMAN: Dr. Sagiv?

DR. SHARON SAGIV: This is Sharon Sagiv from U.C. Berkeley. Thank you for that presentation. So you spent a good amount of time talking about gestational age. And I agree with you that it is very poorly measured, using LMP. I think they probably

have described their methods for deriving gestational age in previous papers. So you might want to check out their papers on gestational age.

DR. WILLIAM BANNER: I couldn't find it.

DR. SHARON SAGIV: They would have had to to get their peer review.

DR. WILLIAM BANNER: Yeah.

DR. SHARON SAGIV: And usually, they use last menstrual period or they use an ultrasound to do that. So I agree with you that it's not well characterized.

However, your claim is that it's an important confounder to control for. And as practice in epidemiology of studies of neurodevelopment, we try not to control for those factors, because they may lay on the causal pathway between your exposure interest and neurodevelopment.

And if you control for them, you may be controlling for an important pathway in which that toxicant works under development. So we actively don't -- even though we have that data, we don't usually control for something like gestational age or birth weight, with other mediators that might lay on

that causal pathway. So I think there was a good reason why they didn't control for gestational age here. So I just wanted to comment on that.

DR. WILLIAM BANNER: That would be true unless, again, you know, with the removal of chlorpyrifos from the environment with the regulations, if practices changed that changed gestational -- that the deliveries and the gestational ages, that would be, you know, something important to know and to characterize because it may be that all your low-exposure-rate children were pushed into higher gestational ages because of the impact of practices changes when they took, you know, when they made that break in exposure, you know. So again, you'd have to know a lot about what was going on because, I mean, I think it's unfortunate these investigators got caught with this sudden change in the -- their -- sort of affected their study design midstream. And then now you've got all these things that would have been randomly distributed or would have affected both ends of the spectrum. Now they're only impacting the low-exposure group in a positive direction. That could have a profound -- you know, if you don't look at it from that perspective, you don't

know. You know, maybe you understand that better than I do, but that's just -- sort of common sense says you've got to take that into account somehow.

DR. SHARON SAGIV: Okay. I'm not sure I'm understanding. This is Sharon Sagiv from U.C. Berkeley. I'm not sure I understand that argument very much. I just know that, in general, you wouldn't want to put that in the model. That's what I'm saying.

DR. WILLIAM BANNER: Well, my point is if you changed midstream and suddenly took away the toxicant and then made other -- there were other changes occurring, in practice, and those changes in practice affect the thing that you're measuring, and they're only affecting the group that was there after the change, it's going to affect your data. And that, to me, seems pretty intuitive.

DR. SHARON SAGIV: Okay.

DR. WILLIAM BANNER: So if we suddenly started not doing vacuum extraction deliveries, for example, which are very stressful and would affect the baby, and those that occurred around 2000, you know, it was going like this over that time period, it's only going to affect the babies that were born after;

or that's primarily going to affect the babies that were born after the change in exposure. So in that respect, you'd have to consider it somehow.

DR. SHARON SAGIV: So you're -- do you have evidence to show that those practice changes occurred at the time that chlorpyrifos was taken out for residential use?

DR. WILLIAM BANNER: Yes. Yeah. I mean, CDC birth statistics. You know, everything -- lots of things were changing.

DR. SHARON SAGIV: Okay.

DR. WILLIAM BANNER: Now I don't know, as I admitted, you know, I haven't been to Northern Manhattan in a while or the Bronx. I used to go as a kid. And I don't know what their hospitals were doing. Were they early adopters; were they late adopters, you know. That's mathematical for, are you ahead of the game or behind the game. You know, what were they doing there? You'd have to know. You'd have to look.

It's sort of tragic for their study that this happened right in the middle of their study. But yeah, there was -- you know, that was the first thing that came to my mind is, oh, my gosh, you know,

what else happened, you know?

DR. SHARON SAGIV: So those changes in practice wouldn't have created an increase in pre-term birth. They may have changed the gestational age slightly. There wouldn't have been drastic changes in gestational age. There would have been slight changes. If, say, they were inducing by standard of practice. So I still don't see how that could impact these findings greatly. But okay.

DR. WILLIAM BANNER: Well, we know that a --

DR. SHARON SAGIV: Well, a couple --

DR. WILLIAM BANNER: -- week is critical.

DR. SHARON SAGIV: -- of other points I wanted to make. You talked a little bit about neurodevelopmental outcomes and using clinically diagnosed disorders, rather than changes in, say, a neurodevelopmental profile for cognition or behavior. And the fact is that these studies are underpowered to look at developmental disorders. They just don't have enough participants to be able to do that. So we really can't do any of these prospective cohort studies looking at the developmental disorders. There

just aren't enough cases to do so.

And there are also some -- there's some good literature showing that looking at changes in behavior and cognition are probably a better way to use our data in cohort studies. And I'm looking at clinically diagnosed disorders. And I can point you to some commentaries about that. So I wouldn't undermine the studies for not looking at developmental disorders is what I'm saying.

DR. WILLIAM BANNER: I think I was agreeing with you.

DR. SHARON SAGIV: Yeah. Okay. Okay. Good. Yeah, yeah. Oh, you had mentioned that neurodevelopmental disorders -- they didn't look at the disorders and so forth?

DR. WILLIAM BANNER: No, no. They did, they did. And I thought --

DR. SHARON SAGIV: Yeah.

DR. WILLIAM BANNER: -- they did -- you can't go to a clinical diagnosis based on what they had.

DR. SHARON SAGIV: Yeah. I agree with you on that.

DR. WILLIAM BANNER: Okay.

DR. SHARON SAGIV: And I made comments about that yesterday that this -- yeah.

DR. WILLIAM BANNER: Okay. I probably said it inarticulately. Yeah.

DR. SHARON SAGIV: Okay. I just wanted to mention that.

DR. JAMES MCMANAMAN: Other questions? Dr. Rohlman?

DR. DIANE ROHLMAN: First, can I go back to Dr. Burns' presentation?

DR. JAMES MCMANAMAN: You can.

DR. DIANE ROHLMAN: Okay. Just a quick comment on your comparison about external validity across -- this is Diane Rohlman. You know, we just need to keep in mind that we have different exposure profiles for all three of these birth cohort studies, as well as other ones and that the plan was set up also not to make the same measurements to do a comparison there. So the fact that there's inconsistent findings, I don't think is surprising as well.

This is a broader question, I guess, for the panel here. Since we keep coming back to this 2000 regulation which reduced the use of chlorpyrifos

indoors, could you just give me some background information on what role Dow played with that decision?

UNIDENTIFIED MALE SPEAKER: In my -- to my knowledge, it was before my time with Dow AgroSciences, but that was a voluntary agreement with the agency.

DR. DIANE ROHLMAN: So -- okay.

UNIDENTIFIED MALE SPEAKER: But I could ask one of my regulatory colleagues in the back of the room if, I'm not stating that correctly for the record, to join me up front and provide that perspective.

DR. DIANE ROHLMAN: So the -- just to clarify, and I'm just trying to wrap my head around this, is that, at that point in time, there was a decision made with the EPA and with Dow to restrict the use because of concerns about neurodevelopmental outcomes?

UNIDENTIFIED MALE SPEAKER: I can't confirm that it was due to concerns about specific neurodevelopmental outcomes. I don't know the basis for that voluntary withdrawal from the residential market.

DR. DIANE ROHLMAN: Okay. So if we can presume that there was some concern about health outcomes, what we might then -- what I'm pondering here is if we look at the levels we see in the Columbia cohort -- and I keep hearing that these levels of the 6.17 is below levels that cause cholinesterase inhibition which seems to be the gold standard for looking at health effects. But yet, we've restricted their use indoors to drop those levels and we have seen that they have dropped those levels here.

I'm just curious if you could comment on why the decision to drop the indoor use. I'm not phrasing this correctly. What's my question here? If you're seeing that the levels we're seeing in the Columbia cohort --

DR. JAMES MCMANAMAN: So, Dr. Rohlman, I don't think that they can address policy questions.

DR. DIANE ROHLMAN: Okay. But -

DR. JAMES MCMANAMAN: So we'll stick to the science.

DR. DIANE ROHLMAN: Fair enough.

DR. JAMES MCMANAMAN: Okay.

DR. KEN RACKE: Ken Racke here from Dow

AgroSciences. Can I make two clarifications? And yeah, to my knowledge, the voluntary withdrawal in 2000 had been based on a change in the assessment due to the FQPA uncertainty factor being inserted into the assessment process.

Again, we were using a cholinesterase-based endpoint and assessments that had passed. You know, one day basically didn't pass the next, based on this cholinesterase endpoint and uncertainty factors through the application of those FQPA uncertainty factors. I think that seemed to be the reason.

And then one quick question back on the mosquitoes. Just to clarify, yes, chlorpyrifos is still approved as a mosquito adulticide, not a larvicide, but their adulticide use is you know, sprays or fogging that I think are still used for public health purposes. So just to clarify from a reg perspective. Again, Ken Racke, Dow AgroSciences. Thank you.

DR. JAMES MCMANAMAN: Thank you.

DR. KEN RACKE: I apologize for misspeaking. It's not something I'm familiar with.

DR. JAMES MCMANAMAN: Other questions? All right. Hearing none, then I think we'll take a

break now.

DR. DALAND JUBERG: I have one concluding slide.

DR. JAMES MCMANAMAN: Okay.

DR. DALAND JUBERG: Could we just put that up?

DR. JAMES MCMANAMAN: Yes.

DR. DALAND JUBERG: It's under Tab 1. And while we do that, I would like to thank, first of all, Dr. McManaman and the U.S. EPA for giving us considerable time this morning. I'd like to thank my co-presenters. And in particular, I'd like to thank this panel for listening to us with respect and giving this time.

Just several points, and these -- just a collective summation. The proposal before for the SAP sets aside what we believe is over 40 years of science and regulatory decision-making. Global regulatory authorities continue to use RBC cholinesterase inhibition as a regulatory endpoint. Unreliable exposure data do not meet EPA's regulatory standards. The causal link between neurodevelopmental effects and in chlorpyrifos exposure has not been established and is inconsistent with other

epidemiological evidence. There are serious questions about the CCCEH study design confounding variables. And the point of departure based on Rauh et al. is untenable. Calculating in a benchmark dose estimate in the absence of the raw data is a major vulnerability.

And finally, EPA's proposal is hasty, unnecessary. And by that, I mean we have a robust PoD currently and not based on sound science. We feel that the FIFRA regulatory process, the commitment to public health, and the adherence to transparency and scientific investigation should demand that a high bar be set when considering such a shift in thinking and regulation. Thank you.

DR. JAMES MCMANAMAN: Thank you. So we'll take a 15-minute break now. So, be back at 5 till.

(Brief recess.)

DR. JAMES MCMANAMAN: Set up public commenters. Like herding cats. Okay. So we have a change in the schedule. Wendy Hessler is not speaking. And Sarada Tangirala is going to read into the record for Wendy Hessler and Sarada Tangirala. Wendy Hessler is a private citizen. Sarada is from

National Campaign Manager for Women's Voices for the Earth.

So I'm wondering if we're going to have an EPA session about decreasing vision as you get older. Okay, I'm reading this verbatim. "My name is Sarada Tangirala, and I'm with the National Organization of Women's Voices for the Earth. Our mission is to amplify women's voices to eliminate the toxic chemicals that harm our health and communities. And today, I want to do just that, amplify women's voices.

So I direct your attention to the written comments provided by Dr. Minako Watabe who is an OB/GYN from Ventura County, California. Dr. Watabe writes: As an OB/GYN in Ventura County where I care for many women who are agricultural workers and where my children go to daycare surrounded by the citrus oranges, I would like to ask for your careful consideration in the data surrounding neurodevelopmental effects of chlorpyrifos.

My expertise is in applying scientific research in practice. If there are human data revealing that a drug has the potential for permanent fetal harm, the drug would not be used in pregnancy,

unless it was determined, with absolute certainty, that there is a threshold dose under which there would be no harm and still have therapeutic value.

The National Academy of Sciences and experts in neurodevelopment would argue that it is unlikely that there is a threshold under which neurodevelopmental toxicants can cause no harm. The aggregate and cumulative effects of neurodevelopmental toxicants on the developing brain occur during the long period of vulnerability and cannot be easily accessible -- easily be quantified and do not fit into the traditional algorithm.

Human science is imperfect. There are always knowledge gaps, as conducting research on humans is unethical. However, let's not forget that the lessons that we have learned from lead, mercury, alcohol and now chlorpyrifos. Our children's intellectual capacity is priceless and cannot be recovered once it is lost.

Furthermore, we will never be able to protect against human error and environment disasters, fires and non-compliance. In California we have experienced wildfires that have spread to agricultural areas, causing chemical explosions in close proximity

to schools, daycares and residential areas. Farmworkers and local farmworker advocacy groups routinely document noncompliance with pesticide safety regulations.

Local regulatory agencies admit that they don't have the manpower to properly regulate pesticide use. We cannot account for all these circumstances, but we can, at least, ban the production of the most harmful pesticides.

We cannot prevent all the traffic deaths, but we can at least put all of our infants in car seats. Public health and epidemiological research in the academic community must be considered central to any decision-making involving the protection of children's health. There is no question that research conducted by industry is subject to financial bias and relying on such research can put the public at risk.

I respectfully request that when making recommendations to the U.S. EPA regarding how to consider the Columbia data and regulation of chlorpyrifos, you will look at it through the lens through of a parent, grandparent and community member and consider all the children to be as precious as your own. Thank you."

Okay. Back up here. So next up then, I have Scott Schertz. From Schertz Aerial Service, Incorporated.

MR. SCOTT SCHERTZ: Hello. Thank you for this opportunity. I am Scott Schertz. I do own and operate Schertz Aerial Service, an aerial retail and distribution company in Central Illinois. I've owned this business for about 30 years. And obviously, we've handled, provided, applied these products on millions of acres and have seen them to be very, very useful tools.

Now, also I was president of the NAAA, the aerial applicators association trade group about 10 years ago, also on the ARA Board and also part of CLA with some other committees and issue management teams.

It is a very important recommendation that you have before you. And it does go well beyond just this one product, the underlying policy of it. You know, other insecticides, the other LPs, perhaps, pyrethroids, etcetera, are definitely at risk. And the scope of this fact actually goes beyond the charge craft since it's been implied a few times with some of the correspondence that is in the docket from OPP to

some of the registrants clearly say that the underlying issues were part of the -- or can be brought into the SAP Charge Questions.

It is important to understand, though, that it isn't just a single, as I mentioned, insecticide. I mean, it's insects; it's mites. Also as one of the last speakers before the break got into, these insects can be vectors for pathogens that affect the food. And also the whole public health concerns are greatly increasing now.

And yes, not only is chlorpyrifos a adulticide, but also that question was probably a little too narrow because the underlying 10X can impact many of the other public health insecticides.

And in this arena, it's really sort of an integrative pest management. You need a variety of tools, both for an ag use and also public health. And when it was asked about chlorpyrifos whether it had a public health label or not, you know, really, it should be what else is at risk, due to this policy shift. And that is clearly aimed at the OPs. And well, you may for a short-term pest outbreak be okay losing a tool or maybe even a class of tools. But when you have a sustained outbreak -- hurricane, you

know, or spider mites in a drought -- you really do need to be able to rotate products. And OPs are definitely a very, very component of this in both the public health area and then also agriculture.

Obviously, as they change the endpoints in this risk assessment, aerial is looked at less favorably. And for many years, aerial has really been the prime application vehicle for insecticides.

And there's a few unique things to this that many people don't realize. For one, we do handle it in bulk and we have true closed systems. We're very concerned on worker safety. And that allows a scale to actually, you know, receive 4,000 or 5,000 gallons and end up having exposure less than dealing with one tin, half-gallon jug when we do it in a closed-loop bulk system.

Also, there's many, many advances in even the 30 years I've been or I've owned this business, as far as the technology. Things such as GPS tracking, where you have and haven't been; smokers; airborne weather systems that can predict drift, not only where it is, but also where it isn't. And you know, this adjustment puts many of these tools at risk.

In particular, the drinking water modeling and surface water is really troubling. And a couple of points on that is it's not every field that gets done, not always max rate. Not all the fields are close to water and the wind doesn't always blow towards the water. And also applicators do take care. But aerial is very important for a rapid response for treating crops, protecting crops, without crop damage.

I will bypass many of the other points here that, you know, obviously have been made by better-informed people. But there are a few process points I would like to make. Even though the agency has talked about their, you know, sound science and attention to detail, there's several missing links, including not responding to comments. And like the 2010 Draft Framework for Incorporating Human Epi and Incident Data.

Also very, very troubling on this particular product is the 2014 Revised Human Health Risk Assessment. The agency has never responded to the comments on it. In fact, it was stated that they were not going to and if you wanted them to be considered, you'd put them in the 2015 docket on it.

So you know, there are a lot of things

moving fast on this. It would be very responsible, I believe, for you to, you know, consider the advice carefully. And I would, you know, be very welcome for the agency to request more time. And you know, we do have many concerns of where this leaves us, particularly, on the broad range of tools and also the public health standpoints. So any questions?

DR. JAMES MCMANAMAN: Any questions from the panel? Okay.

MR. SCHERTZ: Thank you.

DR. JAMES MCMANAMAN: Thank you. The next presentation is from CropLife.

MR. JAY VROOM: Good morning.

DR. JAMES MCMANAMAN: Good morning.

MR. JAY VROOM: So, thank you for this opportunity to appear before this distinguished SAP Panel. My name is Jay Vroom. I'm President and CEO of CropLife America. And I'm pleased to be here with two colleagues from member companies, scientific experts, Dr. Starks and Dr. Chukwudebe. And they will be speaking to our slides. But it's my pleasure to provide a little introductory overview to our association and perspective around what we bring to the conversation here this morning.

The next slide has a brief description of who CropLife America are. As a trade association, we represent about 110 member companies. Is it possible to advance to the next slide or is it here? There.

We represent the developers, manufacturers, formulators and distributors of crop protection chemicals and other plant science solutions, principally biotechnology products for agriculture and pest management in the United States.

And our members obviously support rigorous science-based and transparent process for government oversight and regulation of our products. We're committed to working with U.S. EPA, as we have over the decades is the primary federal agency responsible for the regulation of these products.

Just by way of background, I've been in this role leading this association for over a quarter of a century and was there during the process of the development and negotiations of the Food Quality Protection Act, which President Clinton signed into law 20 years ago, this August 3rd.

I think the most important part of that law that is specific to your deliberations is

scientists evaluating the chlorpyrifos biomonitoring data is the emphasis in FQPA of reliable data. And the Columbia study, raw data being unavailable, in our view, represents a serious question about its reliability.

Certainly, CLA and some of our member companies also have petitioned the agency to consider postponing this SAP because of the questions that we believe remain unresolved with respect to the appropriate role of epidemiology information in the overall risk assessment process for pesticides specifically. Those petitions were all denied.

But we believe that there is a legitimate question associated with the role of epidemiology information as it contrasts to toxicological information. This, in particular, developed under good laboratory practices that are also regulated by the Environmental Protection Agency.

We also wanted to make note of the fact that the court mandate to EPA, in our view, does have flexibility that perhaps wasn't fully expressed by agency representatives yesterday and that the agency does have the ability to go back to the court to ask for additional time, that the June and December

deadlines are not absolute hard deadlines, but can be flexed, should a discovery be made for the need for science that it require more time.

Another point that I wanted to share is that the 2014 Farm Bill does provide EPA with the authority to create an agricultural advisory committee to the EPA SAB and U.S. SAPs. That still is in development. We wish that that organization were in place by EPA. And Congress I know is frustrated by the long lag in establishing that ag advisory committee that could have helped inform some of your work here today and this week.

Finally, the chlorpyrifos agency action is bundled with other organophosphate products. And as the previous speaker just alluded, many of those not only have important agricultural applications, but also key roles in the protection of public health and the management of disease vector control, most particularly, the control of the Zika virus vector.

So thank you very much, and I think Dr. Starks, you're planning to go first.

DR. SARAH STARKS: My name is Sarah Starks. I am a regulatory affairs consultant for DuPont. I also have a Ph.D. in epidemiology from the

University of Iowa. And my doctoral work focused on the neurological and neurobehavioral effects of organophosphate pesticide in farmers enrolled in the Agricultural Health Study. And Dr. Chukwudebe and myself are here today to provide comments on behalf of CropLife America.

So our presentation will be in two parts. I'll be discussing the importance of this analysis for making regulatory decisions. I'll highlight some of the limitations of the Columbia study specifically for its use in human health risk assessment. And I will touch on some items and some concerns that the EPA has yet to address. Then Dr. Chukwudebe will follow up with more technical talk on exposure science considerations and then we'll wrap up with some conclusions and recommendations.

So why is this an important issue for us? Well, as was alluded to earlier, the EPA's use of human epi data in the absence of toxicological data for quantitative risk assessment is precedent-setting.

The EPA has relied on the Columbia study which is a single, unreplicated epidemiology study that is not designed for quantitative risk assessment.

The EPA has excluded a very robust animal toxicological database of studies that have been conducted following accepted test guidelines that have been the historic foundation for pesticide risk assessment. And furthermore, there is a lack of plausible mode of action for the hypothesized association of exposure and neurobehavioral outcomes.

Also, I think it's important to remind the Advisory Panel that the conclusions from this panel and how you address the charge questions may very well likely support establishment of policy for future human health risk assessment approaches which will greatly impact regulatory decision-making.

So we think that the Advisory Panel should consider this fundamental question during your deliberations. Is the Columbia study sufficiently robust and suitable for deriving a regulatory endpoint for human health risk assessment?

Yesterday you heard from the EPA a number of strengths of the cohort study. I'm going to touch on some of the important limitations. As I mentioned, the Columbia study was not designed for us in regulatory quantitative human health risk assessment with does and temporal concordance.

Rather, the Columbia study was designed to assess several different health outcomes and many different environmental factors.

So there are numerous limitations of the Columbia study. Some of them include, as we already discussed, poor chlorpyrifos exposure metrics, the inability to examine or control for some potential confounding factors, limited statistical power, as a result of small sample sizes.

There's a lack of generalizability to other populations and a lack of reliability and repeatability. And because we do not have access to the raw data, we cannot examine this.

So moving on to poor exposure metrics. As you're aware, chlorpyrifos was based on -- I'm sorry, exposure was based on chlorpyrifos levels that were detected in either maternal or umbilical cord blood at the time of delivery.

Maternal blood was collected within two days of delivery. So there's a little bit of uncertainty in the timing there. So this is a measurement that's taken in only one point in time.

The authors assumed, they made a very important assumption, that these levels were similar

to each child prenatally. So given the characteristics of chlorpyrifos and its rapid metabolism in humans, the levels of chlorpyrifos detected at birth do not necessarily reflect the exposures through the prenatal period.

Also, in the statistical analysis, you see that a continuous chlorpyrifos measurement was dichotomized into two groups, a low exposure group and a high exposure group. What happens when you take a continuous variable and you dichotomize it, this reduces the statistical power to detect the true effect.

Also, when we dichotomize, you run the risk of exposure misclassification. This can result in either non-differential or differential error. I think that epidemiologists make a blanket statement that exposure misclassification will likely result in the non-differential bias, a bias towards the null when, in fact, we don't know that. This could be a bias towards or away from the null.

And then finally, there is no biological basis for the cutoff of 6.1 pg/g that was used in this study. Very importantly, the Columbia study cannot be replicated because residential use of

chlorpyrifos was phased out in 2001. So the study was based on exposure circumstances that no longer exist.

Regarding potential confounding, the EPA states in their 2010 draft framework that when evaluating the quality of observational epidemiology studies, the Office of Pesticide Programs will consider whether relevant confounding factors are properly identified, described, measured and analyzed, such that an unbiased estimate of the specific association under study can be made.

Now to the Columbia study's credit, they did examine several potential confounding factors. However, we believe that they did not adequately control or at least examine some important neurotoxicant and nonchemical stressors.

So lead, I'll talk a little bit more about. And we already mentioned that alcohol use during pregnancy was not examined. And then there's some other factors such as nutritional status. So these all have the potential to profoundly affect child neurodevelopment.

Just to give you an example, in the Perera study in 2003, this was an earlier Columbia study, reported that nearly a quarter of the mothers

in that cohort reported alcohol use during pregnancy. However, this factor wasn't considered in later analyses.

In addition, there are factors that do change over time. This includes socio and economic status and different environmental exposures. And these require repeated assessment throughout the study and this was not done. So we believe that the EPA needs to further explore the extent to which the observed neurobehavioral outcomes were influenced by exposure to other factors.

Next is the issue of small sample sizes. And in 2012, the Advisory Panel deemed inadequate sample sizes as the most important limitation of these studies. As we know, that small sample sizes, they limit the statistical power. They create instable risk estimates.

And just to give you an example in the 2006 Rauh publication, they reported statistically significant associations between high chlorpyrifos exposure and neurobehavioral outcomes, such as attention problems, ADHD and pervasive development disorders. So we see here are large odds ratios. But what the EPA fails to acknowledge is that these

confidence intervals are also extremely wide. And this is an indicator that these estimates are not stable.

However, despite the instability of these estimates the EPA indicates in their weight of evidence analysis that these data provide evidence of strength of association between chlorpyrifos exposures and neurodevelopmental effects in these studies.

In addition, small sample size also limits the analyses of potential confounding factors. In talking specifically about lead, in 2001, the Rauh paper reported that there was no correlation between lead, between the exposure chlorpyrifos and the neurodevelopmental outcome.

It's important to note, though, that they only examined lead in a subset of the population which was 34 percent of the study population. So this analysis was likely underpowered to detect an association because of the small sample size. And as a result, they didn't include lead in their final analysis. So the potential confounding by lead was not examined.

So next, I'd like to comment on the use of epidemiology data in health risk assessment. And

the EPA itself has acknowledged the important limitations of these studies are relying on these studies for regulatory purposes. And there was a letter by the former OPP Director Steven Bradbury that acknowledged these limitations.

And further, in the EPA's own draft framework in 2010, they state that there are several important factors to consider, including the characterization of exposure, ascertainment of disease, bias, confounding, data collection analysis and that it is important to evaluate the strengths and the limitations of epidemiologic studies when incorporating them into risk assessment. We feel that this has not been done. In EPA's failure to appropriately consider or address a number of these issues is contrary to the agency's draft guidance.

Next, I think that this slide does a very nice job of illustrating the importance of transparency and the availability of raw data. And Dr. Driver mentioned this in his presentation. But the EPA, as you know, is proposing to derive a point of departure on the basis of reductions in Working Memory Index. So this is from the 2011 Rauh paper. And the EPA has accepted the authors' conclusion that

there is an inverse linear relationship between chlorpyrifos exposure and Working Memory Index.

The authors' conclusions are based on the sparring regression analyses that are shown here in the figure to the left, which are superimposed over scatter plots.

So the point that I'm trying to make is that there's variability. You can't necessarily just look at these scatter plots and come to the conclusion that there's a linear relationship.

Access to the raw data is essential to an independent evaluation of the appropriateness and the interpretation of the regression model used in the conclusions that are drawn, given that a major decision that will be made on the basis of these data.

And then finally, just to mention, a few outstanding issues or concerns that the EPA has not adequately addressed regarding the use of epidemiology data. In 2010, they published their Draft Framework. The EPA has not responded to the 2010 Advisory Panel recommendations or the public comments on this framework. Since it's been six years, we feel that the EPA must finalize this Draft Framework moving forward.

Also, the two Advisory Panels that met in 2008 and 2012, both expressed serious concerns about using Columbia's study. But the yet the EPA has not yet adequately addressed these questions and concerns.

And then most recently, the 2015 Literature Review on Neurodevelopmental Effects and the FQPA Safety Factor Determination. The EPA relied on this study to make regulatory decisions. And the EPA is recommending a significant change in the approach without consideration of limitations from the lack of a full access to raw data from the studies that cannot be replicated.

And I believe my last slide is just to go into a little more detail about the 2012 Advisory Panel issues that have not been adequately addressed. So on Table 13 of page 79 of your chlorpyrifos issue paper, it outlines some of the limitations that were identified by the panel, that has not been addressed. So that includes modest sample size, the large exposure differences needed to see significant effects, the fact that exposures were taken at a single prenatal time point and then issues with the external generalizability of the cohorts.

The EPA will say that they did address these issues by the retention of the FQPA and the 10X intra-species factor. However, these limitations do suggest that the study has not met the necessary scientific criteria for a quantitative risk assessment in that by merely applying these safety factors does not improve any scientific underpinnings.

DR. AMECHI CHUKWUDEBE: Thank you. So my name is Amechi Chukwudebe. I'm a senior toxicologist currently at BASF Corporation. By way of training, I have a doctorate degree in toxicology from the University of California at Riverside, with a minor in organic chemistry and a Master's degree in toxicology from Simon Fraser University in Canada.

So I will start with something right up (inaudible). We always hear about the dose mixed poison. So we do have today a new paradigm shaped toxicity in the 21st century. Other areas of discipline have also migrated in that sense to more future looking. So we have the analyses exposure science in the 21st century which paraphrases exposure science as the collection and analysis of quantitative and qualitative information needed to understand the nature of contact between receptors such as people and

physical or chemical stressors.

So in this sense, exposure science strives to capture special and temporal dimensions of exposure effect with respect to acute and long-term effects on human populations.

So I can parse some of these long definitions. So the beginning of an assay system starts with the collection. And the collection itself, if we parse it to the way the Columbia study was conducted, that is the time, the method of analysis is already going to be factored in. So in a good collection system if they radioisotope dilution experiment were going to be the endgame, there should have been a sample spike at that level, which was not conducted in this Columbia study. The analysis must be tailored to the nature of the compound, whether it's persistent or not and the quantitative aspect has to be specific, precise, and the qualitative aspects also has to consider the biology of the system. Whether there are any excipients (phonetic) that can affect the quality of the analyte looked for or the dynamics. The nature of the receptor has to be looked into in terms of what is the probable mode of exposure? Is it inhalation; is it dermal; is it oral?

All these factors have to be taken into account. And so that in the end, exposure science, as applied today, is so important that it has to be under the purview of the biologist, not the chemist.

So chemical metrology in exposure science belongs with the biologist. It's not something you collect and then ship out to a chemist and then get information back. It's a whole continuous system.

Therefore, exposure science will then encompass properly at applied mechanisms and dynamics. And this is a very complex area like a crowded system with multiple exit ramps. And so to determine the validity or the contextual nature of these studies we need standardized conditions. And this, under best conditions, compares standard operating procedures.

So when we ask for transparency, for raw data it is not in terms of being nit-picking, it is to get the context because every valid matrix requires a context. Without which, the proper interpretation cannot be done.

So to begin with, we don't know whether there was an SOP involved in this and an SOP doesn't have to involve the terminal laboratory that did the

final study. It has to start from sample collection. And throughout the whole documents, there is no idea or indication that a Standard Operating Procedure was in place, which is really the bedrock of transparency of the raw data so that we can look back and see whether the conclusions make sense. So exposure science then is just like the scientific method. It comes with its own power. It also comes with its own limitations. We don't know the limitations of this study.

So continuing, sample collection and exposure analysis in biology require careful consideration, in terms of the validity of exposure analysis performed. So in this Columbia study, we have some concerns including whether the samples were collected without regard to biological dynamics.

So for example, the sampling of exposure in the chemical space for the pregnant mothers, some of the materials were lost, and there was no way, there was no evidence, that sample. The results also show that there was no correlation between presence of chlorpyrifos in the sampling space and systemic exposure.

Storage and shipping of samples is

something that's sounds rather prosaic. But it can be everything. So when the samples are collected, this is a compound that is, in many ways, can be considered an ester.

There are many factors that can study degradation process. The question becomes, if we are going to use an internal radio heavy isotope standard, that is the time to perform the spike in the fortification. That was not performed. And that's also the time to determine whether you'll need an inhibitor to stop the degradation process to keep the sample intact. And this can be over a period of a few minutes. We don't have any Standard Operating Procedure in place from the people collecting the samples, whether the sample has to be at room temperature for one minute or two minutes before we ship it out.

So this is a very blank space that we don't know about. So the samples were shipped. How long was it in transit? And when it got to the lab, what were the processes? We know that it was frozen prior to analysis. At what point was fortification performed? And if fortifications were performed late in the game, what was going to ensure that that's

homogeneity? Because using heavy isotopes, presumes sample homogeneity. And that homogeneity is best assured when the fortification is -- occurs at the time of sample collection.

And there were varying methodologies. Some of the methodologies used HPLC, some used gas liquid chromatographies. And the radioisotope dilution assay is a very good method, has very good sensitivity.

The linear response is not always given, in the sense that when you get a given number, it can also be influenced by the level of fortification, the level of the heavy isotope being spiked. So this is more like if you get a series of objects and you add another object with the same property, that this time would get color insistent that you can see.

So under ideal conditions, they close out the match between your fortification value and the unknown value in the analyte, the more precise your outputs will be.

So in this case, under the best conditions, this is something better, I see it more than once. Repeatability. We don't have any

indication that this was ever done in this study, because this is something that is so important that one support analysis is not enough.

DR. JAMES MCMANAMAN: Dr. Chukwudebe?

DR. AMECHI CHUKWUDEBE: Yes.

DR. JAMES MCMANAMAN: We're running a little short time.

DR. AMECHI CHUKWUDEBE: All right.

DR. JAMES MCMANAMAN: And you're a little bit over. So could you?

DR. AMECHI CHUKWUDEBE: Okay. I'll move it fast. So this is just a summary of what you to consider to be the clear digressions in the conduct of this study and the conclusions. So if you look at the indoor examples, some of the samples were lost and there's no correlation between the presence of chlorpyrifos in these samples and the presence in plasma or meconium or urine samples.

The stable isotope is used. There was no indication in these studies, the nature of the isotopes, whether it's carbon 13, nitrogen or deuterium. And we don't even have a sample of the chromatography because they can't even tell us whether they are square pegs. We don't know whether they were

procedural blanks used, because these blanks also assure that you don't have a mission drift.

And there are other things consistent with the chemistry of the analytes such as the presence of heavy metals that can influence the relative abundance of chlorpyrifos or the oxones. This was not taken into account. And again, the same thing with the urine samples. So there are very important chemical confounding factors whose presence together will help you to determine whether all important considerations have been considered.

And finally, on these exposure considerations, continuing, the lack of all these standard operating procedures is that the lack because it's not there or the lack because the others is considered it not important enough. It makes sense to us that this is no longer a case of uncertainty. It gets to the level of deficiency.

And because we have a crowded system with multiple exist ramps, it's no better than the flip of a coin at this stage. Because at this stage, this is not something that can be remedied by a standard uncertainty factor.

So to summarize here, there are many

significant details missing. Details on the dynamics and stability of the analyte whether it was considered, the kinetics, details on the matrix composition and whether contamination was actually factored in. The response linearity across biological phases, using radioisotope dilution assay has not been considered.

And if you go to page 79 of the review, so based on radioisotope dilution assay no conclusion can be made that that's a relationship across biophases, presence in the meconium or plasma or presence in the urine, because the RIDA assay, it's good on its own. It doesn't translate across biophases.

So to come back again, the centrality of exposure metronomics has not been given adequate strength in this study. So in the prosaic sense, we cannot determine whether the exposure being reported occurred before an effect being reported or vice versa. This is really a study where exposure has not been given due consideration. And in many cases, that should have been the central core before any other elements were being looked at. So exposure has not been demonstrated, and that is a fatal flaw for this

study. Thank you.

DR. JAMES MCMANAMAN: Thank you. Are there any questions for the CropLife presenters? Okay. Dr. Sagiv.

DR. SHARON SAGIV: This is Sharon Sagiv from U.C. Berkeley. Just a few comments from the beginning on the epi studies, just a few things I wanted to mention.

You mentioned that using epi studies risk assessment is probably the wrong path to take. But I just wanted to mention that there are some outcomes that we can't assess with animal studies. So maybe -- do you want to respond to that?

DR. SARAH STARKS: I don't want to say that epidemiology studies can't be used in risk assessment. In fact, I encourage their use.

DR. SHARON SAGIV: Mm-hm.

DR. SARAH STARKS: But I think that we do need other supportive studies, including animal studies. And in this case, there is a very large animal database available that has been excluded.

DR. SHARON SAGIV: Right. But do you recognize that there are some health effects that can't be measured in animals?

DR. SARAH STARKS: I would agree with that. But I still don't think that a risk assessment should be based on a single human study.

DR. SHARON SAGIV: Okay. The other thing and this has come up multiple times is this issue of exposure misclassification and that it sometimes does buy us away from the null. However, in the dichotomization that the Columbia study did, non-differential misclassification will always bias towards the null in a dichotomous exposure. If you had a three-level exposure or a multicategory exposure, then you could have bias away from the null.

But in the case of a dichotomous exposure with non-differential misclassification, it will always attenuate your findings. So that --

DR. SARAH STARKS: I disagree with that.

DR. SHARON SAGIV: Well, that's in Rothman and Greenland and Lash, so I would prefer --

DR. SARAH STARKS: There are a number of publications that do support that you do need to look at it. And you are right, that non-differential misclassification or misclassification of exposure will tend to bias towards the null. And I agree with

that, but there are cases where it does not.

DR. SHARON SAGIV: With a non-dichotomous exposure, it will always bias towards the null. It is a statistical fact. You can look in Rothman and Greenland. If you had three categories of exposure, say, they used tertiles or something like that, then you can have bias away from the null and I can direct you to that source.

DR. SARAH STARKS: My understanding, though, is that if it's only with a univariate analysis, when you're not looking also at multiple covariates in your model and you have a very complex model, then that's not the case.

DR. JAMES MCMANAMAN: So this is meant to be getting clarification and it looks like there is disagreement.

DR. SHARON SAGIV: Okay. I'll stop there.

DR. SARAH STARKS: Okay.

DR. JAMES MCMANAMAN: Okay. Are there other questions of clarification? Okay. Hearing none, I thank you and we'll go on to our next presenter.

So our next presenter is Ellen Webb

from the Center for Environmental Health. Is Ellen Webb here? Is she out in back? So I think if she's not here, then we'll go on to the next presenter, Scott Slaughter, Center for Regulatory Effectiveness. Is Scott Slaughter here? We can just go to lunch.

DR. JIM TOZZI: I'm Jim Tozzi. I'm chairman of Center for Regulatory Effectiveness. We are a regulatory watchdog. And that means we look at compliance of agency proceedings with what we call good government statutes. The statutes that regulate the regulators.

Now we've been following this case, not because we have a particular interest in the substance at hand. But what we are looking at this is this is a precedent, we think, for the way the registration process and EPA is going to take place. So we're looking at this as a precedent-setting exercise a lot more than the merits of this particular registration.

Now, what to do we -- why is our concern in what we think should be done? Oh, here comes Scott. I'll finish.

MR. SCOTT SLAUGHTER: I apologize. I thought I was on later and I was out taking -- I had an emergency trip to the bathroom.

MR. JIM TOZZI: Okay. All right. That was the emergency. So let me just finish. I thought It was an emergency. I didn't know how drastic it was. But in any event --

MR. SCOTT SLAUGHTER: Human nature calls.

MR. JIM TOZZI: Several times. So anyway. Scott --

DR. JAMES MCMANAMAN: So that should be clarify then, right?

MR. SCOTT SLAUGHTER: And I don't want any clarify questions either about this.

MR. JIM TOZZI: It probably is statistically significant. But in any event, before I turn it over to Scott, the bottom line -- and Scott will add to it -- is that when other agencies are going to shift a huge paradigm in the regulatory process, they generally go through a very extensive rulemaking or notice and comment process. And we work in every agency. And let me assure you that, for example, the Federal Communications Commission, when they allocate who gets spectrum length, for issues for years, they would give four or five criteria. People would apply and the staff would rank who got the

spectrum. But recently, they changed. They changed to an option process and that option process was debated extensively on the record. There was notice and comment, there were interactive public documents. There were comments by the best minds of both sides. And then there was a shift, somewhat of a shift, in the paradigm.

So what Scott's going to explain to you in the other eight-and-a-half, nine minutes is that we think that there should be a moratorium on the use of epidemiology studies until which time EPA goes through this process of notice and comment and opens a docket on the role and the critical role that epidemiology should play in the conduct of these studies. Now, Scott. Now that I got you to the emergency, you'll finish.

MR. SCOTT SLAUGHTER: Well, I can't really follow up very well on Jim's excellent presentation, although I would like to note that in 2010, EPA had a draft framework for conducting epi studies in this context. And it was reviewed by an SAP, as had been pointed by several other commenters today. And it seems to have disappeared. I mean, what the agency should concentrate on doing, in our

opinion, is coming out with a final framework that, you know, it tells people how you should use epi studies and incorporate epi studies during pesticide decision -- registration decisions and risk assessment. And why the agency hasn't followed up on 2010Fframework and the SAP review of it after six years is a mystery to me. Perhaps, they can explain it.

I also want to -- and we think that the Department of Agriculture probably agrees with us, because they filed comments on -- and one of the many proceedings at EPA having to do with registrations of OPs. And if I -- and I'm quoting their comments correctly when I'd say that agriculture said that, quote, "If epidemiological studies are to form the basis of the FQPA factor, a standard operating procedure is needed," close quote. We agree completely. It is totally absent here. And if there were one, you know, a lot of the problems being agonized over it at this panel might not even have occurred or might not occur in the future. And this will not be the last time that epi studies are an issue in pesticide registrations and assessments. They will be used for the other OPs, in all

likelihood, and there will be other pesticide registration, where they are a very significant issue.

So what you guys are doing is very important. It's precedential. And it's not going to be applicable just to chlorpyrifos, although it will be applicable to chlorpyrifos, but it will also, you know, establish a precedent framework basis for the future registration and use of epi data in pesticide registrations. And you know that's an important concept and we don't think it should be made on the -- it should be decided on the database available to you guys because it's a really lousy record, to be frank.

Which gets me to my second comment, which is that if EPA makes a pesticide registration for chlorpyrifos, using a PoD based on the Columbia study, it'll violate the Information Quality Act. The Information Quality Act is a federal statute that requires certain data quality standards for federal agencies and the information they violate.

And using the Columbia study, I'm not going to try to repeat all the technical discussion of all the flaws, questions and uncertainties that have certainly not been answered, as far as I can tell, about the Columbia studies. But using at this point

in time, based on this record before you guys, if the EPA used those studies to, you know, establish a PoD based on -- the Columbia studies based on neurodevelopment, they didn't violate the IQA because -- let me give you some examples.

One, the epi studies do not adequately address the possibility of confounding and adverse effects from other compounds capable of causing or contributing the observed neurological outcomes.

Two, these epi studies are not adequate to assess dose-response relationships. Three, these epi studies do not have adequate statistical power. And four, and I'm going to emphasize this one, these epi studies do not disclose their raw data.

If EPA bases a chlorpyrifos decision on the Columbia studies without disclosing all the relevant raw data from those studies, then it will violate a federal statute, it will violate OMB's binding government-wide guidelines implementing that statute and it will violate EPA's own guidelines implementing that statute. And I think one of the panel members earlier asked if there was any kind of requirement that EPA disclose the raw data. The answer is yes, there is.

My final point is, oh, I do also want to mention that the prior SAPs and reviews, the chlorpyrifos issues in 2008 and 2012 and 2010 emphasize the importance of data quality. And the epi study, if you're going to regulate on an epi study, you really have to focus on what kind of -- how good that study is. You know, you have to look at all the problems available. For example -- I'm moving around.

I do have on other comment and that other comment is EPA has not allowed adequate time for this SAP. Other people have mentioned it and other people who, you know, put together far more complex technical documents and presentations than we have have mentioned it. But if you look at the record, the public record for it, this SAP started April 19th. The first entry I saw with any kind of EPA supporting data was April 1st and they continued to add stuff in through the 15th and we -- for all I know, there may be some added today.

There are thousands of pages of highly technical documents in there. This is an issue of extreme importance, both to the manufacturers of chlorpyrifos and to the other OP and pesticide manufacturers and to the general public who are going

to be affected by whatever happens to this regulation. And you know, there just hasn't been adequate time afforded to anyone to prepare and discuss this -- for this important discussion.

And you know, I'd like to conclude that it appears that EPA thinks that the court order has, in some way, dictating what the agency has to do here. If that is the agency's thought process and if that's why the agency is doing what it's doing, then it's surrendering its substantive decision-making authority and role and purpose and duty to court orders and environmental group litigation. And that's just wrong. And a court order, as people pointed out, does not require this SAP or EPA to decide what to do about epi data, in general and in particular, by whatever the court order date is.

And in conclusion, we think pesticides should be regulated on science in a transparent process, not court orders and not missing data, and right now that's what's happening. Thank you very much.

MR. JIM TOZZI: Mr. Chairman, having chaired a number of these meetings, I know the timeframe and I would just like to add one concluding

point. We're not health scientists. This is not our first time at the rodeo.

Scott was a chief litigator in the Department of Justice for a number of years. And I worked for five presidents, President Johnson through President Reagan, and I started a regulatory office in the White House. So we're not bringing scientists, we don't pretend to be scientists, but we know the process and this process has to be looked at. And its precedent-setting portions of that process, we think, needs to be examined. Thank you.

MR. SCOTT SLAUGHTER: And one other thing. What I have done and Jim has done, too, is sit through a lot of science advisory panels. And we can sincerely say that we think this is a very, very important body that makes very, very important decisions and plays an incredibly important role in the regulatory process. And we thank you very much for listening to us today.

DR. JAMES MCMANAMAN: Thank you.

MR. SCOTT SLAUGHTER: Any questions?

DR. JAMES MCMANAMAN: Any questions? All right. Hearing none, I think we'll break for lunch for an hour.

(Whereupon, at 12:15 p.m., a lunch recess was taken.)

DR. JAMES MCMANAMAN: Welcome back from lunch. I think we'll go on with our next public commenter, Elliot Gordon.

DR. ELLIOT GORDON: Good afternoon. I hope everyone had a good lunch. Elliot Gordon, I'm a consultant, toxicology. I have a Master's from Adelphi University in Biology, Ph.D. from NYU in Environmental Medicine.

I started back in '72, 44 years ago, at the Frederick Cancer Research Center and have since worked at various contract labs and various registrants. I've been a consultant since 2005 and one of my clients is Adamov based in Israel, and they do have chlorpyrifos.

After some of the talks this morning, I was thinking of Abraham Lincoln and his Gettysburg Address, because the previous talks were very substantive and long. Mine is rather short. So I'm comparing it to the Gettysburg Address in length only.

I would like to comment on one specific aspect of your review and that is the agency's judgment that the Columbia study is scientifically credible and relevant for the purpose of pesticide

risk management.

In Jacks' -- Jack is here -- in Jack's letter to Cindy Baker Smith requesting postponement of the SAP, it was pointed out that the Columbia study is published, peer reviewed, researched, EPA concludes, represents sound, relevant science. I would like to add a bit of body language to the term "peer review." I suggest to the panel that peer review does not, on its own, assure that a study is properly conducted, accurately interpreted or fit for purpose.

The panel is aware of a bit of controversy surrounding the absence of the raw data from this study. These data would provide access to third-party review.

I've conducted peer reviews and I'm sure you have also. But as is customary and usual, raw data are not provided to us. I rely on the data presented in tables and graphs and take them at face value as accurate reflections of the raw data. And as Jeff Driver said earlier, summary data alone the agency doesn't accept.

After completing peer reviews, my journalist sends me copies of other reviewers' comments. Some are in depth, some are superficial.

One of the guidelines stressed by publishers, Elsevier, for example, is to be sure one is qualified by training and experience to function effectively as a peer reviewer.

Finally, there is the issue of conflict of interest. Dr. Popendorf's question earlier suggested that -- when he asked Dow, did you support these studies? There is -- the literature is rife with discussions of conflicts both financial and otherwise.

Put these concerns together. The possibility of a superficial review, the need to have qualified, competent reviewers, the possibility of conflicts of interest and the absence of raw data. Collectively, they suggest the panel obtain and study these peer reviews. Are they in-depth or superficial? Do the reviewers have requisite training and experience? Is there or isn't there a potential for conflict of interest?

We know, however, that it is unlikely, to say the least, that these reviews would be made publicly available. Accordingly, the importance of independent review of the raw data rises to a higher level. The proposal by the agency to regulate these

epidemiology studies effectively abandons years of research. Research that has established, credible, adverse outcome pathway for organophosphate compounds. It is clearly a monumental shift in pesticide risk management. It shouldn't be taken without full assurance that the studies upon which this paradigm shift rests are rock solid.

I prefer to have the raw data independently validated and suggest to the panel that you consider this course also. Absent a third-party independent credible review of the raw data, the agency's proposal appears premature. I thank you and we'll answer any questions you may have.

DR. JAMES MCMANAMAN: Any questions for the speaker from the panel?

DR. ELLIOT GORDON: Thank you very much.

DR. JAMES MCMANAMAN: Thank you. The next presenter is Jennifer Sass from Natural Resources Defense Council.

DR. JENNIFER SASS: Hello and thank you very much. I'm a Ph.D. scientist in the Health Program with the NRDC, Natural Resource Defense Council, which is an environmental group. I'm located

here in Washington, D.C., and I'm also a professorial lecturer at George Washington University in the Occupational and Environmental Health Department.

The comments that I'm presenting today are being handed out to you, as we speak and also have been electronically sent to the DFO and hopefully, will be put in the docket. And I would be happy for our audience to email them to whoever would like to see them, because they may not appear in the docket for a little while. Sometimes that happens.

They are on behalf of NRDC, my organization, as well as Farmworker Justice, Earth Justice, United Farmworkers, California Rural Legal Assistance Foundation and Pineros y Campesinos Unidos del Noroeste.

I'm going to touch very briefly on just the main points of the comments, because they're 11 pages long.

First of all, in summary, we support EPA's approach here and EPA's recommendations. The SAP builds on prior SAP reviews, which EPA summarized in some of its comments in response to SAP questions yesterday. We're very supportive that EPA has used a systematic review process to complete transparent and

comprehensive literature reviews for the data that it reviewed, including the study that it's reliant upon.

We also support the EPA's retention of the Food Quality Protect Act, the 10X FQPA Safety Factor. We are also supporting the use of the Columbia Study data as the derivation of the endpoint that's used for its risk estimate. Had EPA continued to use the 10 percent cholinesterase inhibition, as a point of departure, as it's had in 2014 Revised Human Health Risk Assessment, we were opposed to this, because that point of departure in the face of EPA's findings and not just the Columbia study, but other studies as well.

Other epidemiologic studies of pre-birth exposed children show that that measurement, that point of departure resulted in damage to children's brains at far lower doses. And so then, it would not be -- EPA's decision would not be sufficiently protective. Here EPA is now proposing to correct that flaw.

We also support the use of cord blood data to develop point of departure. It was thorough and rigorous and in keeping with agency policies. I'm sort of whipping through pretty quick and I'm on page

4, moving to page 5 now. But there's more underneath there.

The agency does provide the code needed to run the simulations in the PBPK model and we support that level of transparency. We believe that EPA's conclusions that they can reliably estimate blood levels of chlorpyrifos for females of child-bearing age from these data and that the blood levels of the mother are a reasonable surrogate for the fetus. This is your Charge Question 1a. We do support that presumption.

The agency on page 6, Charge Question 5b, the agency's use of the benchmark dose approach to drive the point of departure is consistent with data indicating that the associations of chlorpyrifos exposure with Working Memory effects is continuous with no apparent threshold. And we support EPA's use of those data to develop the BMDL.

Charge Question 5c, we are also supporting the retention of the 10X and the point of departure as a 2 percent reduction in Working Memory corresponding to the internal BMDL dose.

We're supporting the use of the 10X default on intra-specifies uncertainty factor, Charge

Question 6a. And in addition, uncertainties that support the 10X FQPA, as I said, Charge Question 6b and c.

So page -- well, it's 7, going on to page 8, there's some tables there that we've pulled from the EPA assessment. Just to highlight that there are exceedances in exposures exceeding the reference dose for basically all of the percentiles of exposure at all time periods considered, ranging from 155 percent at 24 hours, post-exposure in the low percentile of exposures to 32,000 percent exceedances for the maximum chlorpyrifos blood levels and the highest percentile of exposures.

It's very large -- the same with the drinking water. The exposures are deemed to be unsafe. They're exceeding in all scenarios considered for both infants and women of child-bearing age and they're exceeding by thousands of percent.

On the last table, page 10, the occupational exposures, are also unsafe and also exceeding the MOEs are very low. A hundred is an MOE that is -- an MOE of less than 100 poses a risk of concern and none of the MOEs from this analysis even come close to a hundred. Many are below 1, revealing

orders of magnitude of risk greater than acceptable levels.

And some of the speakers, Virginia Ruiz is going to come shortly after me here. She's with us here to talk about exposures to farmworkers. We have other speakers, too, that can talk about the reality, the real-world exposures that people experience.

But there -- I think what the epidemiology again, not just the Columbia study, but half a dozen different studies demonstrates is that it's not being used safely. So -- and I don't think it can be used safely. But clearly, people are being exposed at unsafe levels and I think that that is what is concerning the registrants and the manufacturers so much is that the epidemiology proves that it's not being used safely. There's people that are being exposed and they're having effects and that should be very concerning.

I have a few more minutes, am I right? I want to take just a very quick minute -- a few minutes to touch on some of the points from the earlier speakers today.

One was the small sample size. I've been sitting in this room for 15 years, commenting on

pesticides -- sometimes sitting around the table, sometimes in the audience -- I've never a sample size as large as this epidemiology study. Usually, it's rat studies and usually it's single or double-digit rats.

I mean -- and the variance, when you measure a 10-percent cholinesterase inhibition and you look at the variability in those data, it's way more variable than the data that we're looking at here. So I don't accept that there's a small sample size. I'm sorry. And the statistical corrections -- the statistical analysis that they do is appropriate for the sample size they've done.

So potential confounders, there was a lot of discussion about potential confounders, so I think it's important. And the panel has far greater expertise than I do. So just remember what a confounder is. It's not everything that anybody can think of to throw at the wall that occurs somewhere in the world at the same time as this study is being done. It needs to track the thing you're measuring and there needs to be some reason why it would be more in the group that's exposed than an unexposed group. I made a list, but I'm not going to go through them.

Exposure misclassification was already dealt with. The variability, I don't think you can comment. I don't think anybody could seriously comment on the variability in this study without taking a look at the studies that EPA was using in 2014. Some of the inputs were based on single rats, the 10 percent cholinesterase inhibition into Dow's model.

So I guess that's no variability, right, when you're using one rat. But it's certainly not stronger than these data. There's some missing details. Missing details does not equal uncertainty. And it certainly doesn't equal inaccuracy. It does suggest that there might be less public transparency than the registrants would like. But to conclude from that, that exposure has not been demonstrated is not accurate.

The precedent-setting idea of wanting a moratorium on the use of epidemiology, I mean, my first thought was, wow, OSHA wouldn't be able to do anything. And then I remembered sadly that OSHA isn't actually doing anything. So that was kind of a sad moment for me. But -- so I'll be commenting on in a different form.

But we do actually have standard operating procedures for epidemiology and we've had them for longer than we have for almost every other discipline. Bradford Hill came up with his criteria in 1965 that predates EPA. So for sure, the epidemiology can be held up against standard ways of assessing these data and they have and they've been published and they've been followed through.

So I think the real problem is that the epidemiology is showing harm in real people in the real world. So it's really hard to argue that it's not at that point.

And then my last comment is going to be the idea the EPA is moving too fast. Well, NRDC has had a history on this chemical for over 25 years. NRDC, my organization, we're the litigators behind the court order to set a deadline for EPA to make a decision on this. And we've been doing that for 25 years.

The reason why we're able to go to court is because we're able to show that the decision took so -- that EPA was dragging its feet on this. The "E," actually stands for environment in Environmental Protection Agency, so we actually don't

think that following court orders by environmental groups that are litigating is actually inconsistent or a problem. We actually think the Environmental Protection Agency should be protecting the environment.

And we think that the "P" doesn't stand for protect -- protracted decision-making, that it stands for protection of the environment. And we are very supportive of what EPA is trying to do here and now. We certainly don't think it's too fast and it wasn't fast enough for all the cases in the epidemiologic studies that are presented to you today. Thank you.

DR. JAMES MCMANAMAN: Thank you. Any questions for this presenter? Okay, Dr. Popendorf?

DR. WILLIAM POPENDORF: Thank you for the presentation. Dr. Popendorf here. Just had two questions.

DR. JAMES MCMANAMAN: Dr. Popendorf, could you use the -- get closer to the microphone? Thank you.

DR. WILLIAM POPENDORF: Two questions of clarification. It seemed like somewhere around maybe page 5, you indicated you support the use of

maternal blood, as well as cord blood. Is that my understanding? I didn't see that in here, but maybe it is.

DR. JENNIFER SASS: Oh.

DR. WILLIAM POPENDORF: Maybe I misheard it.

DR. JENNIFER SASS: It was on page 5. It's the paragraph with the little bold, that says, Charge Question 1a. And it says that EPA has concluded that they can reliably estimate blood levels for females of childbearing age and that the blood levels of the mother are a reasonable surrogate for the fetus.

DR. WILLIAM POPENDORF: Okay.

DR. JENNIFER SASS: And that we agreed with that.

DR. WILLIAM POPENDORF: Okay.

DR. JENNIFER SASS: It's a little hard because I jumped around so much, and I'm really sorry about that.

DR. WILLIAM POPENDORF: Yes.

DR. JENNIFER SASS: That's the problem with coming with 11 pages of comments.

DR. WILLIAM POPENDORF: Yeah. I didn't

have my mock meter with me, but that was -- the other question, on Table 1, these are the percents of overexposure. In your referenced dose, is that the proposed reference dose, the newly proposed?

DR. JENNIFER SASS: That's correct. Yes.

DR. WILLIAM POPENDORF: Okay. Thank you.

DR. JAMES MCMANAMAN: Dr. Ehrich.

DR. MARION EHRICH: Okay. Marion Ehrich, Virginia Tech. Do you have any idea how small even 2 pg/g is? And there -- this is .022. That's a 100 for less. I mean, 1 part per trillion is 10 to the minus four drops per 10-gallon swimming pool. That's very, very small. And yet, there was a statement made, this can be reliably estimated. And that's only been done in one laboratory.

Does -- this is a concern with the analysis, if we're basing things on such low, low levels. And how can you regulate it, if you can't measure it? A lot of these things, even in your Table 1, are below the level of detection. So how do you come up with --

DR. JENNIFER SASS: I mean --

DR. MARION EHRICH: -- you make it sound like these exposures are so great. And that -- and they're not measurable, even at the, what you call, the exceeding the RfD doses.

DR. JENNIFER SASS: So one thing is these aren't my numbers, right. We know that. Yeah, so, I mean, your question is how can you regulate something that you can't measure? We're asking for a ban, just so you know. We're not asking that EPA regulate at this level. We're asking that people not -- that chlorpyrifos not be available to people. That's our position.

Our position is that we don't think that the data demonstrate that there is a safe level.

DR. MARION EHRICH: But you also said that you thought that the estimations were -- that was on that statement that you just read that the estimations were reliable. That was on page 5, that they can reliably estimate blood levels of chlorpyrifos.

DR. JENNIFER SASS: Yeah. Well, because they are measuring. I mean, they are -- those studies did do measurements and they -- the Columbia study did do blood measurements including cord blood.

So those are the reliable measurements that we're talking about and that's what EPA is using to base this. What you're -- the pg/g is a .022, the reference dose is not a measurement. The reference dose is not a direct measurement, right, there's some sort of new factors and things built into that.

So the statement earlier where I said I think their measurements were reliable and the study is robust comes from the measurements. The exceedances are the numbers then converted to risk estimates with uncertainty factors. And again, we're not asking EPA to regulate at this level. Our position is a ban. We don't think that there's a safe level.

DR. JAMES MCMANAMAN: Thank you. Dr. Sagiv.

DR. SHARON SAGIV: Sharon Sagiv from U.C. Berkeley. I just wanted to make one distinction and that is that just because the tools we have can't measure levels that are not -- that are that low. It doesn't mean that they're safe.

So I'm not saying that they're not -- that they're causing harm. But I just think we need to make a difference there between our ability to

measure something, which I think the panel is coming to -- it seems to be coming up over and over again that the measure is questionable, because the levels are so low. That's a different issue than whether or not the effect of the chemical is there or if it's safe. So I just wanted to -- I'm not arguing for or against. But I just want to make that distinction.

DR. JAMES MCMANAMAN: Thank you. Dr. Terry.

DR. ALVIN TERRY: Just out of curiosity, what is the position of your organization on any organophosphate?

DR. JENNIFER SASS: We have asked for --

DR. JAMES MCMANAMAN: We -- this is about clarification. We're not --

DR. ALVIN TERRY: That's not -- not available to question -- all right.

DR. JAMES MCMANAMAN: Yeah, yeah.

DR. JENNIFER SASS: -- consistent with chlorpyrifos.

DR. JAMES MCMANAMAN: It's got to be chlorpyrifos. Dr. Pessah.

DR. ISAAC PESSAH: So Isaac Pessah,

University of California, Davis. So I'd kind of like a clarification of how you define reliability or reliable because you've used that term over and over again, with respect to the measures.

DR. JENNIFER SASS: I mean, I think that the study was conducted using reliable methods. I think that the sample collections followed standard procedures. We -- you guys went through that yesterday. I was with CDC, did the measurements. You called Dina Barr who explained how they handle them. And so I'm trusting in that process, that -- I don't see how it could be any worse than anything else EPA uses to regulate a pesticide. I do have to tell you that. That's how they do these studies. They have rats, they take samples, they process it. It's usually all done by the registrant. I think this study followed those procedures. They've published it, they've made it available. Their procedures are used in other studies. So that's my definition.

DR. ISAAC PESSAH: Just a follow-up. So in your view, reliability does not equate to reproducibility or demonstrated reproducibility, given that this is one study?

DR. JENNIFER SASS: Well, I think

reliability would include reproducibility, but this study has been followed up several times and it's also consistent with other studies that are also published, like the CHAMACOS study that have also done.

DR. ISAAC PESSAH: The CHAMACOS did not measure chlorpyrifos, though. And this study is based on chlorpyrifos measurements which has been stated to be amazingly low, amazingly, from an analytical perspective. And has that been reproduced or replicated, I should say?

DR. JENNIFER SASS: Yeah. I believe that the other -- that there are other epidemiology studies that have measured chlorpyrifos. And that this study has a large sample size and that they went through standard procedures working with the CDC, which you guys have raised questions about and which they've published.

So I have to trust in the process. It's not my study. But I feel very comfortable with it and I feel more comfortable with it than I've ever felt by any, you know, rodent study that's come before the pesticide office to base a pesticide regulation on that was conducted by the registrant on no single or double-digit animals.

DR. JAMES MCMANAMAN: Okay. Other questions? Okay. Hearing none, thank you very much.

DR. JENNIFER SASS: Thank you.

DR. JAMES MCMANAMAN: The next presenter is Michael Goodman from Exponent.

DR. MICHAEL GOODMAN: Good afternoon. Thank you for speaking with me today. My name is Michael Goodman and I'm not from Exponent. I actually am an associate professor with --

DR. JAMES MCMANAMAN: Oh, you're -- Exponent, huh?

DR. MICHAEL GOODWIN: -- of epidemiology at Emory University School of Public Health.

DR. JAMES MCMANAMAN: Okay. How do I advance those slides, which probably would be a good idea? By way of introduction, full disclosure, I did work for Exponent some 15 -- 13 years ago and left for academia. And then, a few weeks ago, they asked me to join a -- the review panel and share my thoughts along with other colleagues on this process.

And so, what I'm here today on behalf of three other of my colleagues that represent different areas of expertise. I'll tell them [sic]

who they are in a minute.

And I think there've been quite a bit of declarative statements made today. I would like to change the tenor a little bit and proposed this discussion. I'll try to do it in 15 minutes in the form of questions, rather than necessarily prescriptive statements.

And those questions that I would ask myself, if I were in the panel situation. So the overarching question, and that's what we would call our little presentation is: When are observational epidemiology data suitable for quantitative risk assessment and setting a point of departure?

As I said this, I need to give you full disclosures. I already mentioned that I worked for Exponent more than a decade ago. I don't work with them anymore. Exponent convened the working group that met over a period of a few days and exchanged follow-up emails and drafted a document that should be on the docket. And the money for this group was provided for CropLife America.

These are my colleagues. I am the one listed first and followed by Judy LaKind who is exposure assessment, the risk assessment expert.

Jennifer Seed is a former APA employee. She's a risk assessment, mode of action, developmental biology expert. And Michael Dourson is at the University of Cincinnati. He's a toxicologist.

I'm here because most of the conversation revolved around epidemiology, so I'm kind of stuck presenting.

Again, just to reiterate, it's more of a series of questions, rather than declarative statements. But I think these questions are important and these questions I would ask myself and I think I would invite you to think about those, as well. I do not always have an answer, but I think these questions need to be thought of.

So the overarching question, really in our mind and in my mind and the mind of my colleagues falls into three categories: quality and quantity of the data -- of the evidence. Hazard and dose-response and then finally, PoD.

And there is no controversy here. When reviewing observational epidemiological studies, which are, by the way, hard to do, take a lot of time, a lot of effort, one needs to consider four or five or maybe six or seven, depending who you ask, issues.

Number one issue is design, whether or not design is appropriate for a question. Number two is measurement era, both with respect to exposure and outcome and I should add, with respect to covariates, whether they are confounders or mediators or effect modifiers. Those can also be misclassified.

And then issues of analysis, internal consistency and finally external consistency, which is a very important issue in observation with epidemiology. We build evidence, brick by brick. That's how it works in nutritional epidemiology. That's how it works in clinical trials of drugs. This is how it works in comparative effectiveness research. This is how it works within the issues of health disparities. A totality of evidence is important to consider. That's why we will write literature reviews and try to do it systematically. That's why we do things like net analysis, for example.

Now I should say that all of those things in this day and age, I would say in the last decade or so, there have been a movement towards trying to systematically lay out the steps of evaluating each study and perhaps the body of evidence. We have that for, say, genetic studies.

Usually have a funny acronym of some sort. There is one for diagnostic tests. There is one for clinical trials, like CONSORT. There is one for observational studies of various designs. The checklist or you may call them wish lists, if you will, of experts. But nevertheless, these are the things that people consider. And it's good if folks are on the same page. Now no wish list ever satisfies everybody. But it's good to have some kind of agreement of what constitutes things that one to needs to think about in evaluating epidemiologically, particularly observations with neurological evidence.

Now to some extent, we're fortunate that we have at least a half a dozen publications that came out in the last 10 years -- none about chlorpyrifos at all, but about issues that are very relevant to this discussion.

And now, you know, again, full disclosure, both Judy LaKind and I happen to be co-authors on this -- all of those papers are going to show you. Now, there may be others out there, but these are the ones that I know. These are the ones that I co-authored with a lot of people from different walks of life. You can see there are people from EPA,

NIH, various sectors of academia.

There may be some people from industry as well. So I'll go through them very quickly. The very first one came out 10 years ago and that was at Hershey Technical Workshop on Optimizing the Design and Interpretation of Epidemiological Studies for Assessing Neurodevelopmental Effects of In Utero Chemical Exposure. A lot of the things covered in this publication are relevant today. Most important is things like design.

Then I have another paper that came out more recently in 2010, A Proposal to Facilitate Weight-of-Evidence Assessments. And as I said, there's always a funny acronym. And this one happens to have HONEES. But it was co-authored by people -- again, from various walks of life, the government and academia. And huge input from people that work in psychology and psychiatry, particularly newer developmental psychology.

Then again, since chlorpyrifos is short-lived chemicals, a chemical with a short half-life, there is a paper on Biomonitoring and Environmental Epidemiology of Specifically Short-Lived Chemicals. Because they represent as sort of a set of

different issues. They present a set of different issues that may be different from same biomarkers of nutrition or biomarkers of persistent chemicals.

And finally, the most recent in this series of papers is, again, the name should look familiar. Those were on Improving Concordance Environmental Epidemiology.

Now again, at least three out of four papers that I showed you, or four out of five, were funded at least in part by industry. Some European, some U.S. And so you need to be aware of that. Having said that, I wasn't involved in the meetings and drafting of the documents. We worked by ourselves.

So let's go through some of those considerations, again, with those in mind. And again, I am just borrowing from the papers have been written in the last 10 years or so. Some of them may be relevant, some of them maybe not. But a lot of it is relevant.

So first, what would be the optimal design? I'm talking about a wish list. I'm not talking necessarily that each and every study has to be held with its feet to the fire to those standards.

Nevertheless, what we do have is prospective longitudinal studies that are desirable and the Columbia study is one such study.

What is important, though, if exposure is short-lived and may effect neurodevelopment, it is important to have repeated exposures. There may be a number of reasons why people would do that. Developmental testing and assessment may also be time dependent and therefore repeating the same test at different times is important.

Now again, the Columbia study, and it's strange, at least one of the tests was administered three times, which is an important thing to consider. But you know the other issue is confounders or covariates. I should be broader than that. Not just confounders, but other extraneous factors that may inform the result. Those can be confounders or it can be -- effect modifiers, thought it can be mediators.

So ideally, this is the kind of study that one would want to see when discussing today's issue. What we know about the Columbia study is that chlorpyrifos, and I think that's well established, was measured once. But neurodevelopmental outcomes, as I just mentioned, were assessed several times. And the

covariates, as far as I can tell, were measured only once. Some of them only needed to be measured once. There is no reason to measure, say, gestational age twice, because that's -- it's a one-time thing. But things like home environment, things like certain socioeconomic or behavioral characteristics may change over time. I'm talking about -- and optimal design. And again, I'm not insisting that each and every study has to be held to that level of standard. But nevertheless, this is something we need to strive for.

So here's a question: Is the design available that involves several measures of exposure, outcome and time-dependent covariates better suited for risk assessment in this case? The answer may be no, the answer may be yes. But I think you should ask that question yourself.

Next issue is measurement error. I hate to -- this horse has been dead for a while now, but I have to add a bit of clarification. So we do know that epidemiological studies are subject to error. Outcome and exposure and confounders are subject to error. It's just an observation with epidemiology. This is inevitable. This is -- we have to live with that.

Now I can tell you that a cause of death is hugely misclassified. I can tell you that, even gender or sex is hugely misclassified with, let's say, in electronic medical records. We looked at these issues in a different study. It had nothing to do with this. In Kaiser Permanente they have wonderful data. And yet, males are sometimes misclassified as females, females as males.

So now the issue of nondifferential misclassification and the direction of the bias. And I'm not going to say anything controversial. Misclassification, that is non-differential, is towards the null when both the outcome and the exposure are binary and that's a very important issue. It will always happen towards the null. In a two-by-two table where sensitivity of exposure misclassification and specificity of exposure misclassification is exactly the same in people with different levels of outcome and vice versa. When sensitivity of exposure misclassification and specificity of -- I'm sorry -- of outcome misclassification and specificity of outcome in this classification is exactly the same in people with different levels of exposure.

Then, no argument, then the misclassification will be towards null. Now -- but that's not it. When you have -- where you beyond the two-by-two table -- and we already discussed that today that if you have several levels of exposure, all bets are off -- but even in a two-by-two table, in binary -- exposure binary outcome, if that error is not independent of things they're going to control for, in other words, other sources of error, or it's not independent of, say, selection, inter-study loss to follow up, all bets are off, again.

Moreover, you may have purely non-differential misclassification. With identical sensitivities and specificities across groups. But if it's a huge misclassification, the bias goes towards the null, reaches the null, it goes to the other side. It's called switchover bias. There's a paper by Chen et al, 2013 that wrote about it. And I can refer to the Wacholder in 1995 from NCI. We talk about it.

So now we kind of have to consider that all of those assumptions, which are theoretically possible, need to be met in order for us to, with confidence, say that we know which way the misclassification is going to be.

So I'm saying all that for a simple reason. There is no substitute for good data. And good data are hard to get. In observation with epidemiology in particular, it's very, very hard to do good epidemiological studies. And no study is -- ever should be considered perfect. I'm not aware of any single perfect epidemiology study.

Now what about exposure assessment issues? Again, going back to the little paper on short-lived chemicals, that lines up a few things sort of in the rows and then proposes -- and you don't have to necessarily follow that proposal -- to distinguished studies by level of evidence. Tier 1, Tier 2, Tier 3.

This is just a heat map and the colors are not very good. But imagine, green is a Tier 1, yellow is Tier 2 and then Tier 3 is orange or red or something like that. It's a heat map, has nothing to do with Columbia study. It's just a way of invitation, if you will, to think about exposure assessment through those terms.

Again, I don't want to talk about it at length. But let me just say that, for instance, specificity in the Columbia study should be given the

green light, of course, because you're measuring chlorpyrifos. That is the exposure of interest. It's better than a biomarker that may be nonspecific and that's certainly a strength.

On the other hand, I should say that one needs to take a pause to think about biological relevance of one-time exposure, if we're talking about the endpoint that's measured years down the road. And also, one needs to take a pause when thinking about the variability and how people can move across, say quartiles or, let alone, binary categories.

We don't know much, or at least, we couldn't find -- our group could not find data on the variability of chlorpyrifos. We do have a little bit of data from -- on the variability of TCPy. These are pregnant women with the measures done at different trimesters -- first, second and third trimester. I don't think I need to comment on this figure. I think you can -- you see it for yourself.

Now if one were to dichotomize this exposure based on one or the other time point, chances are people will end up in a different category, depending on the time.

Neurobehavioral testing, that's in the

outcome ascertainment, is another huge issue. I'm referring you to the study by Youngstrom et al. I don't want to spend a lot of time on it. But think about how these studies are done. These -- a lot of those tests and I'm not an expert, though I started in clinical pediatrics and practices for about 20 years before moving on to academia. I know that a lot of those tests are very hard to administer in a reproducible manner, particularly if it's not in a clinical setting.

I would probably refer you to that paper and stop there, other than to say, again, pose a few questions. You know, does a single cord blood exposure estimate reflect exposure of interest, which is prenatal exposure in this case. What is the extent of error associated with administration and interpretation of neurodevelopmental tests? Now there can be no differential or it can be differential, but there's a lot of assumptions that we just discussed that need to be made before one makes assumptions -- before my -- draws conclusions about the direction of association.

And then this internal issue. Newer development takes a long time. It starts during

gestation and continues in the early adulthood. To some extent it's almost unfair to think about the study as a study with an outcome. It's a process, really, that we're trying to capture and understand. And for that reason, I want you to think, what -- you know, visualize the timeline of those changes that maybe started before the data even became available, probably going to continue after the data are available. And then, put on a time clock. Imagine a time clock that exposure assessment and you know, think about it.

Analysis considerations -- and we're going back to the Amler et al. paper 2006. I don't want to spend a lot of time. Just two things, one is, again, I would like to commend the Columbia study investigators for collecting data on the outcome several times and doing repeated measures analysis. It's very important, because we're talking about a process, rather than a distinct outcome. And they've done that. They've done that, although I must say that a lot of discussion revolved around this difference at 36 months of age.

It is important, though, to look at the trajectories, which they've done as well. And what

they've done in analysis of repeated measures, well, the conclusion was that on the left, the two curves are, more or less, the same shape. They did it using mixed linear models. On the right, the two curves are different. But there are all kinds of additional questions that can be asked with repeated measures.

For example, how much daylight is there across the three-year period -- or two-year period, in this case -- between the two curves? We see the daylight in the 36 months. That's, for sure, undeniable and it's supported by statistical tests.

But what if we looked at those two curves at a continuum and looked how much difference is there between them? Maybe the answer will be different or it could be the same? Hard to say. But this will be -- I certainly would want to know.

Then the business of covariates. It really gets difficult because there's so many things that people put on their wish list as favorite covariates. And it's absolutely right that not all covariates are confounders. It's absolutely right that not all -- that the confounders should not be controlled for in the analysis.

But I mean, for instance, let's just

take gestational age. I think there was a discussion about it earlier. So one view is that the gestational age is a mediator. In other words, chlorpyrifos exposure causes and one industry employed causal reasoning here because if we're going to make decisions, we have to assume causation.

Exposure causes change in gestational age. And gestational age, in turn, causes change in neurodevelopment. And that's mediation, that's a classic. Arrows goes from A to B to C. In that case, perhaps, different types of analysis are needed. You should not control. You should do a different kind of analysis, structured regional modelings mediation analysis, to look at the direct and indirect effects, perhaps.

But then the other argument can be made just as well that gestational age is a marker of something that's going on in these women's lives that happens to be a behavioral factor, perhaps, a cohort effect.

The unmeasured thing that affects gestational age which, in turn, affects the outcome. And then that upstream variable affect is -- influences chlorpyrifos exposure. Then if you control

for gestational age you, in fact, are controlling indirectly for that unknown confounder. It's a theoretical argument. I'm not even going to tell you there's one thing, it's right to do this way versus that way. I've been around long enough to know that these -- a lot of it's a matter of judgment.

But nevertheless, you know, these are the types of things we struggle with every day, doing observational studies. And I think I'm inviting you to struggle with me on this, as well.

So if we did longitudinal analysis with repeated endpoint measures across the study period and if we somehow found a way to examine time-dependent confounding, how would that affect our conclusion? May have not. But I'd bet that results may change. Maybe in a different direction. They may -- become stronger. But at the end of the day we're trying to get to the association which reflects what's happening.

And finally, external consistency considerations. In observation of epidemiology and I don't think I'm being controversial in any way. Evidence, as I mentioned earlier, is built repetitively. There is a cumulative effect of

building evidence. And yes, we grapple with the inconsistent data. But when the signal is real, the signal eventually gets picked up and is not drowned in the noise.

There are various ways, very ingenious ways, to do it. But at the end of the day, in order to judge or draw conclusions about presence or absence of associations, causal associations, one is to compare apples to apples.

Studies that examine exposure in the same or similar way, examine the outcome in the same or similar way and did analysis in the same or very similar way. We don't have -- unfortunately, we don't have the luxury of having that body of literature, when we discussed this particular set of issues with chlorpyrifos.

I must say that we were very pleased to see a very recent paper. It may have come out a couple weeks ago, by Engel et al. 2016, that tried to do just that. They took four different studies, examine the associations for the same relevant biomarker. And I know it's DEP, it's not chlorpyrifos. So it will be much stronger if the biomarker of interest was chlorpyrifos and use the

same tests BSID at the same age, 24 months of age, and use the same ways of controlling for covariate. I must confess, I don't quite understand some of the finer point of the analysis. But that's not the issue. I think -- I mean, one option is since I don't quite understand, because how the interaction variables were handled. I just did the random effects analyses and which happen to be very similar to what Engel et al. reported.

This is two months. This is DEP. This is not chlorpyrifos, but it's the same task at the same age. Now you already know that Columbia study did not find anything at two months -- two years of age. I said, two months; I meant 24 months, at two years of age.

They did find daylight between the exposed and non-exposed at three years of age who would love to see data, similar data, at three years of age. I just -- I'm not aware if these -- such data are available. But it is in the spirit of comparing apples to apples, that I'm having this discussion.

Now what about the seven-year-old assessment with -- using WISC? You know, we've established that, that there was an association with

Working Memory in the Columbia study, using chlorpyrifos as exposure of interest.

We also know that Working Memory happens to be the only of the scales that showed virtually no association in the CHAMACOS study with DEP. On the other hand, CHAMACOS found an association with processing speed that was significant and then you hypothesize direction. In other words, it was an inverse association. But look at the processing speed in the Columbia study. It's null. If anything, it's opposite of hypothesized direction. But of course, one wouldn't conclude anything, based on a confidence interval like that. So it gives me pause. Again, the important issue, these are not apples and apples. This is DEP versus chlorpyrifos and the chlorpyrifos is a preferable measure.

Now as far as I can tell, in the paper by Huen et al, chlorpyrifos levels were measured in the cord blood. From memory, I think it's Table 3. And those levels actually turned out to be quite a bit higher than those in Columbia. Wouldn't it be nice to see the results for chlorpyrifos exposure in relation to neurodevelopment at seven years or six years of age in that other study? At least, then we would have a

luxury of comparing a few things, side by side. And maybe these data are available. I couldn't find them.

And finally, this is very recent, just came out and people already discussed that. That's an association between DEP again an imperfect biomarker with WISC at six years of age in the French study by Cartier et al. If anything, the association is in the opposite direction. It's not inversed. It's positive. It's not significant. I would not call this anything but null. But it is what it is. The numbers are simply a screenshot from their PDF.

So going back to consistency. Are the results of one study -- in this case, CCEH, nothing wrong with that study, it's a good study -- but it's one study. It's one cohort. There are multiple publications, of course, we know that. But nevertheless, a cohort is -- it's a single cohort -- sufficient for a formal risk assessment in regular decision-making? If you tell yourselves, well, that's enough and we can move on, more power to you. But at least think about it.

And I'm going back to the questions that I started with. Again, I'm not declaring and I'm not telling you what to do. But think of quality and

the quantity of the evidence. Think of hazard and then of those response and then think how that would lead you to PoD. Thank you very much. I'm ready to take questions.

DR. JAMES MCMANAMAN: Thank you. Questions for Dr. Goodman? Dr. Rohlman.

DR. DIANE ROHLMAN: Diane Rohlman. Just something to clarify is that one of the points you made was that the same test should be administered at each time. And that's an important component of replication and reproducibility. But I think we need to acknowledge that we're looking at changes across a lifespan of the child and therefore those tests are not appropriate to be administered, you know, at different ages, as well.

Also, a second point here is that, you know, the epidemiological studies you keep saying that they are subject to uncertainty. And I certainly agree with that statement, but I'd like to recognize that all studies have some level of uncertainty and that there are many factors that we can't control.

You know, and it is difficult to compare these epidemiological studies. But it's -- also and I believe this was a review by the EPA that

looked at the animal study and also came to the same conclusion that because of the different methods that were used, is also difficult to compare studies across those as well.

DR. MICHAEL GOODMAN: No disagreement there, other than to say that there is sort of a hierarchy of evidence quality. You know, I teach my students, I show them a totem pole. There is a clinical trial on top, followed by a prospective cohort study, perhaps, a nested-case control study, and then other studies go down. Even within those categories, there's a hierarchy. There are some studies that are better, some studies that are not as good.

So one thing I -- again, when I teach my students, I tell them this is one time when you don't collect votes from studies. You look carefully and take a hard look at them and see whether or not they contribute the same or different level of evidence, but no disagreement. I think we are on the same page here.

DR. JAMES MCMANAMAN: Dr. Sagiv.

DR. SHARON SAGIV: Sharon Sagiv from U.C. Berkeley. So thank you. That was an extremely

balanced and well-presented perspective. I really appreciated it and I appreciate the points you made.

I have a question just about your -- you know, what your feeling on this is. So we're in sort of a conundrum where we have one study. And I agree with you. That's a big conundrum, because it's only one study. And I agree with you that weight of evidence is really important here. And it would be great to have more studies of chlorpyrifos, but we don't.

What, in your opinion, you know, what do you think we should be doing here, I mean, in terms of the weight of evidence? How do we do it? Do we go to the studies of organophosphates? Just from your epidemiologic perspective, how do we mitigate that problem?

DR. MICHAEL GOODMAN: Can I be blunt? Don't do it. I don't think you can do it.

DR. SHARON SAGIV: Don't do what? Don't use the evidence from that study?

DR. MICHAEL GOODMAN: Don't -- well, I mean, wait. Get more evidence, get more -- try to get a little bit more certainty in your life, so then you can move on. This is a tough one. I sympathize.

DR. JAMES MCMANAMAN: Thank you. Any other questions? Thank you Dr. Goodman. So our next speaker is Virginia Ruiz from Farmworker Justice.

MS. VIRGINIA RUIZ: Good afternoon and thank you for the opportunity to address this advisory panel. My name is Virginia Ruiz and I am the director of Occupational and Environmental Health at Farmworker Justice. Farmworker Justice is a national nonprofit whose mission is to improve the living and working conditions of farmworkers in the United States.

Farmworker Justice joined other environmental and farmworker advocacy organizations in submitting written comments to the advisory panel, which Dr. Sass referenced in her remarks earlier today.

We support EPA's decision to develop an exposure limit for chlorpyrifos based on the neurodevelopmental harms to children. And we're especially concerned about the risks posed to farmworkers and their children from occupational exposures to chlorpyrifos. My remarks will address these occupational exposures.

EPA used the PBPK model to estimate the internal chlorpyrifos levels that would result from

low-end exposure scenarios for pesticide handlers who are women of childbearing age. EPA used its standard methodology to calculate handler exposures. And the agency's analysis resulted in margins of exposure of less than 100. In fact, none of the MOE's from this analysis comes close to 100. And many revealed risks that are well above acceptable risk levels. All the scenarios and time periods evaluated resulted in MOEs of concern.

And even though EPA used handler scenarios that have low occupational exposure potential, it's still found that these unacceptably -- it still found these unacceptably high risks to workers. Worker scenarios with higher exposures would subject workers to even greater risks, resulting in even lower MOEs.

In addition, EPA found these high risks despite a lot of assumptions about worker exposure period. In its occupational risk assessment, EPA makes assumptions that don't reflect real-world exposures for workers.

In the real world, label directions are not always followed, re-entry intervals are not always observed. Applicators don't have functioning personal

protective equipment and off-target drift happens.

In its risk assessment, EPA assumed an eight-hour workday and the availability of adequate cleaning, laundry and changing facilities for workers. Farmworkers frequently work more than eight hours a day, especially during peak harvest periods. According to a USDA report, 68 to 81 percent of hired farmworkers worked more than 40 hours per week.

Pesticide exposure continues as long as workers cannot change out of contaminated clothing and into clean clothing. It's unrealistic to assume daily showers immediately following exposure. Most workers don't have changing facilities at work and travel home in contaminated clothing. Most farmworkers earn wages that are well below the federal poverty level, live in overcrowded housing, which impedes their ability to bathe within a half an hour or an hour of returning home.

And although the EPA recommends in the Worker Protection Standard and the Pesticide Safety Training, that workers wash contaminated clothing in a machine separate from non-work clothing, many workers don't even own washing machines.

OSHA standards for farmworker housing

require only one laundry tray or tub for every 30 occupants. And some workers lack shower and laundry facilities to ensure that exposures, in fact, stop after the workday ends.

Despite these shortcomings, EPA's analysis confirms that for pregnant workers, current levels of exposure to chlorpyrifos are extremely unsafe. The risks of concern extend beyond food uses of chlorpyrifos to occupational exposures resulting from use on nursery plants, turf grass, Christmas trees and other non-food uses.

To protect workers and children all chlorpyrifos tolerances must be revoked and registrations canceled as soon as possible. Thank you.

MR. JAMES MCMANAMAN: Thank you. Any questions for this presenter? Okay. Thank you very much. The next presenter is Dr. Kunickis. Sorry if I mispronounced that -- I've been doing a lot of that lately -- from the U.S. Department of Agriculture, Office of Pest Management Policy.

DR. SHERYL KUNICKIS: Thank you very much. Good afternoon, Mr. Chairman, members of the Science Advisory Panel, Mr. Housenger, and my EPA

colleagues. Thank you for the opportunity to provide comments. My name is Sheryl Kunickis and I'm the director sat the U.S. Department of Agriculture's Office of Pest Management Policy.

Ensuring that all parts of U.S. agriculture have the crop protection tools necessary to produce a robust food supply is part of our mission at USDA. The recommendations you will make as part of this scientific advisory panel will have enormous impact on the world's food supply.

The shift EPA is suggesting from an established point of departure based on acetylcholinesterase inhibition to a new point of departure, based on the Columbia University epidemiological study, is momentous and cannot be understated.

We at USDA feel very strongly that this type of major change should only be made if the level of confidence in both the results of the Columbia study and EPA's approach for using these results is very high indeed.

Your recommendation for how EPA regulates chlorpyrifos will reach far beyond this one active ingredient and will affect not only how other

organophosphates are regulated, but many other broad classes of pesticides as well.

This is a major shift in pesticide regulation and there are major potential impacts. The cost to our food supply, to our economy, to taxpayers and to low-income Americans.

We at USDA stand ready to have further dialog and assist in the technical details of this issue. In particular, we believe further interagency discussions regarding the capabilities and limitations that the Columbia study -- of the epi study and of epi studies, in general, would be a useful dialog.

In addition, we believe a discussion is warranted regarding the limitations of assessing a single chemical in light of exposure to many different chemicals over a developmentally crucial multiyear period.

For over 40 years, the EAP, Office of Pesticide Programs, has been the gold standard across the world for entities that register and have oversight of pesticides. Because of EPA's, scientifically based, well-vetted and transparent approach, the agricultural community has had the confidence to use pesticides as part of the world-

class agricultural production system. We need that to continue.

Chlorpyrifos essentially is up first and is the subject of this meeting. So let me share the following, noting that it is but an example of the value of pesticides in general. Chlorpyrifos is a tool for farmers in managing a wide array of pest insects and is a critical part of integrated pest management, IPM programs, in well over 50 crops grown across the United States. This is due to its efficacy, broad spectrum activity against multiple pests and it fits with conservation biological control on crops such as citrus, tree fruit and cotton.

Changes to the process that result in losses of important crop protectants will likely have a significant negative impact on the production capabilities and economic stability of producers of many human and animal food crops.

This is true, particularly, where few or no efficacious insecticide alternatives are available. Where resistance management with limited alternatives is a concern, where Maximum Residue Limits or MRLs, for effective insecticide alternatives are not established for export markets and where crops

experience invasive and/or endemic pest outbreaks.

As I stated in the beginning, the implications for the outcome of these questions you're answering are profound with potential costs to our food supply, to our economy, to taxpayers, to low-income Americans. We'd like to work with you to further ensure that the very best science-based policy is the outcome. Thank you.

DR. JAMES MCMANAMAN: Thank you. Any questions for this presenter? Dr. Jett.

DR. DAVID JETT: Thank you for that. This is Dave Jett, NIH. I was just wondering; you were talking about potential alternatives --

DR. SHERYL KUNICKIS: Yes, sir.

DR. DAVID JETT: -- to chlorpyrifos. And you mentioned that there's maybe no OPs that have the broad spectrum and efficacy as chlorpyrifos. Are there -- have you thought about different mixtures that could potentially be used to try to, you know, have a broader coverage?

DR. SHERYL KUNICKIS: Mixtures is a whole other set of a concern. There's a handful of pesticides, depending on the crop that's used and the pests that's being treated and the location of where

it's being treated. It will be dependent on what pesticide can be used.

There's some things that can be mixed. You want to mix different modes of action. It just depends what you're trying to accomplish. But in some crops there are no alternatives. Some crops there are other alternatives or they have more alternatives. But there are some that do not have alternatives to chlorpyrifos.

DR. JAMES MCMANAMAN: Yes, Dr. Pessah.

DR. ISAAC PESSAH: Isaac Pessah. I was just wondering, you had mentioned several detrimental outcomes from, I assume it's a ban of chlorpyrifos. Have you put numbers to the issues you've raised and you mentioned that it was profound and dramatic but --

DR. SHERYL KUNICKIS: It is.

DR. ISAAC PESSAH: -- are there numbers associated with, let's say, end-product costs?

DR. SHERYL KUNICKIS: Well, I can tell you this. If you look in the docket, when there was a proposal to revoke tolerances for chlorpyrifos, there's a number of statements from different countries. And I will point out to you that Canada responded and they're very concerned about this. They

say, for them, the issue will be -- the impact will be $50 billion in trade. That's with Canada alone.

I've seen a chart and I wish I could remember where it was from, but it listed out all the different countries that have commented on the impacts that it would have. Our Office of the Chief Economist has been looking into it. We're not there yet, but we do recognize that this is going to have tremendous impacts to U.S. agriculture if this does, indeed, occur. And that's why we're very interested in making sure that the process is at the gold standard that we know EPA to have.

DR. JAMES MCMANAMAN: Dr. Rohlman.

DR. DIANE ROHLMAN: Diane Rohlman. Just to clarify that the concern is the export of products from the U.S. and the tolerance levels. If you could clarify that or?

DR. SHERYL KUNICKIS: So when we trade between countries, we have established MRLs. And some countries -- or if we don't, some countries don't have them, so we have an issue with the import and export, if one country has them and another country doesn't.

So if we have to go to alternatives, we may not have alternatives that have already

established MRLs for being able to have that for trade. So the chlorpyrifos is an older chemical and those are well-established MRLs. So that would be part of the issue.

DR. ISAAC PESSAH: Sort of as a follow-on, are there other countries that have lower MRLs than we do?

DR. SHERYL KUNICKIS: Oh, gosh, that's -- I would defer to -- that's -- I don't know. There's so many countries I would assume that there are other countries.

DR. ISAAC PESSAH: Don't concern yourself, because it's not a scientific question.

DR. SHERYL KUNICKIS: Right. Okay. So but I will say that there are countries that probably do and there's countries that have no -- they don't use chlorpyrifos. It's probably a range.

DR. JAMES MCMANAMAN: Yes, Dr. Rohlman.

DR. DIANE ROHLMAN: So Diane Rohlman. I'm not sure if this is a scientific question or not, but we won't know until I ask it. So you currently --

DR. JAMES MCMANAMAN: It has to be repeated, of course.

DR. DIANE ROHLMAN: So in your

statement, you said that there are 50 crops currently where chlorpyrifos is registered for use. Could you go back in time and how many were registered, say, in 2000?

DR. SHERYL KUNICKIS: We could. Yes, ma'am.

DR. DIANE ROHLMAN: Okay. You don't know that --

DR. SHERYL KUNICKIS: Offhand, in 2000? I couldn't tell you that offhand. But it's used nationwide on, like I said, 50 crops, but it's used all across the U.S.

DR. DIANE ROHLMAN: Has the number of crops that's registered increased or decreased since 2000?

DR. SHERYL KUNICKIS: Since 2000, the number of crops, I couldn't speak to how many crops. But the fact that the residential uses were removed, I would -- that's not a crop. But the use pattern has probably decreased. But chlorpyrifos, is a powerful -- one of the powerhouse insecticides used nationwide because it is so effective.

DR. JAMES MCMANAMAN: Other questions? Okay. Thank you very much.

DR. SHERYL KUNICKIS: Thank you.

DR. JAMES MCMANAMAN: So at this point, I think before Syngenta presents, we'll take a 15-minute break and come back.

(Brief recess.)

DR. JAMES MCMANAMAN: Get started again. So what we're going to do -- this is a co-presentation by Syngenta and Exponent and we're going to reorganize the presentations just a little bit to accommodate somebody's travel needs. So the next presenter will be Ellen Chang, Dr. Ellen Chang from Exponent, Incorporated.

DR. ELLEN CHANG: Thanks very much. So my name is Ellen Chang. I'm an epidemiologist. I am employed at Exponent and I'm here talking on behalf of Syngenta. I also have a faculty appointment at the Stanford University School of Medicine where I do academic epidemiologic research.

So I can just tell you a little bit about what I'll be discussing. I'll be here talking consistent with EPA's and other groups' efforts to integrate epidemiological and toxicological data to reach science-based conclusions about causation. I'll be discussing that in line with the Bradford Hill

guidelines which are often used in epidemiology. They've been used for several decades.

So most of you probably are familiar with the Bradford Hill guidelines, the nine guidelines that are listed here. I'm going to apologize in advance. I'm going to be going fairly quickly through the nine guidelines. And I don't need to use them at all in a sort of checklist fashion. It's not like a yes, no, it meets these criteria or not.

But due to the time limitations of this presentation, I'll be going through them fairly quickly. I would love to have a longer discussion. And indeed, we have, Rick Reiss and I and some others have a paper that's mentioned up there that's more than 100 pages long where we discuss the balance of epidemiologic evidence with respect to organophosphate insecticides and these outcomes. But here I'll be flying through a little bit quickly.

So the first guideline when considering the balance of epidemiologic evidence is the strength of the association. And so I will be basing my evaluation of the overall epidemiologic evidence for chlorpyrifos with respect to neurodevelopment on 11 total epidemiologic studies that are relevant.

So as we've discussed before, only the Columbia cohort study measured chlorpyrifos directly. But the other ones also do provide information on this causal question, including seven prospective birth cohorts and four cross-sectional studies that measured TCPy which a nonspecific measure of chlorpyrifos exposure or the diethyl phosphates which are an even less specific measure of the exposure.

So overall, the strength of the association in general has not been more -- it's not been stronger than the strength of associations, for example, with certain established confounders or potential -- a measure for confounders or with the strength of potential bias.

So in general, the strength of the observed associations with IQ, for instance, has not been sufficient to exclude confounding or bias as a potential explanation for the associations observed.

The next guideline suggested by Bradford Hill is consistency. So we've discussed this a little bit earlier today. These charts here show results from prospective cohort studies that measured the same outcomes. So those are the same across these studies.

But the exposures are different in the studies that are shown here. So this is a little bit of an apples-to-oranges comparison, although you would expect if there's a strong toxic effect of chlorpyrifos, at least you'll see the same direction of association across different birth cohort studies and you can see that there's quite a scatter of results for the Bayley infant scales at 12 months and 24 months across these three cohorts, the Columbia study, the Mt. Sinai and the CHAMACOS cohort study.

And likewise, with respect to intelligence measures in children, you can see that the results are quite heterogeneous as are the methods again. And so this is a limitation of the body of evidence in terms of the fact that different exposures are used and then the results themselves are not entirely consistent.

The next Bradford Hill guideline is specificity which is not a very strong requirement, I would say, when it comes to chronic diseases. But here we have several studies that have measured nonspecific metabolites with respect to chlorpyrifos exposure and there are numerous other risk factors for neurodevelopmental outcomes that are potential

confounders. So the observations of associations are not specific to either the exposure or the outcome as issue here.

Next issue is temporality which is in the perspective birth cohort studies, one reason why they're stronger than other epidemiologic studies is that the exposures are measured in advance of the outcomes.

However, in these studies we do have persisting concerns about whether the single exposure measure is sufficient to capture long-term exposure to chlorpyrifos. Also, it's unclear whether it is measured at the appropriate time to capture the window of susceptibility to these exposures.

The next guideline is biological gradient, that is whether there is an exposure response trend established. So across the 11 epidemiologic studies that I mentioned, the majority of them actually did not do formal tests for trends. In general, they often assumed that there's linear or log linear relationship between the exposure and the outcome.

In the Columbia study, there were statistically significant linear trends detected for

some outcomes. But then in other studies that did test the trends, there was not a consistent monotonic trend observed. So there's no biological gradient that's clearly established across these epidemiologic studies.

In terms of whether it's biologically plausible for chlorpyrifos to have neurodevelopmental adverse effects at these levels, it's unclear. There's no established plausible biological mechanism in the absence of acetylcholinesterase inhibition. So it's not that it's implausible, it's that there's no established mechanism as of yet.

In terms of whether the human epidemiologic studies are coherent with the animal toxicological studies, here again, there's a disconnect in terms of the fact that no animal neurotoxicity has been observed at exposure levels below, which there's no inhibition of acetylcholinesterase in blood and RBC.

In terms of experimental evidence in humans, there's no true experimental data to evaluate the neurodevelopmental effects of chlorpyrifos. There's some indirect evidence, for example, from the Columbia study that perhaps there are these attenuated

associations after the residential phase-out of chlorpyrifos use, so that could be considered sort of quasi-experimental evidence.

But I think, as discussed earlier, there are other factors that have changed over time, as well as chlorpyrifos exposure. So this is pretty weak evidence. I wouldn't call it strictly experimental, but I won't cross it out up there.

And then analogy is the final Bradford Hill guideline. And there are analogies that supports a causal conclusion as well as analogies against a causal conclusion.

So overall, you can see that if you take standard guidelines for interpreting the overall balance of the epidemiologic evidence, I think there are a lot of remaining questions that need to be answered.

I wouldn't say that we can absolutely reject a causal conclusion, but that the persisting questions give us insufficient evidence to establish a causal relationship between chlorpyrifos and these neurodevelopmental outcomes and that's an important consideration to bear in mind, in terms of whether it's the appropriate time to be setting a point of

departure. And I guess we could pause now for questions, if anyone has them.

DR. JAMES MCMANAMAN: Do we have questions for this presenter? Yes, Marion.

DR. MARION EHRICH: Okay. Marion Ehrich, Virginia Tech. You say the evidence is insufficient for causation. Did you analyze it for -- you think there's an association or did you just cut it off at causation? What were you looking for? Because there's ways of using epidemiological evidence that are not necessarily causation.

DR. ELLEN CHANG: Sure. So here I'm talking about causation. Clearly, there have been some associations detected in the literature. Although most epidemiologists, I think, in an academic setting that I would talk to would want to see replication of associations, even to say that there's an association established.

And I would say that, on the basis of a single study that looked specifically at chlorpyrifos that an association, even in this case, is not well-established.

DR. JAMES MCMANAMAN: Yes. Dr. Sagiv?

DR. SHARON SAGIV: I'm Sharon Sagiv

from U.C. Berkeley. I guess on that list there are few I'd push back on. I think the temporality thing that you crossed out, I think I agree with you that one measure may not represent full pregnancy, I mean, certainly not postnatal exposure. But I think the temporality assumption is that exposure comes before the outcome. And I think technically that's met -- I mean, I don't know.

It's -- I'm not such a big fan of these Bradford Hill criteria, to be honest. But if we're going to go through them one by one, I would push back on that one a little bit. The other one is on slide -- - can I refer you back to a slide?

DR. SHARON SAGIV: Sure.

DR. ELLEN CHANG: On consistency. I think it's before this. We can go back to Slide number 8. I think that's it. The one with the -- no, the one after that.

DR. SHARON SAGIV: Yes.

DR. ELLEN CHANG: Sorry. Following that. I mean, they're both are kind of going down. I don't know. I would push back on that one, too, and that's a judgment call. If you are a significant -- a statistical significance person who only looks at

whether or not the null is within the confidence interval, then maybe you have a leg to stand on there, but I don't subscribe to that either. And I think that, especially when you're looking across a lot of different studies, if you're seeing most of the dots, to the left of the null, I don't know, I would push back on that one, too.

DR. ELLEN CHANG: So I would say, with respect to temporality, I agree that in perspective birth cohort studies, there's no question that the exposure is measured for the outcome. And so, in those cases, the direction of temporality is clear. But I think that they're -- temporality is not such a simple question.

DR. SHARON SAGIV: Right.

DR. ELLEN CHANG: And so, as you mentioned, there are other concerns that need to be taken into account when you're evaluating temporality. But -- and again, I don't like using these as a checkbox sort of criterion list.

With respect to consistency, I think it is important to take the confidence interval into account. Again, I'm not going to say statistically significant or not statistically insignificant is how

I decide if something is consistent.

DR. SHARON SAGIV: So the weights of the confidence intervals you're referring to?

DR. ELLEN CHANG: Yeah. I think that in these cases, we can't assume that if the studies were larger that the point estimates would be the same. That assumes the absence of bias in these studies which we can't assume. And so we don't know exactly what would happen if we tightened up those confidence intervals.

And then for a couple of the outcomes, the French study, which did not evaluate all of the outcomes here, found pretty different results. And if they -- they did not report the results for processing speed for perceptual reasoning, I believe, and then for Full-Scale IQ. We don't know what those would have shown.

I think in the charts for which you see the verbal score, which is the middle one and the memory, the Working Memory, the two where the French study actually contributes, then you see less consistency. And so if there's one study that can sort of change how you view the overall consistency of the evidence, then I feel that it's not very strong.

DR. SHARON SAGIV: Well, I mean, I think it's not very strong because you're looking at different exposures here.

DR. ELLEN CHANG: There's that, too.

DR. SHARON SAGIV: So that alone. But I would say, you know, I haven't seen a lot of groups of studies that have shown this much consistency. This looks pretty consistent, to me. But that's just me.

And then the -- one other thing I would point to is the dose-response.

DR. ELLEN CHANG: Mm-hm.

DR. SHARON SAGIV: And p for trends are important for looking at linear dose-response, but they assume that there's a linear dose-response. And if you don't have a linear dose-response, the p for trend may show non-statistical significance when there may be a threshold or there may be a slight curve or linear association. So I would note that I think that looking at the splines which is what the Columbia group did, is very appropriate, rather than just looking at a p for trend, which basically boils it down to a linear dose-response.

DR. ELLEN CHANG: Yeah. Here,

actually, there weren't a lot of studies that did a p for trend. And so when I considered whether they looked at a biological gradient, it was actually not just testing p for trend, but whether, for example, they categorized into quartiles and then looked at whether the relative risk estimates increased across quartiles. And then also looking at spline. So yeah, I agree that it takes more than just a p for linear trend.

DR. SHARON SAGIV: Yeah. And also that if you don't have a consistent increase across quartiles, it could mean that there is a threshold effect.

DR. ELLEN CHANG: It could.

DR. SHARON SAGIV: So that's not -- doesn't rule out an association.

DR. ELLEN CHANG: That's right. Although in those cases, often the PE for linear trend will still be statistically significant.

DR. SHARON SAGIV: Thank you.

DR. DAVID JETT: Okay. I think you have a flight to catch, so I'll just make this more of a comment. In terms of pushback, I would just say that, for those of us who've been looking at this for

a while, I think your assertion that there's no evidence. And you know, the evidence -- you can critically review the evidence, but to say there's no evidence of noncholinesterase mechanisms for neurotoxicity or toxicity, both in vitro and in vivo, I don't think is quite right.

DR. ELLEN CHANG: The plausibility one?

DR. DAVID JETT: No, I think it was coherence, I think.

DR. JAMES MCMANAMAN:

DR. ELLEN CHANG: Coherence.

DR. JAMES MCMANAMAN: I think you said that there were no animal studies indicating that it was lower.

DR. DAVID JETT: Yeah, I'd push back a little bit on that. I --

DR. ELLEN CHANG: Right. I think I would say established.

DR. JAMES MCMANAMAN: Okay. Okay. So Dr. Rohlman.

DR. DIANE ROHLMAN: Good comments. I -- good discussion. I think just a point to make about your temporality, too, about new information of long-term exposure is really -- specifically, the Columbia

cohort is not looking at long-term exposure. They're looking at prenatal exposure.

So you know, the goal is not to look long-term. In fact, they've -- use various reasons we've discussed about that. So you need to emphasize that at least that study is focused on prenatal exposure which has long-term effects.

DR. ELLEN CHANG: Yeah. I guess I would question whether the cord blood necessarily captures all prenatal exposure.

DR. JAMES MCMANAMAN: Dr. Pessah.

DR. ISAAC PESSAH: I just wanted to emphasize what Dr. Jett said. I think there are -- well, I would ask you, in making that statement, did you review the literature for behavioral outcomes in mice or rats that couldn't correlate those changes with cholinesterase, whether they be brain, blood or otherwise?

DR. ELLEN CHANG: I personally did not review the literature. I relied on other reviews that have been conducted and I looked at their summaries.

DR. JAMES MCMANAMAN: Dr. Popendorf?

DR. WILLIAM POPENDORF: Hi. Will Popendorf. Just a question on Slide 14 that you had

up earlier, just what do you -- what are you really saying there. For instance, Mt. Sinai, no monotonic trends by DEP, parenthesis (not tested)? Several "not tested." So what do are you saying?

DR. ELLEN CHANG: Yeah. So here they looked at the relationship between categorized exposure. So they -- I think it was either tertiles or quartiles of DEPs and then they looked at this with respect to the outcome, which here was a neurodevelopmental outcome. And they did not see that the risk of the outcome increased monotonically across increasing categories of exposure. So they didn't statistically test for it, which is why I put "not tested." It's just when you visually look at the relative risks, they don't increase with increasing exposure categories.

DR. WILLIAM POPENDORF: So if you don't see it, you don't test for it, basically. That's what you're saying that's what they did, right?

DR. ELLEN CHANG: I'm not going to say why they didn't test for it, but --

DR. WILLIAM POPENDORF: Well, okay. Good point.

DR. JAMES MCMANAMAN: So you making a

point up here that there is a linearity between the -- the Columbia study between chlorpyrifos and what was it, Full-Scale IQ. So how do you get a linearity trend when most of the data points, in terms of the concentration, are below the level of quantitation? I don't understand that.

DR. ELLEN CHANG: I think it's that scatter plot has been shown a number of times where there was quite a bit of scatter. And I think, you're right, the vast majority of the exposure measurements are in that very low range. It's just statistically when they ran a linear regression they detected a statistically significant trend. But this is something that has come up that, you know, many investigators out there would like to have access to the raw data so that they could, I think, examine the robustness of that trend.

DR. JAMES MCMANAMAN: Yeah. So in your view, if most the data in that linear trend is below the level of quantitation, is that a valid -- would that invalidate that portion of the study or does it -- or is there still value in it?

DR. ELLEN CHANG: I wouldn't want to say it's invalid. I think it needs to be questioned

and examined more with regard to how sensitive it is to excluding the non-detectable levels.

DR. JAMES MCMANAMAN: Okay. Thank you. Other questions? All right. Good luck on your flight.

DR. ELLEN CHANG: Thanks.

DR. JAMES MCMANAMAN: Next presenter is Dr. Hinderliter from Syngenta.

DR. PAUL HINDERLITER: All right. So I recognize that we're running quite long on time here, so I will endeavor to do this as quickly as I can. So I am not an epidemiologist. I am a pharmacokinetic modeler by training and that's what we're going to focus on in the next few minutes. So bear with me here. This is going to be quite a different talk than we've heard from any of the other public comments today. So we do have detailed written comments on the docket. You should have all received them.

For a matter of background, I was at the Pacific Northwest National Lab for many years. During that time, we had a contract with Dow AgroSciences and I was involved from about 2007 to 2011, through the 2011 model SAP and the development of the PBPK model. I am now not currently affiliated

with Dow AgroSciences or any of them. I am at Syngenta.

So our comments here today are based on the methodology for including pharmacokinetics and pharmacokinetic models in the applications of the biomarkers to the quantitative risk assessment.

So having said that, my comments are going to be more generic to the methodologies than to chlorpyrifos itself.

So as the EPA has acknowledged, there's been a big change in what's actually going on in the risk assessments over the last few years. The 2014 assessment used acetylcholinesterase. The current assessment uses a nonspecific neurodevelopmental endpoint.

The pharmacokinetic model that underpins both of the assessments has not changed. But the application of it has, as I will demonstrate here, has changed quite a bit. So there's a lot of implications for these changes that haven't really been covered in the current analyses. And I would say that given all of the things that I'm going to show, that we don't have a tool that's sufficient for doing a quantitative risk assessment at this point in time.

So the PBPK model, it was developed, as most good models are, across an entirety of a dataset. So there's chlorpyrifos, it's metabolized to the oxone. There's TCP and then there's a pharmacodynamic component to the model which we've shown in the EPA's diagram where there's inhibition of cholinesterase in plasma blood, RBCs and then in target tissues of brain and diaphragm.

And what's happened here is that all of that dataset goes in comprehensively into the model development. The application currently for the model, however, now focuses on parent chlorpyrifos. One piece out of the entire string of data that went into this model development and arguably one of the weaker sets of the data because it's apparent that disappears fairly rapidly. And when you fit the entirety of the model, you don't focus on just one thing. You try to fit the entire unit. So I've got a graph coming up that'll demonstrate hopefully, fairly clearly, as to why this covers -- why this is such an important change.

If you were to just work on chlorpyrifos parent, you'd probably need to re-parameterize this model and I don't know what that

would look like. So predictions that are based on this model might not have any bearing on what a chlorpyrifos optimized model would be. And the prior validation exercises don't cover that.

So here's a set of some data that was used in the model parameterization. The colors are a little difficult to see, unfortunately on the screen. You have them on your printouts. Each of the colors represent a different dose level. So the greens at the top are -- the points are blood levels are measured in chlorpyrifos, following an oral dose to a rat. The green line is a simulation of that data. So there's five dose levels in this dataset. There's less data, as you get down into the lower reaches and you start to run towards your limits of quantitation and detection.

Let's point at couple of things on this graph then. So this is just chlorpyrifos. It's an adequate fit of the data, if your goal is to fit acetylcholinesterase inhibition as a pharmacodynamics endpoint.

For fitting pharmacokinetics of parent chlorpyrifos, it lacks a whole lot of detail on it. So if you look at the two red arrows I've drawn there

overlaying on the left side, for the second -- and actually, the two dose levels, the peak concentrations, they're close to the right magnitude. They're often timed by several hours. The lower dose level, which is actually of greater import, because we're extrapolating this, as you'll see. Quite a bit below this model dataset doesn't fit at all. It's half an order of magnitude off.

If you look at the time points that have the large red bracket there on the right-hand side, those are our 12-hour time points. The last measured chlorpyrifos samples in these bloods. They measured out further, I believe, but they didn't detect any. And those aren't also very well fit by the model. You can see that the green curve undershoots, that the blue curve overshoots the yellowish curve, I think it is, overshoots it quite a bit. And then there's this behavior to the right-hand side that isn't parameterized. We don't know what happened out there. It's hypothesized that this is potentially correct, because the rest of the dataset fits. But that was over an entire set of data which we're now neglecting in the current assessment.

In addition to that, as I mentioned,

when you get off to the further time points and into the lower concentration ranges, you're getting beyond where the model has actually been validated. The experimental doses, they're -- and you know, 1 to 1000 milligrams per kilogram. They're obviously higher than we're talking about here. And that's not necessarily a bad thing. You extrapolate PBPK models all the time. That's one of their utilities.

But I would argue that their best utility is cross-species extrapolation, cross-dose route, cumulative dose routes. Extrapolating to lower doses is one of the weaker things that happens, particularly in this application where you're going down in order of magnitude or two, you're going down six or eight orders of magnitude. It's a huge difference.

And something was made in the EPA presentations that they're not using the model to derive the point of departure. That is technically true. They're taking the point of departure off of the benchmark dose fitting of the blood levels and the -- whatever the pharmacodynamic endpoint study was.

But they do use -- turn right around and use the model in the calculation of the RFDN and a

margin exposure. So it's used in the same concentration level. So they didn't use it on the point of departure, but it is used in the assessment.

So here's the same data put on the pg/g concentration scale. So the data points up at the top are the same ones that I've shown on the graph a few minutes ago. The curves down at the bottom are simulations I took from the model code that was presented in the docket. So the greenish line that's labeled as the 99th percentile is one of the simulations that were run out of the EPA's presented model for human at the 99th percentile. It goes above the LOD for a little while and then drops back down by about 12 hours.

If you were to take a single dose or some terminal dose, you get this sort of pseudo-steady state that they've made great -- put great import on and we'll see why in a minute. That's even down a couple of orders below the LOD and six or eight below where your experimental data are.

So the model isn't validated in this range. And I'll show you in a second on another graph why that's such a problem. So the model predicts this behavior that we've seen these saw tooth patterns a

lot of times where it drops down, you get another dose, drops down and it goes, you know, ad infinitum.

There's a different behavior, though, that happens below the levels where that rodent data that the model was calibrated on. And it's this long-tailed path life that allows you to actually have a pseudo persistent compound which chlorpyrifos is not, but it gives you that. And there is data out there in rats from an older study from Smith and a human poisoning case where there is a longer half life. It's probably due to something, you know, it's got a high fat partition, so it's probably some sort of sequestration in the fat. But this isn't anything that was ever demonstrated in the model, so we don't actually know whether or not the model does this. It's just sort of consistent with it, which is a pretty weak argument.

For the acetylcholinesterase assessments that were done 2014 and prior, it's not as much of a problem because they fit in much higher concentration ranges. So you're moving to an endpoint that is less accurate and less precise. I'll leave it up to others to decide which is the more appropriate one. But you're moving into areas where you don't

know pharmacokinetically what's actually happening.

So here's a saw tooth. It's -- you know, this is one of the ones I think I took out of a water exposure, which is why it doesn't have quite the same decline that you're seeing from the home, but you get this repeated exposure.

If you turn off the exposure, you get the orange curve, which goes down and has a rapid drop for about 12 hours or so and then there's this long half-life that goes on. And if you take it out, you'd expect to see that there ought to be some folks that, if they've got this long half-life and that, you know, it's monthly or even sub monthly, when you talk about the worker exposures that the farmworkers may not have quite as much protection, you ought to see people that have higher blood levels and that have been observed.

My point here today, though, is that this data is below where you actually know what's going on. So you've -- here you've got this model that predicts the saw tooths. And there's some data in this range. Then it declines at this different behavior.

Well, it could be any one of these dotted lines and they're not terribly inconsistent

with the observed experimental data on longer half lives and they're all well below the limit of detection for these things, so you don't know what's going on. So your dose metric that you're taking for the cord blood has huge amounts of uncertainty, you know, in its timing and other things that was mentioned before, but just in terms of where the model actually says the thing is. You don't know.

So -- and this question has come up a couple of times. I was asked by the panel of the EPA that -- what does this actually mean in terms of a mode of action. So acetylcholinesterase we have a fairly good idea of what happens. It's -- the dynamic response is quite a bit slower than the kinetic response. The kinetic response happens over a few hours and then there's this long tail. The pharmacodynamic response to the acetylcholinesterase has a much longer half life. So if you get a dose today and dose tomorrow, a dose the next day, you're going to start to see this depression in the acetylcholinesterase, but you need a cessation of exposure for it actually come back up to its baseline levels. So it makes a difference if you've gotten exposure one day a month and then another month, as

opposed to day 1, 2, 3.

But when you move to a nonspecific endpoint you don't know what the behavior of this thing actually is. Is it something that is a peak effect? Does it matter if you go over it for one day? Does it matter if you stay over your exposure for a longer period of time? Does it -- what exactly does the shape of the pharmacodynamic response look like? And this is different from all of the work that's been done to examine the exposure. And they may have a fairly good, you know, from all of the worker SOPs and residential things. There may be a fairly robust estimate of what the exposures look like. That doesn't mean that you know what the dose metrics should be and what the response would actually be. That just means that you can explain what some of the exposures look like. That's different from actually knowing what that exposure does.

And the other wrinkle in that is that most -- so PBPK isn't biomonitoring, it's a great idea. It's a tool that isn't quite ready, though, because what you've done -- most of the successful illustration of PBPKs in biomonitoring are persistent chemicals, things where you have a longer, you know, a

longer reservoir and longer measured samples, you know what's going on over time.

The chlorpyrifos PBPK model, there is some -- it was mentioned by one of the EPA folks, there is a repeat study that was simulated by this. But when I went back and looked at it last night, they don't actually simulate the chlorpyrifos levels over the entirety of the sub chronic feeding study, you notice they don't simulate the chlorpyrifos levels. They simulate acetylcholinesterase inhibition. So that doesn't mean that you've actually validated the model over the range of what you're looking and the endpoint that you're looking.

Someone asked -- also mentioned yesterday the sensitivity analysis would be a fantastic idea for this because we don't know what's actually important in this. And that was the subject of a lot of the work in 2011 was what does population variability look like.

So in explaining acetylcholinesterase, we had identified the metabolizing enzymes and then the acetylcholinesterase variation. You can go and look and see what the variation in the population is in these particular key things that were identified by

a sensitivity analysis and see how the population variability might play into this response.

I'm not entirely sure how you do that on a nonspecific endpoint. Is it the metabolism of the chlorpyrifos or not? I don't know, because we don't have a clear dose metric on this.

So having said that, I think the agency has been asked to do an undoable task at this point, which is to take a non-quantitative endpoint in the epidemiology study, take a quantitative model which was designed for a different purpose, and try to fuse them together.

If we were talking about a different chemical under a different scenario, it might be something that works. But under the situations that we have here, it doesn't come together quantitatively and that's sort of the magic word that ought to wake you up in the middle of the night thinking about this is that this is a tool for quantitative risk assessment. So until you can do the quantitative parts along all the way through here and all of the wrinkles about limits of detection and mechanisms and all of these things, they're not just trivial things where you can take one tool, throw it against another

one and have something actually come together.

With that, I hope I -- I talked a little longer than I intended. Sorry. I'll take any questions that there are.

DR. JAMES MCMANAMAN: Thank you. Any questions for -- yes, Dr. Hayton.

DR. WILLIAM HAYTON: Yes, I have one. The issue paper makes quite a lot out of the five-day --

DR. PAUL HINDERLITER. Yes.

DR. WILLIAM HAYTON: -- log linear phase for the elimination of chlorpyrifos. And it seems to be, to me, what you're saying is that that is a very soft number. They also have these 10-hour post-peak and 24-hour post peak. And there's quite a bit of import put on that. Could you comment on that?

DR. PAUL HINDERLITER: Yeah. So the model does -- that's what the model predicts. So if your presumption is that the model is adequate, then you run the simulations and it says at 10 hours you get this, at 24 hours you get that. That's the way PBPK models typically get used.

The point I'm making is that longer, that 120-hour half life isn't something that was ever

parameterized into the model. So when we developed this -- and it started long before I got to PNNL, but with Chuck Timchalk's work, the focus had always been on acetylcholinesterase. So we were looking at a typical pharmacodynamic endpoint, not at the behavior of the parent chlorpyrifos.

So there were some slides in the 2011 SAP variability presentations where we showed that the rodent doses were in this range and you could explain the variability and you draw it down to the human and there's some -- you know, it's in this range. But we never actually tried to quantitate it because it was beyond the range of where we thought the model was valid. So we just said, rats, humans, that's a big difference. But now they're moving into actually using it for a quantitative assessment and that's not -- we don't consider that to be valid. Dr. Sagiv.

DR. SHARON SAGIV: Sharon Sagiv, U.C. Berkeley. Were you done?

DR. JAMES MCMANAMAN: You're welcome.

DR. PAUL HINDERLITER: Sorry.

DR. SHARON SAGIV: I'm sorry I interrupted that very important comment. So I'm not a toxicologist or a risk assessor.

DR. PAUL HINDERLITER: Neither am I.

DR. SHARON SAGIV: So this might sound like an ignorant question. But in epidemiology, it's often the case that we see effects of a toxin exposure on an outcome without a mode of action and we speculate on what it might be. And we just don't have maybe the data or the animal model or whatever it takes to isolate a specific mechanism.

Are we saying with this that we shouldn't be basing any risk assessment on exposure outcome associations that don't have a specific mode of action?

DR. PAUL HINDERLITER: No. No, I'm not saying that at all. Actually, we have several examples of PBPK models that don't have a clear mode of action, but work has gone into examining whether or not it seems to be a cumulative effect or a peak effect. So if you can at least get an idea of what this sort of behavior looks like, then you can do something with it.

So it's not that you have to have a specific pharmacodynamic model, but in this particular case, rolling it back to the point where it is now, I don't think any -- it doesn't sound like from the

discussion I have heard so far, anybody really has a clear idea of what a dosimeter would be on this. And that's why I keep coming back to quantitation is that that's fine for an association in a weight of evidence and those sorts of things.

But when you're talking about having a quantitative number for calculating an RfD or a margin of exposure, that's where you actually need a defined dose metric.

DR. SHARON SAGIV: And I would point to a lot of other chemicals, lead being just a legacy chemical, where it's not clear when and at -- if it's -- they don't know if it's chronic or acute. They don't know when the hit is, but they know that lead affects intellectual development. So that's clear. And I don't know that we would be able to develop a PBPK model for lead. But there isn't. All right. Okay. Whatever.

I know from the EPI -- I mean, from the EPI studies I know they don't know if it's a multiple hit model, a one-hit model, a chronic model. I don't think they have isolated the exact time when lead is most harmful in development in neurodevelopment. But we know that the effects are there.

So I guess it's troublesome to know that we, in the absence of that exact data we can't set some standards here, is what I'm saying.

DR. JAMES MCMANAMAN: Other questions? Dr. Rohlman.

DR. DIANE ROHLMAN: Go ahead.

DR. JEFFREY FISHER: So could you go back to the --

DR. JAMES MCMANAMAN: This is Dr. Fisher.

DR. JEFFREY FISHER: Yes, that's Jeff Fisher.

DR. JAMES MCMANAMAN: Not Dr. Rohlman.

DR. JEFFREY FISHER: Could you back to the slide with the simulations showing, I guess, rat data at the beginning?

DR. PAUL HINDERLITER: I think I -- this one?

DR. JEFFREY FISHER: Yeah, a rat. So what model is being used here? I mean, it's not the EPA human model.

DR. PAUL HINDERLITER: Yeah, so this is -- this is the model that -- so there is only one model. It's just parameterized differently for the

rat and the human. This is taken from files that were provided by Dow to simulate their data. It is the same model that is in -- that is used by the EPA in the risk assessment. Just -- it's used here for the rodent, instead of for the human.

DR. JEFFREY FISHER: So the publication of this is by what author?

DR. PAUL HINDERLITER: The data from this is from one of the Timchalk publications. It's from around 2002.

DR. JEFFREY FISHER: Okay. Okay. So is this in it, this publication?

DR. PAUL HINDERLITER: I don't know that this exact graph is. Because it's interesting, when you go back and look through all of the papers that present the model, there's not much made of parent chlorpyrifos. There's many graphs of acetylcholinesterase and of TCP, chlorpyrifos, there's less data. It doesn't fit quite as well. There's not as much made of it across the publications.

DR. JEFFREY FISHER: I agree with that, because I went looking for all the rat time-quest data for chlorpyrifos and human data. There is data, but not as much as you might think. But there's a lot of

model development work when you account for metabolism in pharmacodynamics, as you said. But this is like over a decade's worth of work. And I'm just surprised you didn't think the modeling is ready.

DR. PAUL HINDERLITER: Well, you have to remember that the decades' worth of work was focused on an entirely different goal. All along, the development has been to support acetylcholinesterase inhibition. So that's where all of the effort has been focused.

Can you take dietary exposures and predict human acetylcholinesterase inhibition across a varied population? That doesn't really talk very much about parent chlorpyrifos. And that's my point in this. This is one of the better developed PBPK models I have ever been involved with. There is a large amount of data there. There has been a lot of assessment on this model. There's been a lot of interest in it, but not for this application. So this strips away.

And you know, I found it a little bit troublesome that all of the graphs or all of the schematics of the model show the entire model. You know, they showed the parent and then the parallel for

the metabolites and then the pharmacodynamic model, as if that's what's being used, because it's not. What's being used here is just the parent chlorpyrifos.

DR. JEFFREY FISHER: All right. So do you believe that the fat, the way their plasma partition co-efficient is a potential real driver for a long half-life?

DR. PAUL HINDERLITER: Potentially, yes, because it does have a quite high partition co-efficient -- like I said, there is a human poisoning case that shows a half life that's consistent with this, but it's not. You know, it's a poisoning case, so it's up in the range of the rodent data. Does that kinetics actually translate down in the range of the population exposures that we're considering here and I don't know.

DR. JEFFREY FISHER: Thank you.

DR. JAMES MCMANAMAN: Dr. Rohlman.

DR. DIANE ROHLMAN: Diane Rohlman. So I'm moving outside my comfort zone, so I hope you can help me clarify. On Slide 10, if you could go there, this is the human oral exposure. I'm trying to understand many things. But right now, let's focus on -- according to this model or this picture and I think

you've had a nice explanation. I just want to confirm that I'm understanding it.

DR. PAUL HINDERLITER: Okay.

DR. DIANE ROHLMAN: Is that the level of uncertainty really occurs if we follow that orange line down, after that first exposure there?

DR. PAUL HINDERLITER: Yes.

DR. DIANE ROHLMAN: And that as we get lower and lower, we don't think the model, the PBPK model is predicting things accurately?

DR. PAUL HINDERLITER: Yes. And in that, I've drawn it here after a single exposure, but these are the same drafts that you would see like the -- in the EPA and the Dow presentations where, if it's after a month's worth of exposure or something, when you cease exposure you see this sort of decline.

DR. DIANE ROHLMAN: So we would be concerned about levels that were down at those low levels about their accuracy?

DR. PAUL HINDERLITER: Yes. And that's what the -- how the cord bloods are being tied back. So that the presumption and why there's so much discussion about the time of labor is that they're making the assumption that the time of labor is long

enough that you're sort of out of that initial alpha-phase decline.

And you're somewhere into this beta phase where it's a -- not a steady state, but it's a much slower decline, so it doesn't matter. You know, once you get out of that rapid decline, being an hour or two off doesn't make a whole lot of difference.

DR. DIANE ROHLMAN: Sure. And most of the cord blood levels were below the limit of detection.

DR. PAUL HINDERLITER: Yes.

DR. DIANE ROHLMAN: So therefore, we give them the half at the limit of detection, just so they're not a zero in our data analysis.

DR. PAUL HINDERLITER: Mm-hmm.

DR. DIANE ROHLMAN: And that's a common metric that's frequently used.

DR. PAUL HINDERLITER: Yeah. Well, and I would say if you look at this graph, you know, half of the limit of detection is an arbitrary and high number, so.

DR. DIANE ROHLMAN: Is arbitrary?

DR. PAUL HINDERLITER: Arbitrary and high. Higher than I would expect. If you were, and

this is just one dose, but if you get over the first 12 hours of the sensation of exposure, you get almost, I would say about a three-order of magnitude decline, a two-order of magnitude decline in the blood level. So it's likely to be significantly lower than the limited detection at the levels that we're talking about.

DR. DIANE ROHLMAN: But then the other group, the cutoff is at 6. something.

DR. WILLIAM POPENDORF: 6.17.

DR. DIANE ROHLMAN: P/pg, which would be at the top of those peaks, if I'm not correct -- if I'm correct.

DR. PAUL HINDERLITER: Yes.

DR. DIANE ROHLMAN: If I'm correct.

DR. PAUL HINDERLITE: Yes.

DR. DIANE ROHLMAN: So part of the reason or part of the discussion here has focused a lot on the use of two groups with the Columbia data. And there's been uncertainty about those values there. But it seems that the model is more robust at coming up with those higher values.

DR. PAUL HINDERLITE: Yes and no.

DR. DIANE ROHLMAN: Well --

DR. PAUL HINDERLITE: So if you look at this graph, this is one of those saw tooths there in that 99th percentile line. So it does rise up and, the EPA's bar graph shows this, that it will rise up for a few hours. But if you get down into the -- even from the 6 milligrams, if that were your peak, even from 6, by 12 hours, you would be -- or even by about 6 hours, you would be back below that limit again.

DR. DIANE ROHLMAN: Right. But the cord bloods were measured hours after the exposure, presumably, up to two days after the exposure. Yet, we still are seeing levels up around 6 or higher.

DR. WILLIAM POPENDORF: Cord blood.

DR. DIANE ROHLMAN: Cord blood.

DR. WILLIAM POPENDORF: It was in (inaudible).

DR. DIANE ROHLMAN: Right. So we would expect, if you go back to the previous -- well, if you could stay here. Either one works. We would expect that exposure has ended and they drop down. So the fact that we're seeing levels at 6 or higher picograms, means that the exposure has declined significantly. So --

DR. PAUL HINDERLITE: Yes.

DR. DIANE ROHLMAN: -- in fact, that six in the cord blood could be underestimating the actual exposure?

DR. PAUL HINDERLITE: Well, so that was what -- a big point of a lot of the EPA presentations was is that, with that, it depends on when you pick that time to actually be. So they showed it with a 10 and a 24-hour matching of that of some certain number and then you'd draw back to what the peak would have been at that. And yes, that is significantly higher when you're at that peak. But I'm not sure how you'd draw the exact computation.

DR. DIANE ROHLMAN: I guess the point is that the levels that are measured in the cord blood we can assume are underestimates of the exposure because they are taken several hours after --

DR. PAUL HINDERLITE: Well, they're a snapshot of the exposure. I don't think anyone said that they're the peak of exposure.

DR. DIANE ROHLMAN: I didn't say they were the peak. I said they were an underestimate of the actual exposure, because of this model, which has showed me --

DR. PAUL HINDERLITE: Well, yes. What

I would posit is that, given the shape of these curves, all you can actually probably say is that the exposure was higher for the preceding day or so. Beyond that, you don't actually know what the exposures look like at all.

So you can draw, you know, sort of one-day window off of that. And if you then presume that you know something about the actual environment, you can potentially reverse engineer what their exposure might have looked like. But you don't -- that cord blood dosimeter actually only tells you about maybe a day's worth of exposure.

DR. DIANE ROHLMAN: Mm-hm. Okay.

DR. PAUL HINDERLITE: Yeah.

DR. DIANE ROHLMAN: Thank you.

DR. JAMES MCMANAMAN: No questions? All right. Thank you very much.

DR. PAUL HINDERLITE: Thank you.

DR. JAMES MCMANAMAN: The last presenter is Lynn Heilbrun. UTE School of Medicine, San Antonio.

DR. LYNN HEILBRUN: I'm not sure how this -- it's on.

DR. JAMES MCMANAMAN: Yes.

DR. LYNN HEILBRUN: I appreciate the opportunity to speak to you today. My name is Lynn Heilbrun and I am researcher and a mother of three. I am here to comment as a mother who has had to watch her children suffer for 25 years from infancy through adulthood with the neurological effects associated with chlorpyrifos.

Our exposures began in 1990 when we realized that our home was flea-infested. We called in an exterminator service. I did not know that I was pregnant. Even though our exposures occurred prior to the indoor ban, pregnant women and children are still being exposed through pesticide drift, agricultural use and food intake.

My symptoms during the first trimester are what I now recognize as a classic OP toxidrome. I was struggling to stake awake, had trouble with concentration, chronic nose drainage, uncontrollable diarrhea, confusion, and severe headaches.

I was diagnosed with rhinitis at pregnancy, migraines due to hormonal changes and irritable bowel syndrome with no prior personal or family history of any of these symptoms.

My son was born full term in 1991 and

had severe colic with explosive bowel movements. He screamed night and day for months on end. As an infant and toddler, he suffered from recurring ear infections and was chronically ill with other infections.

His weight fell from the 50th percentile at birth to the 5th percentile by 12 months. His pediatrician ran tests that indicated immune system irregularities, but they couldn't figure out what was wrong. Meanwhile, we continued with chlorpyrifos treatments.

As time progressed, my son showed developmental delays. I would call his name, but he wouldn't respond and all of his hearings tests were normal.

When he was five, he could not carry on a two-way conversation. His loud, aggressive and sometimes explosive behaviors had become so troubling at school and at home that we sought a professional diagnosis. He was diagnosed with memory and attention deficits, gross motor delays and speech delays and social problems. The majority of these deficits are observed in the Columbia cohort. In spite of an IQ of 121, he could not read until he was almost eight years

old. Lead tests fell within the normal range.

At nine years old, he was diagnosed with fine motor disability. At 13, he was diagnosed with PDD on the autism spectrum. The majority of these deficits or this diagnosis -- I'm sorry, this diagnosis, is associated with chlorpyrifos exposure in the Columbia study.

His younger brother was born in 1994. His colic wasn't as severe as his brother's, but he too suffered from recurrent otitis media and fell off the growth chart within a year. He was noticeably hyperactive at three years old.

And his first-grade teacher suggested holding him back because he spent more time under his desk than in his seat. His evaluation at that time revealed visual motor deficits, however, his IQ was 136. And his superior oral and verbal reasoning scores placed him at 11 years old.

In the third grade, he was diagnosed with ADHD, dyslexia and auditory processing disorder. The last chlorpyrifos exposure in our home occurred in August of 2000. I need to clarify that we have had no family history of any of these diagnoses. My boys, ages 6 and 9 developed bad coughs and I thought I had

a GI flu.

About two weeks following the extermination, a copy of *U.S. News and World Report* caught my eye. The cover page was about environmental poisons being linked to learning disabilities. The story was about the new restrictions for indoor use of chlorpyrifos and diazinon, how children could inhale up to 250 times the safe levels after a basic crack and crevice treatment.

I panicked and called Poison Control and they told me that my boys' symptoms were not a symptom of this exposure. I decided to take my sons to the emergency room anyway. Fortunately, the ER doctor had just received special training in OP compounds and recognized the symptoms.

When I told him what Poison Control had said, he replied angrily, "Oh, hell, yes, they are a symptom of this exposure. People die from respiratory failure from this exposure."

They received breathing treatments in the ER. They had no previous history of asthma. The physician advised me to move out until I had environmental clean-up. I took the children straight from the ER to a friend's home.

That night, I was awakened by my nine-year-old who was crying and gasping for air. He was in acute respiratory distress. We rushed to the ER. His radiology report showed symptoms consistent with reactive airway disease and sections of his lungs were collapsed.

Over the next year, I remained very ill, losing more than 30 pounds. I could not work. Fortunately, I had taken the MCAT the day before the exposure, but had to have help completing my applications and be driven to my first medical school interview because I was so tired and weak that I couldn't make the four-hour drive by myself.

I made a personal commitment during my recovery that I would educate families and physicians on the health effects of chlorpyrifos. I regained enough cognitive function the following year to pursue a career in environmental health and was awarded an EPA fellowship to pursue a Master's degree in public health.

I had my home tested for chlorpyrifos by the same lab that was used in the Columbia study. The levels were consistent with the Columbia study's levels where they were seeing developmental deficits.

This was four years post application with no pesticide use.

I had the levels in 2010 again measured and it was still detectable 10 years post application. That same year, I was recruited to join the South Texas Autism Research Group as their research coordinator. A year later, we discovered chlorpyrifos metabolites in children's baby teeth.

I will never forget the day that I received the email that chlorpyrifos metabolites were detected in my sons' teeth. It was gut-wrenching. It showed that my sons' bodies were storing this toxic compound.

The same year we submitted our blood for genetic analysis and PON1 status. It turns out that my sons and I are below the 10th percentile in the ability to detoxify this pesticide. Human PON1 studies show a tremendous range of vulnerability to chlorpyrifos and therefore the 10X intra-species extrapolation is an appropriate rationale.

Meanwhile, my children's teeth hold clues to their in utero and early childhood exposure to chlorpyrifos. We have documented levels in their teeth and in our home. My son's IQ scores were

significantly lower than his previous test, following his last chlorpyrifos exposure. And there are major diagnoses are deficit for deficit in line with those found in the Columbia children.

These are all neurological deficits that your panel is familiar with. But I would like to translate what it means to a child and to our family. For my oldest son, it translated into uncontrollable meltdowns that lasted for over an hour. We could not take him to restaurants or public places for fear of the meltdowns or his wandering off.

The motor deficits translated to a child who was last off the starting line in PE every time the whistle blew, who was dead last in every event, in every swim meet, in spite of how hard he tried and did not give up for over eight years.

It translated to a child that can score well on exams, but can't seem to find his shoes, books, or homework, even though he had them just a minute ago.

It translated to a child who, even at 18 years old, can't sign his name or tie his shoes, a kid who has an IQ in the 94th percentile. His social deficits translated into an awkwardness that attracts

constant bullying from elementary school through college and in the workplace.

He is in his seventh year of undergraduate school in college and is busing tables at a restaurant over the last year. For my youngest son, it translated to a child whose self-esteem was so low that he didn't want to go to school and would cry because he couldn't read until well after the third grade, in spite of having an IQ in the 99th percentile. It translated to impulsive behaviors which led to a traumatic expulsion in the fourth grade and calls throughout middle and high school from principals.

Today my boys are 22 and 25. Both suffer from severe anxiety and episodes of depression, symptoms consistent with chlorpyrifos exposure in adults. Both of these children had IQs in the gifted range, but chlorpyrifos robbed them of their full potential and neurologically handicapped them.

The continued use of acetylcholinesterase inhibition as a point of departure is unconscionable when we have evidence from several cohorts that these neurological deficits are occurring at levels far lower than indicated by acetylcholinesterase inhibition.

The Scientific Advisory Panel has an obligation to protect the most vulnerable children and mothers by using the most protective measure available. I implore you to use the best available science for the point of departure. Columbia cord blood and maternal blood levels provide real exposures, the best data there is for this decision.

In closing, it is my opinion that the EPA should revoke all use of chlorpyrifos. Thank you.

DR. JAMES MCMANAMAN: Thank you. Any questions? Okay. Thank you very much. So this ends our public commenters time. And if there are any other -- anyone else in the audience who would like to make a public statement related to this charge topic, please come up now. We'll provide you some time. If not, then we will move on to the charge questions. If the agency's okay, we'll take a quick break, five minutes.

DR. ANNA LOWIT: Yes, one question for you. Are you planning to go past 5:00? Are you going to stop at five? Some people are asking.

DR. JAMES MCMANAMAN: The plan is to stop at 5:00, but if we happen to be in the middle of something, we may go a little bit longer.

(Brief recess.)

DR. JAMES MCMANAMAN: All right. So on reconsidering, we went a little bit longer than we intended to today. We were supposed to finish up tomorrow. So it could be a long day today or it could be a long day tomorrow.

So why don't we try to go a little longer today and get as much done as possible without making everybody brain dead. So if we can get started, we can have the first charge question read into the record.

MR. MARK DYNER: This is Mark Dyner from the EPA Office of General Counsel, before we do that, we do have a couple of clarifying responses to the comments, if we could, just to put into the record, if that's acceptable?

DR. ANNA LOWIT: We'll be quick.

MR. MARK DYNER: We'll be very quick.

DR. ANNA LOWIT: Very quick.

DR. JAMES MCMANAMAN: Okay. Okay.

MR. MARK DYNER: I do want to make a couple of clarifying legal points for the record, in response to the comments. There was an assertion by a commenter earlier. I believe, it was the Center for

Regulatory Effectiveness, that suggested that EPA could not rely on the Columbia study lawfully in a regulatory setting without having access to raw data.

While we agree that EPA administration policy, including EPA's Information Quality Act Guidelines encourage transparency in our assessments, to the extent possible, nothing in law, policy, or regulation actually requires that EPA have access to the raw data, underlying published literature in order for us to consider these data in setting regulatory standards. And in fact, the D.C. Circuit has upheld on two occasions, the EPA's use of peer-reviewed epidemiological data in setting cleaner act standards where EPA did not possess the raw data.

And the courts have made clear that no such raw data requirement exists in law and that if the EPA were, in fact, required to review underlying raw data in all instances in order to consider any public literature in the regulatory process, it would have to forgo consideration of a lot of important science.

The other remark I'd like to address is about the litigation on chlorpyrifos in the 9th Circuit and whether the court can modify the December 30, 2016

deadline for completing action under tolerance.

To clarify, on June 30th of this year, we must submit a status report to the court. And in that report, we must address if there are any extraordinary circumstances making completion of the rule by December 30 impracticable. Not impractical, but impracticable. We will address that issue and make that determination at that time. But obviously, we will need a strong basis for any extension request to the court of the final deadline.

That's all I have on the legal points.

DR. SCOTT SLAUGHTER: This is Scott Slaughter.

DR. JAMES MCMANAMAN: Well, I think I'm going to say no, and I'm going to say no for this reason is that the panel is evaluating the science and we're not evaluating the regulation and we're not evaluating the legal situation.

So we appreciate Mr. Dyner's comments, but they really have no real bearing on the issues in which we're going to evaluate today and during our deliberations.

DR. ANNA LOWIT: Thank you. This is Anna Lowit. I've got a really quick one. And so we

heard -- it's been a long day of public comments. I just wanted to point out that Dr. Driver's presentation on behalf of Dow this morning included many inaccurate comments that we don't have time to go through nor is it necessary.

However, it's important for you to understand that his statements about the spiking the samples above 15 pg/g with respect to the Barr lab is inaccurate. With every run they did, they spike samples at the LOD to verify the LOD with every run batch.

DR. JAMES MCMANAMAN: Thank you.

DR. ANNA LOWIT: One more comment from me and then Cecilia is going to make some comments on the PBPK. Just one other point to clarify.

DR. JAMES MCMANAMAN: No. We can't. I don't think we can do comments. We've --

DR. ANNA LOWIT: Oh, no, I just mean clarifications of the comments that were made.

DR. JAMES MCMANAMAN: Okay.

DR. ANNA LOWIT: Sorry.

DR. JAMES MCMANAMAN: All right.

DR. ANNA LOWIT: We do, the EPA, it has been said the EPA does not use published literature to

fulfill data requirements and that, in fact, is not the case, we do. And Cecilia?

DR. CECILIA TAN: This is to respond to Dr. Fisher's questions, clarifying questions because --

DR. JAMES MCMANAMAN: We'll take that up when we do the deliberations. And you'll have a chance. If there's any uncertainty or any clarifications needed --

DR. CECILIA TAN: I just want to provide him the reference.

DR. JAMES MCMANAMAN: Oh, okay. That's fine.

DR. CECILIA TAN: And he was asking for the data and model simulation where it is, you can find it in the Prueitt 2014, includes both rat and human model and data and then you can evaluate of whether or not that model is appropriate.

DR. JAMES MCMANAMAN: Okay, all right. Thank you. It's a tough job.

DR. BETH HOLMAN: Hi. This is Beth Holman, OPPHED. I'm just going to start reading the questions into the record.

DR. JAMES MCMANAMAN: Yeah, Charge

Question 1a.

DR. BETH HOLMAN: Okay. Do you want me to switch right to Question 1.a.? Do you want to read -- there's an initial paragraph before Question 1.a.?

DR. JAMES MCMANAMAN: Go ahead. Read the initial paragraph.

DR. BETH HOLMAN: Okay. So first question is: Life stages for consideration and this is looking at Section 4 of the issue paper. The preamble paragraph says, fetuses may be exposed to chlorpyrifos through the mother, while infants and children are exposed directly through dietary exposure, food and drinking water.

The agency has conducted case studies to use blood data as a surrogate to evaluate the health impacts on fetuses and infants from exposure to chlorpyrifos in Section 6.

Based on the available data -- okay, based on the available data, there are several assumptions that are being made in order to assess exposure for specific life stages.

Moving on to the -- okay, Question 1.a. is on fetal exposure. Without a gestational model that is parameterized with chlorpyrifos information,

fetal exposure cannot be assessed directly. However, maternal and cord blood concentrations on chlorpyrifos from Columbia are highly correlated, as seen in Figure 1 and preliminary evaluation of the Dow gestational PBPK model suggests little differences in blood levels between pregnant non-pregnant women. Therefore, the agency has concluded that the paramaterized model which is available for females 13-49 years old, can be used as a reasonable surrogate for estimating fetal exposure. These comments on the agency's proposal to use female blood levels as a surrogate for fetal exposure.

DR. JAMES MCMANAMAN: Okay. The discussants on this are Drs. Fisher, Carr, Hayton, Popendorf and Sobrian. Dr. Fisher is the lead discussant.

DR. JEFFREY FISHER: Well, this is my first time. So, I would like to say that our group really wanted to know the intent of the question and, as a consequence, when each individual talks, I think you'll hear a variety of comments.

Most people agreed and said, yes, a simple answer to the question. Now I'm going to read my particular comments beyond a "yes." The term fetal

birth cord blood, chlorpyrifos concentrations, are correlated with mother's blood concentrations. That's been discussed a lot and we've seen the graphs several times. So they do track each other.

I think obtaining raw data is important, in particular, the data for the mother-infant pairs, 64 samples. If the levels are detectable that would provide the most informed information about this relationship, if that's possible. It would reduce uncertainty, I think, in comparing the two blood samples.

The blood has been used, to me, means whole blood, but really a lot of the samples are plasma. And in the modeling world, there's a big difference between whole blood and plasma. So I think when the collected data is plasma and the model simulations are plasma, plasma should be used in the document. That's the end of my comments.

DR. JAMES MCMANAMAN: And Dr. Carr?

DR. RUSSELL CARR: Simplicity, simply is the -- please comment on the agency's proposal to use female blood samples as a surrogate for fetal exposure.

The answer is yes. But that answer is time limited. You cannot take a blood sample and then use that one sample to estimate the exposure that happens months prior. That blood sample -- we've been using the pharmacological kinetic model. It's only good for about 30 days.

DR. JAMES McMANAMAN: Dr. Hayton.

DR. WILLIAM HAYTON: Well, I'd like to, first of all, echo Dr. Fisher's comment about the interchangeability that seems to exist between, you know, using blood versus plasma. And there, as Dr. Fisher pointed out, they're in pharmacokinetic models, they're not the same thing. So I just think that can be straightened out. But I think it should be.

And a lot of that – some of that confusion comes right out of the Columbia studies themselves where they – Whyatt's 2003 paper where they'll talk state in that paper that blood samples were drawn and centrifuged and plasma was collected and sent on for analysis and then they'll present the data in tables. Sometimes it's blood, sometimes it's plasma, so I don't put that on the agency as their error. Timchalk's paper does a similar kind of thing, between blood and plasma.

Getting more to the question at hand of whether the female blood level can serve as a surrogate for field exposure, I think the evidence for that is that the cord blood and the maternal blood, even though they're separated in time by a day or two, perhaps, or less, the fact that they're similar, that their ratios are about one. And you could expect differences based on the different lipid contents of the mother's and the cord – the fetus's blood and the time interval between the samples. But I think given that and given the high correlation between the two, to me, it makes sense to use female blood level as a surrogate for fetal exposure.

Now – and then I would hasten to add that that's at the time of measurement. So then, how good an index is that of exposure for the preceding -- you know, you can't go back nine months on that one point.

You know, so if the 120-hour terminal half life is valid, I think you could go back a couple of half lives, say 10 days, with some confidence. And then before that, you pretty much have to say, well, environmental exposure that led to that measured level, if you assume that's more or less a constant

over the pregnancy then, you know, making that assumption that it is a surrogate.

Let me see if I have anything else here. Oh, I had a brief statement and it's fairly obvious. You could use the lifestage PBPK model to actually simulate – well, I say that now, but after hearing one of the recent comments about how the model really wasn't designed to simulate chlorpyrifos, maybe this isn't so true. But anyway, as an exercise, you could use the lifestage model and simulate the mother's and the fetus blood level timed profiles or not.

MS. CECILIA TAN: Cecilia Tan.

DR. JAMES McMANAMAN: No.

MS. CECILIA TAN: Can I respond?

DR. JAMES McMANAMAN: Go ahead. Sorry. You'll get a chance in just a minute.

DR. WILLIAM HAYTON: Okay. Thanks. That ends my –

DR. JAMES McMANAMAN: Are you – your comments are finished then? Okay. Dr. Popendorf.

DR. WILLIAM POPENDORF: Yes, thanks. Mine is probably is one of those that had the most uncertainty exactly what the question was related to.

And I – so I was thinking if the question relates to using the PBPK model to female blood levels as a surrogate for pregnant women's blood levels, I was comfortable with that. In fact, I think that's really preferable to using cord blood because it's the most stable within the range of the sample collection protocols used in the Columbia studies.

If the question related to the use of female blood as a surrogate for the 8 percent missing cord blood values used via the maternal cord blood pairs, I actually have some serious concerns with that because the results found by Whyatt et al 2004 are very non-linear and show a fairly wide range in some areas of levels. We don't know where those data come from and I'm going to address that more in a further question. But that is a concern.

And then I concurred with the comments about, you know, using the female blood data, it does – you really don't have the ability to detect changes beyond 10 days or so. If there were changes in exposure, it's the most stable, then you can assume constant exposures. But if it did change, you couldn't tell. Nonetheless, it's the best available, in my opinion.

DR. JAMES McMANAMAN: Dr. Sobrian.

DR. SONYA SOBRIAN: The answer to the simple question was, yes. I broke it down into pros and cons. As previously been said, there has been a correlation that's listed as .7 to .9 between fetal and maternal blood.

The other pro was that you could use the – you could do modeling, PK modeling from the parameters from the mother, but not from the fetus. And then, but the major problem with that, with the whole idea is that there's a single exposure sampling and that's, you know, for the cord blood. And then the sampling for the female is up to two days.

I think the question I wanted to ask was are you confident that all the maternal samples were taken at the birthing place before they had a chance to go home and then come back, because that might have changed the exposure?

The other thing that was problematic about using single exposure information was the fact that yesterday on somebody's slide, it was number 66, you showed that various – four different exposure parameters actually gave you the same point. So the "yes" is a simple yes. It's the best and as I said

before, it's the best -- of the choice, it's the best, but it has its problems.

DR. JAMES McMANAMAN: Okay. I will open this question up to the other members of the panel for comments. Yes, Dr. Sweeney.

DR. LISA SWEENEY: Lisa Sweeney. I would agree that the simulated nonpregnant female blood levels can be used as an adequate substitute for predicted levels in pregnant females. The data in Figure 1 are generally supportive of the proposed practice, but did not provide paired data for mother and child.

A better approach would be to derive maternal and cord ratios from the original care data, rather than to a limited number of unpaired values at discrete percentiles.

And what appears to be an unpublished draft manuscript from 2014 in Dr. Hattis' comments, Hattis and his colleagues, which included members of the CCCEH study group report doing such an analysis for 191 records where both samples were available and they determined the geometric mean of 1.2, the ratio of maternal to fetal with the 95th percentile range of 1.065 to 1.35.

I would support using modeled female blood in place of modeled fetal blood levels, preferably, with an adjustment for the ratio determined by Hattis in conjunction with the Columbia investigators.

I would note that that doesn't account for pairings where the mother – where one might have been a nondetect and one a detect, which might seem to fall outside that ratio, especially if you look at the 98-99 samples, the 25th percentile cord blood sample was a non-detect of the 25th percentile maternal sample for the same year was 2.6, but they're different numbers. These aren't paired data, so it's a little hard to say whether that suggests that there might be some outliers. But of course, it'd be preferable if we had the original data. But since the data where we do have paired data, that does seem to be a pretty tight distribution at somewhat less of a concern.

DR. JAMES McMANAMAN: Other comments? Other panel members? So I have a – Dr. Popendorf.

DR. WILLIAM POPENDORF: Just to check, you were aware that the Whyatt 2004 was paired data and they had a – you know, a nonlinear log-log equation that they developed?

DR. LISA SWEENEY: But did they show the data? So I –

DR. WILLIAM POPENDORF: They did not show the data.

DR. LISA SWEENEY: So I – so we don't know if they included the nondetects at the – if you have a bunch of nondetects where you had the same detection limit for mother and child and called them both .5 and you put them into that correlation? That's why you'd need to know the end and whether or not detects or nondetects were excluded. I don't think we have that level of information available for analysis.

DR. WILLIAM POPENDORF: Right. Nor did they really provide any confidence interval or our squared value. So it was --

DR. LISA SWEENEY: And I don't remember all the details.

DR. WILLIAM POPENDORF: -- it was paired data. That's – but you're right --

DR. LISA SWEENEY: Right. But we don't have the --

DR. WILLIAM POPENDORF: -- about the other points.

DR. LISA SWEENEY: -- not -- the pairs include nondetect.

DR. JAMES McMANAMAN: Dr. Pessah.

DR. ISAAC PESSAH: I was just wondering if there was an issue in the lipid values for pregnant female versus nonpregnant females? They can be quite different. Does that alter the PK model, I guess, or is it already accounted for?

DR. WILLIAM HAYTON: William Hayton. I – it was addressed by Dr. Dale Hattis in the materials that he gave us. And I read through that a while back. And he did draw a distinction, gave the differences in the lipid levels. I don't recall that he carried it through to the point of what would the equilibrium, you know, concentration ratio between the two, what would be the consequence of that different lipid profile. I don't know if he did that.

DR. JAMES McMANAMAN: Okay. I have a question for my panel colleagues. What are your considerations in terms of the correlation between the paired data, when nearly all the levels were below the level of quantitation, not below the level of detection, but below the level of quantitation? How do you make judgements about the relationships who say

that there's good agreement, there's not a good agreement, when we're not in in a quantitative range? That's where I have the biggest confusion. So I'll open that up to anybody.

UNIDENTIFIED FEMALE SPEAKER: If you'll look at Figure 1 and you – I think we're talking about the combined data which is at the top. And yeah, but when you go further down and look at correlations that you can't measure, that's a problem, too. I guess that's why the correlations are ranged from .7 to .9.

DR. JAMES McMANAMAN: Right. Dr. Hayton, you had a – help me out here.

DR. WILIAM HAYTON: Well, I didn't think about it in such a sophisticated way. I would say the – I just looked at the – I think it's called Figure 1, it's a table, anyway, in the white paper.

DR. JAMES McMANAMAN: Right.

DR. WILIAM HAYTON: And it shows, you know, ascending concentrations.

DR. JAMES McMANAMAN: Yeah, they showed a pretty good correlation, but how reliable is that data if they're below the level of quantitation?

DR. WILLIAM HAYTON: Well, I suppose the lower percentiles for – you know, they were showing .0025 or something like that in both columns.

DR. JAMES McMANAMAN: Okay.

DR. WILLIAM HAYTON: In both mother and cord probably are the undetects.

DR. JAMES McMANAMAN: Dr. Sweeney.

DR. LISA SWEENEY: We had the issue paper before we had the Hattis comments. So when I looked at the issue paper, mostly I just looked at the percentiles for which there were detects and looked at those and came up with about the same ratio as the Hattis analysis and came up with about maybe 1.3 and said, well, it seems like there's quite a large number that year. Not to me. And sort of, you know, back of the envelope, and came up with about 1.3. And when I saw the Hattis analysis, said, oh, well, that's similar, but there is the early data that has the -- you know, like I mentioned that the maternal levels were detectable and when the fetal levels were not at the same percentile. That's the only thing that really gives me pause about the ratio is did you have mother-child pairs that had -- that you would infer that the ratio had to be substantially higher than

1.2, just based on what the level was in the mother when you couldn't detect it in the child?

DR. JAMES McMANAMAN: Okay. Dr. Popendorf.

DR. WILLIAM POPENDORF: Dr. Jenkins, could you pull up that slide, the Popendorf slide, first one? We can kind of go on, while he's pulling that up. But it's just a graphical presentation of the formula that's given by Whyatt 2004 based on pairs.

Again, we had just mentioned the fact they didn't really tell us what data. It was around 100 or so radiate --paired points. And that equation, because it's not linear, goes way – I mean, it goes to ratios of 3, 3-1/2.

And the formula before that by Perera 2002, I think, had ratios going as high as 5. If you were -- if they used data that covered the spectrum of values that were measured up to like 16 for cord values, in order to use that formula, if you get a 60 – yeah, the one that slides, not the one that's – oh, no, not that one. I see. I didn't realize that was mine. Yeah, the other one.

Perera, anyway, the Perera equation which they used before the Whyatt equation was even more nonlinear and had ratios up to five within that range. So you know, without having the data, they've got conflicting information.

So that's the graph there with the maternal blood on the bottom, umbilical cord on the vertical scale. The solid line is the Whyatt equation, and the dotted line would be the 1:1 value. So FYI, it's different information, depending on what you look at.

DR. JAMES McMANAMAN: So the question about it is using one a reliable estimate of the other?

DR. WILLIAM POPENDORF: Well, you know, we've got, again, conflicting information. Where that equation came from, they didn't explain why they did a log, it's a log-log relationship. Wasn't it, yes. Log-log relationship. Let me think about that, yeah, that they used to derive that equation. So on the Whyatt, it's maternal blood to the 0.76 power. Without knowing what samples, what the values were that they used to generate it, we don't know how valid it is. We don't know why they picked a log-log.

And we have the information that Dr. Sweeney was talking about from Hattis. And again, he didn't run a regression. He just has within a range, most of the data is pretty close, so I suspect most of the data is, as we know from the dots, is down around the 10 picogram range on the cord side, which is pretty close to 10 on the maternal side. But there must be some range of the data they actually measure that go way off of that.

DR. JAMES McMANAMAN: Yes, Dr. Fisher.

DR. JEFFREY FISHER: Yeah, I just think, and it's been said several times, having data would help people draw their own conclusions, including the agency, on how to proceed.

DR. JAMES McMANAMAN: So as a panel, is that a major concern is not having that data and being able to make an accurate assessment of this?

DR. JEFFREY FISHER: I think so, because it anchors everything they're doing here, these blood samples. So to me, not having data was just amazing, flabbergasting. What's going on?

DR. JAMES McMANAMAN: Any other comments? All right. So, Dr. Rohlman.

DR. DIANE ROHLMAN: I don't know if it's appropriate to ask why we don't have the data or why the data is not available or not?

DR. JAMES McMANAMAN: I'm not sure that it's --

DR. DIANE ROHLMAN: Okay.

DR. JAMES McMANAMAN: -- clear to why the data is not available. I think it's been requested. But for some reason, it's not available. And so we have to go on with what evidence that we have. So if there are no further questions or no comments, then I'll send it back to the agency.

MS. CECILIA TAN: Clarifying comments or comments in general?

DR. JAMES McMANAMAN: No, no, not comments in general.

MS. CECILIA TAN: Okay, clarifying comments.

DR. JAMES McMANAMAN: If our comments were not clear.

MS. CECILIA TAN: Responding to questions.

DR. JAMES McMANAMAN: Yeah.

MS. CECILIA TAN: Okay. Cecilia Tan, EPA. In response to Dr. Hayton's questions, the lifestage model does not include the gestational component. So it doesn't have a fetus. So the lifestage is from birth on, until whenever. Yes, to a certain body weight.

And then also you have now the members probably have some reservation about the use of PBPK model to predict chlorpyrifos concentration in blood, after hearing the public comment. And what I would like to ask for the members is for you to draw your own conclusion.

DR. JAMES McMANAMAN: No, no, our conclusion is clear to the agency.

MS. CECILIA TAN: Okay. So we don't have to.

DR. JAMES McMANAMAN: That's – yeah.

MS. CECILIA TAN: Okay. Again, I just want to mention everything that you're looking for is in that paper and that you can just compare whether or not you're comfortable.

UNIDENTIFIED FEMALE SPEAKER: Your answer to the question is clear. And then you've answered the question. Thank you.

DR. JAMES McMANAMAN: All right. So we can move on to the next question.

DR. BETH HOLMAN: Question 1.b., Infant (>1 year old) exposure. Studies of chlorpyrifos in laboratory animals do not suggest any specific critical period or lifestage, but instead, suggests both pre- and postnatal periods of susceptibility.

In contrast, there are limited epidemiological evidence regarding postnatal exposure to chlorpyrifos or other OPs to infants and children. Because brain development continues through childhood, and due to the concern that acetylcholinesterase inhibition may be not be protective of the neurodevelopmental outcome, the agency is proposing to use the chlorpyrifos cord blood data from CCCEH as the most relevant source of information for deriving a PoD for infants (See Appendix 4.0 for further details).

Please comment on the agency's proposal to use cord blood data as a surrogate for assessing infant exposure.

DR. JAMES McMANAMAN: Thank you. This Charge Question is led by Dr. Fisher. And Dr. Carr, Hayton, Popendorf and Sobrian are the associate discussion. Dr. Fisher.

DR. JEFFREY FISHER: So I will get started and then the group will provide their comments. This Charge Question, I think, was viewed differently by people within the group. So I think there's less consensus about going ahead and trying to do what you're proposing.

But at the same time, there was a lot of discussion about what do you really mean with this question and what are you going to do? So that was part of the discussion. And you'll probably hear that from people in the group.

For me, I had a hard time trying to understand how you would use it. And then I started thinking from a pharmacodynamic standpoint that if you wanted to use these blood levels that come from in utero exposure that may be associated with adverse effects, you would then use those blood levels in doing simulation studies of the infant. And so you would simulate the infant which is in the document and compare your simulated exposure levels to the cord blood levels. That's where I took it. That's how I interpreted the question.

I think because there's not a window of susceptibility, it's difficult to go into the infant

and use a point of departure from a fetal exposure and there's great uncertainty in doing that.

So my first thoughts are, no, it's probably not a good idea. It could be a good idea to do what I said as a feasibility study and exercise in understanding what kind of exposures might occur in infants, relative to the in utero exposure. I was unclear in the lifestage model if, from the newborn on, if the newborn included the body burden of chlorpyrifos from in utero exposure when you start the simulation.

And so, I guess the point I'm trying to make is that maybe for a few weeks or so, in utero exposure might mimic or the infant exposure might mimic the in utero exposure, then it really falls apart. And without a window of susceptibility, it's really difficult to associate those simulations with strictly postnatal effects. That's the end of my comment.

DR. JAMES MCMANAMAN: Thank you. Dr. Carr?

DR. RUSSELL CARR: Cord blood data cannot be used as a surrogate for assessing infant exposure, unless you're studying the toxicological

effects of that gestational exposure. Once the birth occurs, the exposure of the infant is totally separate from that of the mother. The only exposure connection between the infant and mother would be breast milk.

Otherwise, the initial exposure would be through food and water. However, if the infant becomes mobile six to ten months and spends more time crawling on the floor, dermal and potential inhalation exposures may occur. These exposures are totally independent of the cord blood values.

DR. JAMES MCMANAMAN: Thank you. Dr. Hayton?

DR. WILLIAM HAYTON: I agree with what the first two speakers said, that at the time of birth, I think that that's an index of exposure. But from then on, it's going to depend on the input rate into the infant. And I think Dr. Carr outlined that very well.

And then whatever the -- you know, the pharmacokinetics of distribution and elimination and I don't know how much is known about the developmental time course of metabolism and so forth, so it's been a problem. Thanks.

DR. JAMES MCMANAMAN: Dr. Popendorf.

DR. WILLIAM POPENDORF: Well, I basically agree with Dr. Carr, as well, as far as the general infant exposure characterization. I'll also say if -- I wrote a paragraph here that may or may not occur in this or be included in this section. But you know, I personally don't really think that cord blood is usable as an exposure assessment for anyone here, really.

So it would -- and part of the answer to this would be, no, in that case. But I think the other points I already made. I agree more with the other points that have previously been made.

DR. JAMES MCMANAMAN: Dr. Sobrian.

DR. SONYA SOBRIAN: My answer is no, also. I think we thought that maybe for the -- as for a neonate for the first 30 days of life, that cord blood might be a relative surrogate.

But other than that, no, I wrote cord blood is like -- underestimate the exposure to infants. While cord blood data may be directly relevant to fetal exposures, it's relevant to infants and children. Levels and routes of exposure are likely to differ between the fetus and the infant, while the fetus that's exposed to chlorpyrifos only

through the mother, which is primarily the oral route, the infant is also exposed directly through the skin and maybe through inhalation, as well. So the answer is no. Not for the infant, maybe just for the neonate.

DR. JAMES MCMANAMAN: All right. This is open to the rest of the panel. Dr. Sagiv.

DR. SHARON SAGIV: This is Sharon Sagiv from U.C. Berkeley. So one thing that we haven't really talked about and I had a conversation with Dr. Pessah about it yesterday is the fact that -- I didn't realize this -- chlorpyrifos is lipophilic. And so I know they're not persistent -- it's not persistent. I studied persistent chemicals mostly. So when things are lipophilic, we think about them being in breast milk and has anybody considered that? I mean, you did mention breast milk. I think Dr. Carr did mention breast milk as a potential source of exposure. But since these aren't persistent, I don't know that that's actually valid.

DR. RUSSELL CARR: If I recall -- Dr. Carr -- but if I recall, someone mentioned that breast milk had not been put into the model. And am I incorrect about that?

DR. SONYA SOBRIAN: Yeah. I wrote and said, I've had the current model for PK research does not include gestational or lactational exposure. However, there are other models of lactational exposure available.

While the modified model reasonably simulates the physiological changes during pregnancy, meaning the model I used here, the model's predictability to simulate internal dosimetry of chlorpyrifos cannot be properly evaluated, since there was no chlorpyrifos-specific pharmacokinetic data available during pregnancy. So there are other models. It's just -- it's not from what I read - if I'm wrong -- that it's not being used in this -- in the model that's here.

DR. RUSSELL CARR: And that -- you know, like that's just one source. But that -- I mean, if you could -- that is a connection to the mother.

DR. SHARON SAGIV: Well, even -- it's -- this is Sagiv here again. Even if the chemicals aren't persistent, if the mother is continuing to be exposed to residential spraying or however she's exposed, I assume it would transfer to the infant via

breast milk. So I don't know that the persistent question is an issue here. I would be curious to know if there are chlorpyrifos levels in breast milk and you know, how they compare to, say, cord levels?

DR. JAMES MCMANAMAN: Well, that's -- those are very interesting questions, but they're not part of the charge questions. Dr. Pessah.

DR. ISAAC PESSAH: I actually had a question. So are you saying that the uncertainty would err in underestimating or overestimating neonatal and juvenile exposures, given that there are other routes once birth occurs?

DR. RUSSELL CARR: The question says, cord blood data. And once that cord is severed, that source is eliminated. All others -- the sources may come through breast milk, they may come through the environment and they may come through food and water. But once that cord is severed, there's no more -- no longer a relation to cord blood. That animal -- I mean, that baby is on its own and so it's -- you know, exposure wise.

DR. JAMES MCMANAMAN: Is that clear?

DR. ISAAC PESSAH: Maybe I can rephrase my question. It's been a long day. So postnatal

exposures would be higher or lower than cord expected?

DR. RUSSELL CARR: I would expect them to be higher.

DR. SHARON SAGIV: I would agree with that. I think cord blood is an under -- would be an underestimation.

DR. JEFFREY FISHER: So --

DR. JAMES MCMANAMAN: Dr. Fisher.

DR. JEFFREY FISHER: -- through simulations, the answer to your question could be derived, if they haven't calculated that with a life stage model with all the assumptions about exposure and you can do comparisons -- the table and the appendix that we looked at last night.

DR. JAMES MCMANAMAN: Are we looking for this. This is -- okay, while she's looking -- this is Dr. Hayton.

DR. WILLIAM HAYTON: Just to respond to the question, the -- you know, whether it's going to be higher or lower. To me, I don't -- I have no idea. But the you know, big part of it is how quickly metabolism enzymes mature. And somewhere in all of the reading, I saw a graph that sort of showed that maturation of -- and there -- you know, over the first

two, three months, the activity of enzymes was just all over the place, from zero all the way up to fairly high. So I would expect in that neonatal period that the exposure -- in terms of systemic exposure or concentration in the blood -- could be all over the place, too.

DR. JAMES MCMANAMAN: Dr. Popendorf?

DR. WILLIAM POPENDORF: I don't know if it would help. Your comment, Dr. Hayton, was helpful. I think to try to get a handle to provide information about why we think what we're thinking.

And I think going back to Dr. Carr's comment and some others, I guess, there was really kind of two parts to the answer of is it higher or lower, because in neonatal is primarily going to be exposed through breast milk. They're pretty, you know, not mobile and well protected. So their exposure probably would be less, depending on what level is in the breast milk.

But once they become mobile and start crawling around, they're going to be on ground zero in terms of getting exposure. And so, then you know, six months to the year, they're going to get more exposure. So it -- I think the answer depends on just

what part of that year you're talking about, so.

DR. WILLIAM HAYTON: But by exposure, you mean input rates.

DR. WILLIAM POPENDORF: Yes.

DR. WILLIAM HAYTON: But systemic exposure you also have to look at how fast is it getting eliminated and you know, after six months the maturation of metabolism picks up quite a bit. So even though there's a bigger intake, it might be it's just really hard to say is what I would say, but you can't focus just on the input or the rate of elimination. It's a balance of the two, the ratio of the two, really.

DR. WILLIAM POPENDORF: Right. And I agree with that. And perhaps I shouldn't say dose would be more. So, Dr. Popendorf again.

DR. JAMES MCMANAMAN: Other comments? This is Dr. McManaman. Then if I could summarize the committee's view on this is that there is the use of cord blood as a surrogate is probably -- there's no justification for that. There's limited evidence that it would be a good surrogate.

And the committee seems to feel that focusing on cord blood, as opposed to other routes of

entry, which could also contribute to an infant exposure less than one year of age would be -- is shortsighted and we should -- there should be other -- other routes should be considered. Is that accurately summarized?

DR. STELLA KOUTROS: Can I ask a clarifying question?

DR. JAMES MCMANAMAN: Sure. Sure.

DR. STELLA KOUTROS: This is Stella Koutros. I heard that for -- this is what I think I heard. For Question 1.a., that the discussants said that, at first, that they would accept the agency's proposal to use female blood levels as a surrogate for fetal exposure. If the correlation could be confirmed by the Columbia investigators with respect to the raw data on the mother-child pairs. That's what I think I heard. Is that not correct?

DR. LISA SWEENEY: Lisa Sweeney. I would say that's not exactly what I said. But I would say it's more that the simulated levels for the mother properly reflect the levels that you would predict for the fetus. That's not exactly the same thing as saying measured maternal levels are the same as measured fetal levels. I guess that's a nuance, but

not quite.

DR. JEFFREY FISHER: My only issue is time, what you do with the time. You know, the relationship between the mother and fetus, there's a ratio of error that could be modeled or figured out. But as far as you can't take one time and use it for the entire nine months.

DR. JAMES MCMANAMAN: So I think the upshot is that there was -- this is Dr. McManaman is there was uncertainty about how to actually make those correlations. Dr. Sagiv.

DR. SHARON SAGIV: This is just -- keeps niggling at me. And maybe EPA can respond -- when they respond, about the non-pregnant versus pregnant women. And I know this was in the last charge question. Could I just put it out there?

Given the hemodynamics in pregnancy, is the reason why we can use non-pregnant women as a surrogate for pregnant women because we're talking about measuring blood two days after the delivery when the hemodynamics may have settled down or because we're not looking at persistent chemicals? I would just think those hemodynamic changes the GFR and if these are lipophilic, the hemodilution. I feel like

that would be an issue during pregnancy, especially if you're taking blood sample during pregnancy. Is it not an issue because you're taking the maternal blood after pregnancy?

DR. JEFFREY FISHER: I think several of us at this panel have developed human pregnancy models and there are many differences, as you know, physiological, biochemical, that could be important in understanding kinetics, dosimetry. And for me, and it's probably primarily because of lack of data and through simulation, they did develop a pregnancy model.

In 2014, the POET model, someone who's been in the PBPK modeling for a long time and did theoretical simulations. And by that, I mean, no data, and compared that to a simulation of a non-pregnant female with all the physiology and there's very little difference. So that's the basis, I think, for EPA going to the non-pregnant female as a surrogate.

DR. JAMES MCMANAMAN: That was Dr. Fisher. Dr. Popendorf.

DR. WILLIAM POPENDORF: Will Popendorf, just to follow up with that and to clarify, I think

there was also the simulations were made with a weight increase on the female to simulate the additional lipid content to pregnancy. I don't know what those numbers were, but someone else might. So it's not just apples to apples, it's pears to apples.

DR. JEFFREY FISHER: Yes. There's tables listing all the physiological differences they accounted for in the model.

DR. SONYA SOBRIAN: Looking for it, it's in Appendix 6.

DR. JAMES MCMANAMAN: It was Dr. Sobrian. So -- this is Dr. McMananam again. So for my clarification right now there are no models that would allow the use of cord blood as a surrogate for infant exposure, that you're not aware of? Are you aware of models that would allow cord blood as a surrogate for infant exposure, validated models?

DR. WILLIAM HAYTON: No.

DR. JAMES MCMANAMAN: Okay. Other comments or questions for clarification?

DR. SONYA SOBRIAN: I think I'd just like to make a comment, because I know Dr. Fisher started off with the word "intent." And we had some trouble with that. But I think we just looked at the

word "use" without knowing what you want to use it for. So our answers are sort of just for the -- you know, if -- what would be a good surrogate? But it's just an answer. But it doesn't say that -- for what you want to use it. And now I think that's what you meant by intent. I just wanted to clarify, unless somebody think that's not.

DR. JAMES MCMANAMAN: Well, we can't ask that question at this point. We just have to -- yeah. Right. So in your report, we can make that as a consideration that -- for the agency. Other comments, questions? Okay, then I'll take it back to the agency. And --

DR. ANNA LOWIT: So we did want to answer your question about the breast milk and then I had a clarification on what I heard.

MS. DANA VOGEL: So we do have, what's it about, 40 samples, more or less, from the pilot part of the National Children's study. They collected breast milk samples and chlorpyrifos was one of the compounds that was monitored. So there is some data that we have not -- a significant amount and I think it was only in a few locations. Right? A couple -- two?

DR. ANNA LOWIT: That's right. This is Anna Lowit -- from two locations and a relatively small number of moms who provided samples. But given the small samples, there are detects. There are detects of chlorpyrifos in breast milk. And we can, although understanding their limitations to the dataset that we have, we cannot -- because we don't have that lactational compart of the model, we can't predict from today's exposure what might be in the breast milk.

However, we can use those breast milk data in the same way we've used the water case studies that we showed yesterday to use those levels in our simulations of an infant drinking breast milk every few hours at a certain volume.

So we are able to do some bounding exercise, using those data to get a sense of what may be in the infant from a breast milk feeding scenario.

DR. JAMES MCMANAMAN: So that was Dana Vogel and Anna Lowit. So for this question that's been brought up, the committee has the capability of making recommendations or suggestions for the agency to include breast milk samples in their modeling, if required. But it's -- that may be just a way of

addressing the limitations of this use of cord blood. So back -- any further clarifications needed, with respect to this question?

DR. ANNA LOWIT: Yes, on this question. And I think it's going to be also in the next question, because I think I know what we're going to hear.

Just based on what you just said now, I think some of these issues are going to come back in Question 5, related to the point of departure, because one of things I'd like for all of you to think in the back of your mind, is that when we go to do a risk assessment, that we have to assess children at all ages.

So as you think about the relevance of what the cord blood is telling us, it's a metric that connects the neurodevelopmental outcome to an internal concentration, that connection, how we would then think about assessing the hazard piece of the infant and also the toddler, which is kind of the next one.

So these issues will come back again in Question 5. And so if there's still a lack of clarity amongst the group on how we would use those, we can bring back the case studies and add that.

Jeff and I had an exchange yesterday on -- we could put a line on the graphs. We can do that if that would help you conceptualize what the numbers would look like. So that's my clarification, number one.

My question to all of you is, I think there's a clear answer of, no; however, I heard from Dr. Fisher and from Dr. Sobrian that for one said a few weeks, one said the first 30 days, that those data may be relevant because temporally they're closer in time.

And I did not hear others comment on that. Because have with the PBPK model, we can limit an evaluation to that first 30 days of life. And keep in mind that many infants are breast fed, but many are also formula fed. And that those formula-fed infants will be exposed to chlorpyrifos from the water that's used to reconstitute the dry formula. And so we will have to assess that life stage also.

And so, if you don't mind, if some people can comment on that first month or so or first few weeks or whatever you want to call it

DR. JAMES MCMANAMAN: I think that in the panel's response, they can comment on that in

terms of limitations of using cord blood, what the limitations might be and what some other avenues of exposure could be.

But specifically related to the cord blood question, I think that they have to -- you know, it has to come out --

DR. JEFFREY FISHER: I have the answer for him.

DR. JAMES MCMANAMAN: Okay. Good.

DR. JEFFREY FISHER: So it's related to the question I had about body burden. So at birth, so you have cord blood that represents the fetal exposure.

But in the model, the gestation model, the model simulates the whole body, all the compartments, the total mass of compound in utero, even though you just look at cord blood.

So at birth, that mass transfers to the newborn baby and that was my question. You then simulate that under your exposure scenarios and you can understand the role of the body burden of chlorpyrifos at birth in terms of how long that body burden persists.

DR. JAMES MCMANAMAN: If we can move

on. So we can come back to the --

DR. LISA SWEENEY: I guess, if I could ask a question and you could determine whether or not EPA could answer it?

DR. JAMES MCMANAMAN: Well, all we're asking for is their clarification, whether we've answered this question.

DR. ANNA LOWIT: Dr. Fisher offers, I think, a really good suggestion on something we could do. But I didn't hear the answer to my question about what other panelists thought about that first 30-day window, because you had two panelists suggest the first 30 days may be appropriate with some caveats. But I didn't hear anyone else respond.

DR. RUSSELL CARR: Judging from that beginning body burden, if it's large enough, it could possibly last through the 30 days. But that just depends on the level of that amount in the cord blood. I mean, if we're going to measure how much is in the cord blood, relative to how much is the body burden of the infant, then you could use that for what you're talking about, as far as the first 30 days. But it would just depend on what that level is.

If it's really low, it's not going to

last long, unless the infant goes back what you say into a more -- you know, exposure situation through the breast milk. Well, then you have another aspect of the model.

DR. JAMES MCMANAMAN: That was Dr. Carr. So Dr. Carr, this is Dr. McManaman, then if that's the case, then would we not have to have pharmacokinetic data that would -- a model that would support that -- use of that body burden? And does that model currently exist?

DR. RUSSELL CARR: I do not know if that model currently exists. Maybe some other modeler -- so I'm not a modeler.

DR. JAMES MCMANAMAN: Oh, that -- okay, Dr. Sweeney?

DR. LISA SWEENEY: Yeah. I mean, you could set up a life stage model such that you start with an initial burden and then you'd have to make additional assumptions about what the ongoing exposure are. But it would be parameterized for infant physiology, neonatal.

DR. JAMES MCMANAMAN: And those models are available?

DR. LISA SWEENEY: Yes.

DR. JAMES MCMANAMAN: Okay. Dr. Hayton.

DR. WILLIAM HAYTON: And I'll just concur with that, if you're looking for quotes. But I think the closer you -- in time you get to the -- at the time of sampling, then the better it is as a measure.

DR. JAMES MCMANAMAN: This is Dr. McManaman, does the panel have an opinion about what that cutoff might be? At what point past birth, using cord blood would the data become very unreliable?

DR. WILLIAM HAYTON: I think it's all going to depend on the kinetics of elimination and what's the exposure rate. And I -- I don't know those things.

DR. JAMES MCMANAMAN: Okay.

DR. WILLIAM HAYTON: So I can't say.

DR. JAMES MCMANAMAN: So there's uncertainty? Dr. Fisher.

DR. JEFFREY FISHER: Well, there's uncertainty, but the EPA has an infant life stage model and they could simulate and calculate five half-wise or something. I mean, it could be determined theoretically.

DR. JAMES MCMANAMAN: So this is Dr. McManaman again. If that's -- so if an infant is exposed both at the time of delivery through the cord blood and through breast milk or through reconstituted formula, models are available to take that into account in order to determine the overall exposure?

DR. JEFFREY FISHER: We let EPA verify that's available?

DR. CECILIA TAN: Yes. The life stage models -- sorry, Cecilia Tan, EPA. The life stage model does account for all the physiology and then also metabolism rate differences between infants and adults, it is included in the life stage model.

And may I ask clarify questions? So Dr. Fisher, let's say, if I understand the part that there is this transfer of chlorpyrifos -- mass transfer of chlorpyrifos to the fetus and then the newborn. And if we just assume that -- if we modeled -- the system model does not have the fetus compartment. We will not be able to predict that transfer. And then in that case, if we are able to estimate good exposure -- the concentration, say, from formula-fed infant, water concentration of exposure, well, wouldn't you say that we will be underestimating

the blood concentration of infants in that case? That will be a --

DR. JEFFREY FISHER: Yes.

DR. CECILIA TAN: -- and -- okay. Thank you.

DR. JAMES MCMANAMAN: Okay. Dr. Popendorf.

DR. WILLIAM POPENDORF: You know, I guess I've sort of been listening without trying to see if there was consensus but I mean, again, I'd be a very strong no to this question of using that for the infants. A lot of that cord blood's going to have a four-hour half life, not a five-day half life.

And I also point out, you know, am I'm sure you know that Table 1.1 in our issues paper has a lot of that infant data in there, which was based on that model that you're referring to. So yeah, it exists and we even have some of that for drinking water and food, including infants less than one-year-old.

DR. JAMES MCMANAMAN: Other panel members? We've got one "maybe" and one -- a couple of "yeses" and a "no." And we're getting a partridge in a pear tree here in a minute.

DR. SONYA SOBRIAN: Yeah. I think most of us said, if I remember, most -- I think that the answer was generally no. The only caveat was to use maybe the first -- look at the neonate.

And I know from medical people who work in pediatrics make a difference between a neonate and an infant. And I'm going to actually look at some of the pharmacokinetic changes. I could put it in the record so I can add it to this.

But I think the overall answer to that question was no. You can't use it for the infant. You might be able to use it for a very small part right after birth. But is that right? The general answer is no.

DR. JAMES MCMANAMAN: Okay. Is that clear now?

DR. CECILIA TAN: Clear as mud. And I appreciate you letting that extend a little bit longer.

DR. JAMES MCMANAMAN: So we're uncertain about the uncertainty. Okay. Next Charge Question 1c.

DR. HOLMAN: Quick question, 1.c. Children (ages 1<2 years old) Exposure. At this

time, the agency had not included a case study for evaluating the health impacts on children one -- less than two years old. However, the agency is aware that this age group often has the highest exposure from food consumption, as is the case for some food commodities for chlorpyrifos exposure. Children 1<2 two years old have not yet been included in the case studies as these ages are temporally removed from gestational exposure; as such, the relevance of the cord blood data to predict the outcomes in toddlers is unclear. Please comment on the strengths and uncertainties of using the CCCEH cord blood data as a surrogate for assessing children ages 1<2 years old exposure to chlorpyrifos.

DR. JAMES MCMANAMAN: Thank you. This charge question, Dr. Fisher is the lead discussant. Dr. Carr, Dr. Hayton, Dr. Popendorf and Dr. Sobrian are the associates. Dr. Fisher.

DR. JEFFREY FISHER: Yes. Jeff Fisher. So this question is an extension of the last question. And I think most people in the group say no for similar rationales.

I'd like to point out, though, that pediatric PBPK modeling is a huge active field in

drugs. And if you look at what's done across many drugs now, where they fail, usually is in the neonatal period, the first 30 days of life or in pre-terms from predicting dosimetry of drugs.

So the point I want to make is that the ability of the model, the infant model, to predict is probably better for this age group than the very young that you categorize from newborn to one year. And so I'd be more comfortable with model predictions in this age group, but not in relation to using cord blood.

DR. JAMES MCMANAMAN: Dr. Carr.

DR. RUSSELL CARR: I agree. Cord blood data can't be used in one- to two-year-old children. The connection from the mother is beyond that and the child is basically being exposed in different -- through dermal and oral exposure routes.

DR. JAMES MCMANAMAN: Dr. Hayton.

DR. WILLIAM HAYTON: Utility of cord blood data for this age range would derive primarily as a metric of the chlorpyrifos exposure provided by the home environment in which the child lives and this assumes that the home environment exposure over the period of interest was similar to the exposure around the time of birth and an assumption that is fraught

with uncertainty.

The life stage PBPK model could be used to gauge the blood concentration in the child over one to two years using a chlorpyrifos dosing scenario that corresponded to the cord blood concentration. Absent the connection to the mother, this dosing scenario would likely lead to a model predicted blood concentration quite different from the cord blood concentration.

DR. JAMES MCMANAMAN: Dr. Popendorf.

DR. WILLIAM POPENDORF: Well, I will agree with Dr. Carr, in particular, he also mentioned earlier and I'll give him credit for pointing out that, in fact, in the one- to two-year range those who might have had a high exposure are going to go through the cancellation period. So that would be another reason this would be no because we know their exposures would have changed. Well, we don't know that. But we can predict that many of their exposures will have changed.

DR. JAMES MCMANAMAN: Dr. Sobrian.

DR. SONYA SOBRIAN: I really agree with all that's been said. The answer to that is no for the same -- even for reasons similar to the one before

that, except that the infant from one to two is even further removed and often their dietary intake of chlorpyrifos might be higher.

DR. JAMES MCMANAMAN: Other panel members? Dr. Sweeney.

DR. LISA SWEENEY: I'm wondering if the question is not so much for any particular individual that you have a cord blood measurement for is that indicative of what sort of exposure they have at an older age?

Perhaps it's -- maybe the question is really if you have a reference concentration that's derived based on cord blood data and how do you assess the postnatal developmental risk of someone else who happens to be exposed to that exposure level at that age, irrespective of what their prenatal exposure was?

I'm not sure if that's the question we're supposed to be trying to answer is, okay, what do we do with these simulations of two-year-olds that I have a scenario?

Is it okay to then say, okay, we had this cord blood data and we have a risk of an effect at age seven that we think is important. We say we don't want -- we want to make sure that one- to two-

year-olds are not exposed at that particular level. Is that the question? Do we think that's the question? Do we think we're answering that question with the answers we've provided so far? I'm not sure.

DR. JAMES MCMANAMAN: The discussants on that -- anybody want to respond to Dr. Sweeney's question? Did you think you were answering the correct question?

DR. WILLIAM HAYTON: So that was my answer on 1b, assuming that it was a pharmacodynamic question and that you're looking at equivalent exposure giving rise to the blood level and an infant that corresponds to what happened in utero, at least at term birth.

And so that -- and I've said probably you cannot do that because the effects during development in utero are probably different than postnatal, the period of time if an infant was exposed and have blood levels similar to the cord blood levels, because there's very little postnatal data only, but some, as I understand it. You're uncertain about the consequences or the adversity. I guess that was my point on 1.b.

DR. JAMES MCMANAMAN: This is 1.c.

DR. WILLIAM HAYTON: Right.

DR. JAMES MCMANAMAN: Yeah.

DR. WILLIAM HAYTON: But she's bringing up the same issue, I think, as I brought up for 1.b. And I don't know the answer to what we're trying to answer.

DR. ANNA LOWIT: Would some clarification help?

DR. JAMES MCMANAMAN: Sure.

DR. ANNA LOWIT: Okay. So I appreciate Dr. Sweeney trying to put herself in our shoes and think about it from a risk assessor's perspective. So I want to thank you for that. And as I indicated earlier these Questions A, B and C on number one, are really directly connected to the conversation you all will have on Question 5.

Implicit in Question 5 is this issue of how the agency will assess hazard, as we think about calculating risk is that hazard assessed on the traditional acetylcholinesterase endpoint or is it assessed with a neurodevelopmental outcome?

If it's assessed on acetylcholinesterase endpoint, we have existing points of departure, but then we have an uncertainty of how

to then link that to the neurodevelopmental and what is that window -- window is the wrong word -- the gap, thank you, Dana -- the gap between the acetylcholinesterase endpoint and the neurodevelopmental outcomes and how do we ensure that point of departure is safe?

On the other hand, if you go with the neurodevelopmental outcomes, the only quantitative metric is derived from the Columbia cord blood as an internal concentration, internal dose metric linked to the neurodevelopmental outcomes.

So from a risk assessor's point of view, that's why these questions are so connected because we have to -- assessing the female is far more straightforward because the cord blood was derived from a female who had been pregnant. And there are females who eat food and work in fields. That's a -- the comparison there is apples-to-apples.

As we think about how we would assess the risk and the hazard to children one day to 30 days and 30 days to 365 days, how we would make those connections, either from acetylcholinesterase endpoint with some sort of additional factors in how we would then quantify those factors. Or using that internal

dose concentration for the neurodevelopmental, understanding there's a temporal gap and a lack of understanding on the postnatal on the Columbia. So is that making sense of how those are connected?

DR. JAMES MCMANAMAN: Right. So as I understand it, the ultimate goal here is to help the agency connect the dots and the gaps between the exposure levels and outcomes. And I think that what we have to do as a panel is we have to address the individual dots and ask -- and look at the reliability of using these surrogates as indices of exposure.

So with that in mind, is anyone's response to this charge question, does it change? Because this is -- we have to answer this charge question and to the best of our ability and about the uncertainties. And then the aggregate effects will have to be -- maybe we'll be able to address in Charge Question 5.

DR. JAMES MCMANAMAN: Dr. Sobrian.

DR. SONYA SOBRIAN: I know that comes back to intent. You know, we were trying to answer the questions just as individual questions. But when we were talking about this, we were saying -- we talked about the use of a single measure as a -- how

valid was that, which I think goes -- I think maybe you've put some of it in here. But it makes it -- I wouldn't change the answers. But I think it changes the discussion that I'm going to put in mine. But I did mention that that we thought one of the cons was that single-exposure sampling, which occurred just may not be a good measure. But I'll expand on that.

DR. JAMES MCMANAMAN: No, I think that what we should do is, since it is in Charge Question 5 as for the intent of Charge Question 5, here okay, we'll try to address those questions, those concerns at that time.

DR. ANNA LOWIT: Yes. Sure, that's fine.

DR. JAMES MCMANAMAN: Okay. So but is the agency clear on the response to this particular charge question?

DR. ANNA LOWIT: Yes, it's clear.

DR. JAMES MCMANAMAN: All right. So let's move on to Charge Question 2. And that will bring us to the end of where we're supposed to be today. So we can break and go -- pick it up tomorrow.

DR. BETH HOLMAN: Beth Holman, EPA. Question 2, Uncertainties with Using Biomarker Data

from CCCEH for the Point of Departure of PoD. Section 7.1 describes the key uncertainties in using the cord blood biomonitoring data from CCCEH as the PoD.

While biomarker data are arguably superior to conventional exposure data in that they reflect chemicals that were absorbed in the body from all roots and sources, they do not provide direct measure of environmental exposure levels.

Chlorpyrifos in cord blood represents a snapshot of the concentration at a particular point in time. Uncertainty also exists when establishing a quantitative relationship between chlorpyrifos concentrations in blood and adverse health outcomes.

For neurodevelopmental effects investigated in these epidemiology studies, the adverse outcomes pathways, toxic moieties and biological targets were all unknown. The key assumption is that measured biomarker levels reflect exposures during time windows that were critical for disease onset. It is also not clear whether cord blood concentrations measured at birth reflect exposure levels during the critical time windows.

However, there is reasonable likelihood that chlorpyrifos was applied multiple times in the

apartments of the women in the cohort over the course of the pregnancy, potentially one month, increasing the potential for exposure during these unknown critical periods.

In addition, in the context of the uncertainties associated with using the Columbia blood data and quantitative risk assessment, there is a concern that the point of departure is based on acetylcholinesterase inhibition, see Appendix 1, may not be adequately protective of human health. For example, given an external dose required to achieve 10 percent acetylcholinesterase inhibition for a female worker who was exposed dermally to chlorpyrifos eight hours a day, five days a week for three weeks. The blood concentration of chlorpyrifos peaked at 120,000 pg/g and was still above 100 pg/g at 32 days after the last exposure.

Similarly, at a food exposure level leading to 10 percent acetylcholinesterase inhibition, chlorpyrifos concentrations in blood never goes below 100 pg/g over the continuous 21-day exposure simulation and is around 7,000 pg/g at the daily peaks.

Please comment on the agency's

characterization of the uncertainty associated with using the Columbia blood data in quantitative risk assessment.

DR. JAMES MCMANAMAN: The discussants on this are Drs. Carr, who is the lead discussant, Dr. Ehrich, Dr. Pessah and Dr. Terry. Dr. Carr.

DR. RUSSELL CARR: These comments are the pooled assessment of all of the discussants and I'll let them add whatever they would like to after this.

As a stated by the EPA, the key assumption as to the measured biomarker levels reflect exposures during time windows that are critical to disease onset. This assumption relies on several unknowns that are recognized as uncertainties by the agency. The panel concurs with the agency, but has significant reservations that the steps taken during the quantitative risk assessment have clarified these uncertainties.

First, as mentioned in the document, the magnitude of exposure cannot be determined using the blood data. A high blood concentration may result of the low exposure sample within hours of after termination of exposure. A low blood concentration

may be the result of a higher exposure occurring weeks prior to sampling.

The toxicological impact of these two exposures will be quite different. Assuming that the blood concentrations were occurring at the asympto period when blood levels concentrations were fairly stable across several days would be an inaccurate reflection of the magnitude of the different exposures. In addition, this would inaccurately reflect the magnitude of response of the exposure scenarios.

Second, no particular window of exposure within a perinatal period can be identified as the key period for the effects reported in the CCCEH study, other human cohorts or in animal studies. Without knowledge of the sensitive window of exposure it's difficult to determine the magnitude of exposure necessary to recapitulate the effects reported in the CCCEH study. The current risk assessment paradigms seems to treat delivery as the critical window by using blood concentrations obtained at that point to derive a PoD for neurodevelopmental outcomes. This added an additional level of uncertainty.

There's an accumulating body of animal

and in vitro evidence to suggest that organophosphates affect a variety of biological targets in addition to acetylcholinesterase. A few of these studies, particularly in vitro experiments, suggest that these targets may be affected at levels that are below the threshold for ACHE inhibition.

However, to our knowledge, very little of this evidence would, so far, suggest that blood levels of chlorpyrifos in the pg/g range would have significant deleterious neurotoxicological effects in a million species.

Without any evidence in the animal literature or elsewhere of this mechanism of action, that could explain how pg/g levels in the blood could impair IQ and/or Working Memory there does not appear to be a biological plausibility. This is a significant uncertainty.

Several panel members were concerned with the lack of dose dependence. For example, where a range of doses, concentrations are evaluated and no a dichotomized low-dose, high-dose designation subjected to a regression analysis against a behavioral measure, and the absence of a (inaudible) dependence. For example, a deleterious effect that

gets worse as time of exposure increases, instead of changes based on chlorpyrifos detected in cord blood at the time of delivery, as compared to later, after chlorpyrifos is no longer used in the household or when it is lower and undetectable.

There is considerable uncertainty associated with the CCCEH blood data when there is uncertainty with the analytical results. Replication among analysis of individual samples undergoing a same extraction procedure plus apparent lack of calibration curves for quantitation of each batch of samples analyzed decreased confidence in the data at the very low pg/g or parts per thousand level used to provide an arbitrary division of subjects in the low and highly exposed groups.

Although it may be deemed acceptable in certain situations, providing quantitative values when the concentration of an analyte is less than the detectable level provides more uncertainty.

The reliance on a single cord blood measurement from only one study, i.e., the Columbia study, as the primary basis for a highly impactful regulatory decision appears to go against standard practices of science in the field of toxicology and

pharmacology.

The idea that the responses observed, for example, the neurological effects, would be detrimental primarily by the blood level of chlorpyrifos at the time of delivery is not logically supportable.

Peak or time weighted averaged concentrations during pregnancy or a portion thereof are more logically supported metrics. Such metrics could, in theory, be back calculated from the blood biomonitoring data using a valid BBB model if one has data on or can confidently make assumptions about aspects of exposure patterns labor delivery, blood collections and other cofounding variables.

If such computations cannot be made with confidence, then core blood data should not serve as a basis for quantitative human health risk assessment.

DR. JAMES MCMANAMAN: Thank you, Dr. Carr. Dr. Ehrich.

DR. MARION EHRICH: Okay. Some of my comments were incorporated in those of Dr. Carr. I would like to correct one thing he said, it's parts per trillion, the concentration level. But there's --

for using this cord blood, it's really necessary that such a precise and sensitive analysis be reproduced and quantitated in multiple laboratories with data available for scrutiny and that is not available here.

Now Dr. Barr has been gracious enough to send a second piece of information. And I've been asked to kind of read that in, so it's on the record.

And she says, that the -- I asked about the level of quantitation. She said, It's technically defined as three times the level of detection, usually calculated as three times the level, the LOD, which is the level of detection.

She said, "there can be errors in measurement. She said this visualization of the peak must be consistent at the LOQ, which is a quantitation such that the peak is identified 100 percent of the time and -- as was the case in the LOD that is reported in the paper.

At my laboratory at Emory, I report that LOD and LOQ both to avoid confusion. But that's not in that paper. So we still don't really know what she has there.

Now I asked about a calibration curve. She notes that most analytical journalists do not

include the calibration curve. And that is, indeed, true. She said, more importantly, a report the error about the slope which gives an indication of goodness of fit of data to the slope. This is a single most important calibration value.

The arrow for the slope of chlorpyrifos was .5 percent. And error less than 3 percent is going to set an excellent agreement of the data with the calibration line.

The question about using this one paper with lack of much analytical data, a multiple subsequent data. She says, most epidemiological studies relegate the analytic chemistry to a single paragraph or two and a paper without proper quality control or validation data.

We're happy we provided more extensive data in that paper. So it could be reviewed and evaluated by others, which is probably why I had so many questions, because I didn't think they would -- but she did provide it and that brought out more questions than maybe some people would have thought should have been brought up.

Okay, we also note the paper was peer reviewed and accepted by analytical chemists familiar

with this type of methodology. That still doesn't give us some of the information.

Now what were the recoveries? Were the recoveries always as low as 18 percent? That was recorded in that Barr paper. She said, "The extraction recovery was quite variable, which is common in the case with complex matrices, such as serum" and this is definitely a true statement.

The use of internal standards fully corrected for the recovery. This value was within the FDA guidelines at 80-120 percent. So I'm not quite sure why she reported 18 percent in that paper.

She says, it's important not to confuse extraction recovery with relative recovery. Farmers provided for chemists, only if they need to implement the method without such labeled standards. The latter is a value important for quantification.

Then how are samples quantified when only the LOD was provided and no calibration was given? And the second question I had was, were they further concentrated when she talked about when there were numbers used below the LOD, she said, no. When the calculated value was zero or below the LOD. So she calculated that value as zero. It was reported

merely as less than the level of detection. Values of greater than the level of detection were provided as a numerical value.

Please note that I very much disagree with the approach of using the LOD as a cut point for epidemiology studies. The LOD has no clinical significance and, thus, detect not detect should not be used to categorize data.

This opinion has developed strongly over my 30 years in the field. So this sort of summarizes the data that -- the information that she provided to us.

DR. JAMES MCMANAMAN: Thank you, Dr. Erich. Dr. Pessah.

DR. ISAAC PESSAH: I think all of my conclusions have been summarized by Dr. Carr and the concerns just read remain concerns for me regarding the large number of samples that were imputed as non-detect.

DR. JAMES MCMANAMAN: Dr. Terry.

DR. TERRY: Pretty much have the same sentiment as Dr. Carr covered pretty much all of my comments in his initial.

DR. JAMES MCMANAMAN: Other panel

members. Yes, Dr. Sweeney.

DR. LISA SWEENEY: I also contributed to the summary statement Dr. Carr gave and I'd -- so I'd like to indicate that I do concur.

DR. JAMES MCMANAMAN: Dr. Popendorf.

DR. WILLIAM POPENDORF: Yeah. I did -- I want to clarify one thing, maybe add another. But today I recall, Dr. Carr, you said in your statement that calibrations weren't run or weren't always run. And in the letter that Dr. Carr sent back says a calibration was generated on every single run. So is that going to be changed or am I --

DR. JAMES MCMANAMAN: That comment was generated by Dr. Ehrich.

DR. WILLIAM POPENDORF: Okay.

DR. MARION EHRICH: We didn't have that information at the time. But I just submitted my comments to Dr. Carr.

DR. JAMES MCMANAMAN: So she -- he asked will it be changed?

DR. MARION EHRICH: Yes.

DR. WILLIAM POPENDORF: Okay.

DR. MARION EHRICH: But we're basing -- what you have to remember, this is Dr. Erich, you have

to remember that we're basing things on what she said after the questions were raised.

DR. JAMES MCMANAMAN: Right. Before -- yeah. And you wrote that before you got this.

DR. MARION EHRICH: Only thing we have hard copy is the hard copy of the printout of her email. It's not in any of the publications.

DR. JAMES MCMANAMAN: Yes. Okay. The other question -- the other point, I guess, is kind of a question, because she also said about -- talking about spike recoveries and what she calls a relative recovery, which was 96 percent. But I guess I haven't seen any data about -- did she report relative recoveries, because if relative recoveries were 96 percent, then the question is, you know, how variable were they? And she also says it was between 80 and 120. Does that mean we've got to -- was it variable within that range? Do we -- so, I guess, do we have any of that information?

DR. MARION EHRICH: She does say in this email, she said, "The extraction recovery was quite variable. So she said her internal standards fully corrected for the recovery, yet, she reported in that paper 18 percent. Here she's telling us that it

was about 96 percent well within the FDA guidelines in the 80 to 120 percent. So there's some discrepancy between what's in the paper and what she says now.

DR. WILLIAM POPENDORF: Well, I don't read it quite that way. I mean, because she writes, "The use of isotopically labeled internal standards fully corrected for recovery. And in fact, the term "extraction recovery" is meaningless and spike recoveries are our ability to actually quantify the value was 96 percent and talks about relative recoveries as being the important term. So I think her internal spike, she got back pretty -- well, somewhat consistently. All she says was the 96 percent and she used that to adjust the chlorpyrifos. So I think she did a pretty -- you know, I think that method adjusted pretty well, but we don't know how variable that 96 percent is.

DR. MARION EHRICH: But yet, she reports in the table, Table 4, that R2000, she has a line that gives you what the recovery rates are. I think it's on Table 4. One of these tables, anyway. That's what she does say. So -- and also that could have been a recovery rate for something other than chlorpyrifos because they did a whole series of

agents. So I think there's a lot of unknown in that paper, even though she tried.

DR. WILLIAM POPENDORF: Okay. I think it's not uncommon, in my experience, working with this, when you use an internal standard in some form -- and apparently this is an isotope -- that you make the recovery. And as long as you're -- an adjustment for low recovery, as long as that is consistent, you can recover.

Chlorpyrifos you only get back 18 percent. But you know by putting in a standard, goes through the same process, you can make an adjustment. It's a fivefold correction. And that's used fairly commonly for these kinds of low values. But again, the question is that 96 percent, is that 96 percent, plus and minus a percent or is it 96 percent plus and minus 20 percent, staying within the FDA guidelines. That's the part that we don't know.

I mean, I think what she's saying is she makes an adjustment for that, whatever it was, 19 percent or 18 percent number. So she can adjust for that using this method. But then, like you say, it's probably within the 20-percent range, maybe even better than that. We don't know.

DR. ANNA LOWIT: Actually, it's in the table. I have the Barr 2002 paper open. So the comments that -- this is Anna Lowit. Popendorf are saying, are accurate. So the 18 percent is derived from -- hold on -- Table 3 in the 2002 paper and the methods.

The spiking recovery that yields the 96 percent comes from Table 4 in that paper. And that's where the slope -- there on the slope and the intercept to the calibration curves occur along with the co-efficient of variation on the number that you're talking about. So it's hard to read crooked. It looks like, if I'm reading correctly, crooked, that the chlorpyrifos co-efficient and variation is 16, I think it says -- 16, yeah. I believe so, yes.

DR. MARION EHRICH: And actually -- this is Dr. Ehrich -- commenting on Dr. Popendorf that I wrote on -- I have to sign off on papers in analytical lab and what you've said is quite true.

Spike was an eternal standard, you check your recoveries on that and that's how you make your adjustment. So it's -- she thinks she's really clear in this 2002 paper, but it's not all that clear. And I think that it was really helpful that she was

willing to provide some extra data with these emails.

DR. JAMES MCMANAMAN: So -- this is Dr. McManaman. So that clarifies the issue about extractability and recoveries. So we're -- so we have an error of 16 percent.

Other questions from the panel or other comments. So maybe I misunderstood this, but if -- and this is Dr. McManaman again. If there -- if Dr. Barr included anything that was non-detectable as non-detectable, yet, it seems to me that the data was used as if it's non-detectable, it was used one half the lower detectability limit. There seems to be a discrepancy there. But maybe I'm just misinterpreting that. Because if you're using. If it was non-detectable, then the -- did the paper say that they took every non-detectable level and called that one half of that non-detectable level or was it not or were those data not included in the analysis?

DR. MARION EHRICH: This is Dr. Ehrich. In the Rauh 2006, I think that they taught -- they actually in their method, they said they quantitated their below levels of detection at one half the level of detection. And I've heard from some of the epidemiologists that's not uncommon.

But she says right here, I very much disagree with the approach of using the LOD as the cutoff for epidemiological analyses. The LOD has no clinical significance and thus detect, not detection, not be used to categorize data. This opinion has developed strongly over my 30 years in the field.

DR. JAMES MCMANAMAN: So based on that, what does the panel feel about the reliability of this data if the person who is a primary contributor to this, they disagree with the use of this approach?

DR. STELLA KOUTROS: I don't -- this is Stella Koutros.

DR. JAMES MCMANAMAN: Okay.

DR. STELLA KOUTROS: I feel uncomfortable commenting on her comments, when she's not here to respond to them. I don't even understand what exactly she means by she feels uncomfortable not using the cutoff. She might just mean she doesn't agree with dichotomizing above and below the limit of detection. It's unclear from her statement without her being here to explain to us exactly what she means. I don't think we can draw any further conclusions.

DR. JAMES MCMANAMAN: Okay.

DR. MARION EHRICH: But the data was used in Table 1.

DR. JAMES MCMANAMAN: Okay.

DR. MARION EHRICH: That's the only data -- actual data that we have and that's a summary data. And --

DR. JAMES MCMANAMAN: Well, since -- you're absolutely right. So we won't include these comments that can't -- I mean, we can use them in terms of assessment of variabilities. But we can't use them. Dr. Popendorf?

DR. WILLIAM POPENDORF: I think I may be -- contributed clarification, perhaps, the normal process is that she would report non-detects or the laboratory would report non-detects. And the EPA, by policy, puts in the half of the LOD. The lab usually doesn't do that, in my experience and I -- again, I'm without her concurrence, we don't know that for a fact. But it is the EPA policy to use half the LOD.

DR. JAMES MCMANAMAN: Okay. Well --

DR. SHARON SAGIV: That's Columbia's. I think you're talking about Columbia.

DR. JAMES MCMANAMAN: Well, okay.

DR. SHARON SAGIV: Yeah.

DR. JAMES MCMANAMAN: Columbia may do it, too. But the laboratory -- Barr doesn't do it. So --

DR. SHARON SAGIV: No. Well, Barr gives you and LOD and then she -- if it's below that, she'll give you the less than the LOD. She won't give you the number.

DR. JAMES MCMANAMAN: Right. Okay.

DR. SHARON SAGIV: Right. But I think what she's saying, Dr. Ehrich said, this is Dr. Sagiv from U.C. Berkeley, is that she doesn't agree with dichotomizing at the non-detect. So in other words, using the non-detect as the cutoff, everybody below the non-detect is unexposed and everybody above that has a detectable level is exposed. I think that's what --

DR. STELLA KOUTROS: I don't think we know what she means.

DR. SHARON SAGIV: No, I think.

DR. STELLA KOUTROS: That's what I'm saying.

DR. JAMES MCMANAMAN: Well, so --

DR. STELLA KOUTROS: We can't draw the conclusions.

DR. SHARON SAGIV: It was clear to me from that that that that's she was saying.

DR. JAMES MCMANAMAN: Yeah. So -- right, we kind of tried to get a clarification. But in a way, we've got ourselves into a bit of quagmire. So I think what we'll do is we'll say we cannot accept this. We can accept her explanations for how the procedures were done. But her interpretations of what was going on, opinions, we can't include those into our --

DR. SHARON SAGIV: I don't think it -- Columbia didn't do that. So I don't think it matters.

DR. JAMES MCMANAMAN: Okay. All right.

DR. DIANE ROHLMAN: Just to emphasize -- this is Diane Rohlman -- is that Columbia didn't use the level of detection as the cutoff. So that's -- we need to just be clear.

DR. JAMES MCMANAMAN: Okay. Red herring. All right. Other -- other comments? All right. So back to the agency.

DR. ANNA LOWIT: So I heard a consensus response among the respondents. So to the extent that there is a clarity because there was a consensus response written. So I think the answer you're

looking for is yes. But just like the issues in Question 1, I think some of this comes back again as we think about the latter questions on -- that we have.

DR. JAMES MCMANAMAN: Okay. So I think the -- just to clarify, I think what I heard was that there was a lot of uncertainty about that and that there was -- is that fair that we didn't -- the panel didn't feel like that that was completely reliable? Okay.

DR. SHARON SAGIV: But remember, the question we're asking is about our characterization. So I would hope that your response --

DR. JAMES MCMANAMAN: Okay.

DR. SHARON SAGIV: -- comments on the extent that we have actually accurately captured the uncertainty and where maybe we had missed things.

DR. JAMES MCMANAMAN: Stand corrected.

DR. SHARON SAGIV: In my first -- in the first paragraph, I said the panel concurs with the agency, but had significant reservations to the steps during the quantitative risk assessment taken have clarified these uncertainties.

DR. JAMES MCMANAMAN: Good enough? All

right. Okay. It's 10 to 6:00. It's time to get some dinner and refreshments. So we'll meet back here at 9 a.m. for the remaining charge questions.

(Whereupon, at 5:50 p.m., the meeting was adjourned)

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DAY 3 - APRIL 21, 2016

DR. JAMES MCMANAMAN: Welcome back to the session on chlorpyrifos. What I'll do is, just for the record again, I'll ask all the panel members to introduce themselves. We can be very brief. I'm Jim McManaman. I'm from the University of Colorado.

DR. DAVID JETT: Dave Jett, National Institutes of Health.

DR. MARION EHRICH: Marion Ehrich, Virginia Tech.

DR. ALVIN TERRY: Alvin Terry, Augusta University.

DR. LISA SWEENEY: Lisa Sweeney, Henry M. Jackson Foundation.

DR. SHARON SAGIV: Sharon Savig, UC Berkeley.

DR. DIANE ROHLMAN: Dr. Diane Rohlman, University of Iowa.

DR. WILLIAM POPENDORF: Will Popendorf, Emeritus, Utah State University.

DR. ISAAC PESSAH: Isaac Pessah, UC, Davis.

DR. STELLA KOUTROS: Stella Koutros, National Cancer Institute, National Institutes of

Health.

DR. WILLIAM HAYTON: William Hayton, Ohio State University.

DR. WILLIAM FUNK: Bill Funk, Northwestern University.

DR. JEFFREY FISHER: Jeff Fisher FDA.

DR. RUSSELL CARR: Russell Carr, Mississippi State University.

DR. JAMES MCMANAMAN: Okay. So --

DR. PANOS GEORGOPOULOS: Panos Georgopoulos, Rutgers University.

DR. JAMES MCMANAMAN: Thank you, Dr. Georgopoulos. Before we go on to the next charge question, a couple of issues. There was some uncertainty amongst the panel about the ultimate, the risk assessment goals of this session that the EPA would like to have us address. So the EPA is going to answer those questions, answer those queries with a couple of quick slides to help us understand and clarify the risk assessment questions that they have.

The other is, I want to remind the panel that this is a deliberation amongst ourselves. We're addressing the EPA questions, but our deliberations are between this panel. And that all

panel members, including those who aren't really assigned to a particular charge question, should feel free to comment about this. And we encourage you to do so at every level. Okay. So with that, I'll send it back to Dr. Lowit.

DR. ANNA LOWIT: So this is Anna Lowit. Thank you, Dr. McManaman. So we did hear some lack of clarity amongst the panel on some of the issues. So we've brought back a few of the slides from Tuesday to reorient and maybe be a little bit more explicit than we were on Tuesday. So just to start at maybe the 10,000-foot level, as we think about the health effects of chlorpyrifos, remember we've been at this for almost 10 years now, and you're the third panel to look at these issues.

And two panels before you, in 2008 and 2012, both found the epidemiology studies to be of high quality and to be of utility in the hazard assessment for chlorpyrifos. And given the strengths of those recommendations and actually the compliments that we received from the 2012 paper on our analysis on EPI, we largely did not bring those issues back even in the issue paper or in the charge questions. So one of our starting points in this issue paper is

that the Columbia data is very strong. It's not perfect. There are uncertainties, but it is a very strong study.

On the other side of that is the acetylcholinesterase inhibition pathway, the traditional pathway leading to cholinergic toxicity, which has for a very long time been the source of point of departure in the red blood cell 10 percent cholinesterase inhibition. Let's remember, there's also uncertainties there. These are data derived from animals, largely in studies of animals with 5 to 10 animals per group at largely high doses.

So on one side, we have uncertainties associated with epidemiology, and on the other side, we have uncertainties associated with extrapolating high dose animal studies with small sample size to the diverse human population. Neither side of this flow chart is a perfect answer, but those are the two sets of information that we have in front of us to determine a safe level of chlorpyrifos as we move forward with the regulatory action on this chemical.

As I'll show you in a minute in a more explicit way that we didn't show on Tuesday, the internal blood concentrations for the 10 percent

cholinesterase inhibition are actually almost two orders of magnitude higher than the levels found in the perimeter carpet, in the perimeter treatments that the agency has already decided is unsafe. They're just the wrong direction. So on the left side, the point of departure with the traditional hundred-fold safety factor per the 2014 risk assessment is actually not health protective of infants and children.

And so in order to move forward with that end point, we would need to make some adjustments using additional uncertainty factors to ensure that end point was safe for all of Americans at every life stage. So in the event that this panel determines that there's too much uncertainty in the cord blood, we will, in Question 5, need your help to figure out how to assess the science that would underline those extra factors. On the right side is the other approach, the one that we're proposing in our issue paper, which is to use the cord blood data directly with all of its uncertainties.

It's not perfect, but we're confident that it would be protective of the neurodevelopmental effects. So let's sort of explain how the numbers are used. So the point of departure, whether it's

cholinesterase inhibition or neurodevelopmental, is divided by uncertainty factors. And in the 2014 assessment, for women of childbearing age, we have a value of 100, and we're continuing to propose a value of 100 today. That can be used in any way, whether it's the point of departure divided by the factors or using the factors as a target.

Either way, we're looking for the current exposures to be 100 times lower than the point of departure. That is entirely consistent with EPA policy for many, many years across decades. We want environmental exposures to be well below the points where we see adverse effects on the population. So in the case here, we're looking for our current exposures to be about 100 times lower than the point of departure. So you've seen this many times now. This is our PBPK output from the perimeter application to the carpet.

Keep in mind that this use was cancelled in 2000 because it's not safe, right. The agency found it to be unsafe and that's why it was cancelled. And in fact the Columbia study affirmed that determination by the agency in what happened to be a serendipitous dose response with the children

born before the cancellation and after. Where the kids born before the cancellation have higher levels in their cord blood and also see effects in mental delay, psychomotor delay, attention, ADHD, and Working Memory.

So the agency's determination in 2000 that the perimeter applications and the indoor uses not being safe turned out to be the correct action. Okay. So what's on this slide? What I've done here is overlay this exact same information from this plot. The blue on this plot is the same blue on the next plots. So on the left side -- on both graphs the orange is the PBPK output of internal dose to predict 10 percent cholinesterase inhibition from dermal exposure to a worker. And the blue is the PBPK output from that perimeter use that the agency cancelled because it wasn't safe.

And as you'll see, on the left side is a linear scale, and the blue is so small that you can't see it because it's little blips on the bottom. The right side we put on a log scale so you can actually see the blue. The blue is actually lower than the orange, which is actually the wrong direction. And in fact whether it's the peak value

that you look at or the lowest point on those graphs, the internal concentration from the dermal worker point of departure is about 100 times higher than the internal dose from the indoor use. Again, this is the wrong direction.

So we're proposing to use the neurodevelopmental effects from the benchmark dose derived from the Rauh study using a two percent change in Working Memory. That sort of is at a balance between, at the one percent the values would be near the LOD, and above that in the three to five percent range we're starting to hover around the point of that top tertile where those effects in the children were observed. So here's the exact same graph again with our proposed point of departure on it.

So you see the orange which is the 2014 dermal point of departure, the blue which is the perimeter which we've now established is not safe, and then the green below it which is our current proposal. So our current proposal would actually provide health protected point of departure as it is fairly far below where we see the blue. Whether it's the top of the blue or the bottom of the blue, the current proposed PoD is where we want it to be. Okay. So let's

translate that into a risk assessment.

So this graph you also saw on this chart, it's from Tuesday, this is evaluation of today's exposures in females who eat conventional food. So one of the things that in our program we have spent many years working on, we have very, very robust exposure assessment approaches. Our dermal assessments are probabilistic; they're based on real monitoring data near the point of consumption. So these values are very meaningful, they're almost very close predictions of what real people get here in the United States.

Okay. So the food exposure across the distribution. Exactly what you saw the other day. So I've got the same two points on the distribution, the 10 and the 99.9. But what I want to highlight your eyes to is that the point of departure we're proposing is 2.16, so divide that by 100. Although we fully acknowledge that you couldn't measure that number, what's measurable and what's safe are two different things. We need to keep those concepts separate. So if you move your eyes to the right side, even at 24 hours post-exposure at .021 we're essentially equal to the RFD.

And if you look downward at larger percentiles we actually begin to exceed the RFD. So that plays out on these graphs I have. This is the exact same graph from the other day. All we did was add the green, which is the proposed point of departure and the RFD at .022. And you can see at the 99.9, to an adult female here in the United States, the exposure across the entire 24-hour period is either bigger than the point of departure or also greater than the RFD across the entire 24-hour period. So remember, we're using her, the female, as a surrogate for her fetus.

So if this were a pregnant woman her internal dose would exceed the level all 24-hours of that exposure for the RFD. Same graph, different percentile. This is the tenth percentile, you don't see the orange PoD on this graph because it's above the top. But you can see even at 24-hours post-exposure the internal concentration in a female of a child bearing age is essentially equivalent to the RFD and is above that for most of the day. Okay. So we have a worker scenario. This is the exact same worker scenario we showed.

So this is an individual, a female who

would be handling chlorpyrifos to treat crops like broccoli and kale for example. The last date of the exposure. The only difference on this slide is that we've had to change the scale on the right side for the last day to a log scale. So that you can see that the entire distribution of the exposure profile is substantially higher than the point of departure and orders of magnitude higher than the internal RFD. Same series of plots for the water.

This is an adult female. Keep in mind she's a surrogate for her fetus. On the left side we have modeled values from a relatively low use pattern, bulb onions in Georgia. You can see for the entire 120-day modeled they were above the RFD and for many of the days we actually exceed the point of departure. On the right side is measured values and we sort of, you see the same pattern. The infant -- so this is a newborn so day one would be birth all the way out to day 120.

Put a box there to represent that neonate, the one to 30 day neonate. And you can see that if we coincide the peak of the predicted water concentrations compared to against the internal dose of the infant drinking a bottled formal, that the

internal dose of the infant is orders of magnitude higher than the point of departure and the RFD. The right side we see the same kind of pattern with the measure of concentrations for symbacrete (phonetic). Okay. So back to our problem. We have a challenge and all of you are seeing the struggle with the challenge.

There's two lines of information, there's acetylcholinesterase data which is the historical point of departure, RBC cholinesterase inhibition. The 2014 risk assessment, as we have shown in the slides and we have stated in the paper, is not protective of human health effects. As I walk through the points about, we cancelled the indoor uses, we see that play out in the Columbia -- the before and the after, the agency's decision to remove those uses for being unsafe plays out in that study and we see that.

The current point of departure is actually higher than that by a lot. So we would need your help to figure out how to adjust that to ensure that we're protective of all life stages across the United States. The alternative is to move to the cord blood, just a different set of uncertainties, but we

believe that would be protective. And that should be the last one. Yeah.

DR. JAMES MCMANAMAN: Thank you. So this was to help clarify for Charge Question 5, I believe. And if there are any specific questions that the panel has in deliberating this clarification from the agency we should probably discuss those now or we can wait until Charge Question 5. I mean because that's where we're really going on. But if there's any burning questions or issues that you have related to this we can go now. Yes?

DR. STELLA KOUTROS: I understand that a lot of what we just heard is relevant to Question 5 but I also feel like some of the discussions that we had late in the day yesterday are related to making some of these decisions or interpreting the data. And I personally feel that I don't understand some of the discussions we had yesterday about the first two charge questions. And I was perhaps suffering from some late afternoon fatigue and I have some additional thoughts about those questions and I don't know if others do as well.

But at some point I would like to enter into the record, which are relevant to what we just

heard as well. And I wanted to know if others felt the same way about our deliberations, quickly at the end of --

DR. JAMES MCMANAMAN: Feel free to -- now's the time if you have --

DR. STELLA KOUTROS: So I think most notably I wanted to give my interpretation of Question 1 and Question 1.a., which is that regarding the agency's proposal to use female blood levels as a surrogate for fetal exposure, my understanding from yesterday's discussion was at first that the discussion said that yes it could be but then no it couldn't be. 5And just amongst ourselves just this morning I'm not sure if anyone said -- if there was a final decision or some kind of consensus. And I don't understand the interpretation of why the data that are presented don't support the agency's proposal.

So specifically, in Wyatt, et. al., 2003, they showed that chlorpyrifos in maternal and in umbilical cord blood has a Spearman rank correlation of .76 in 180 mother/child pairs. Then in 2009, *Wyatt, et. al.*, showed the levels of chlorpyrifos in maternal and umbilical cord plasma were highly correlated, .9 in 64 mother/child pairs. These high

levels of correlation suggest that tracking the blood concentrations of the mothers is a reasonable surrogate for the fetus.

And if there is a question about the Spearman rank correlation coefficient amongst the panel members, I suggest that those with expertise in expidemiologic methods and biostatistics offer those opinions.

DR. JAMES MCMANAMAN: Anyone want to respond to Dr. Koutros' question?

DR. SHARON SAGIV: This is Sharon Sagiv from UC Berkeley. I don't have anything to add except that I want to support that opinion. I believe that those Spearman correlation coefficients do seem to suggest that they're correlated pretty highly. I think there was question of getting raw data at some point but I think the quality of the investigators in the Columbia study give me reassurance that these are probably accurate. So getting the raw data would just delay things. I'm not so sure I see the point of that.

DR. JAMES MCMANAMAN: Dr. Sweeney?

DR. LISA SWEENEY: *The Wyatt, et. al.*, correlations lacked transparency in that we couldn't

see the data, we couldn't see how non-detects were treated. So if you have two non-detects and you assign both of them the value of half the LOD they're going to be perfectly correlated even though you have no absolute numbers. So not being able to exclude the possibility that they used half the LOD in place of a value, it's a little harder to be confident based on the reporting in the Wyatt papers.

I take more comfort that maternal is representative of fetal from the summary information in, I guess it's called Figure 1 but it's really a table, in looking at some of the percentiles and that those generally match up pretty well. And the additional analysis done by Dr. Haddis and his coworkers, which unfortunately we also don't see a picture of, but where they report what seems to be, to me, to be a better approach which is to look at specific pairs, mothers and infants, and take the ratio and compare the ratios to each other instead of just sort of generally doing a correlation.

I think looking at the ratios is a good approach and the distribution of the ratios is pretty tight. So I think that is stronger evidence for correlation than the Wyatt data.

DR. JAMES MCMANAMAN: Thank you. Dr. Rohlman?

DR. DIANE ROHLMAN: Diane Rohlman. So I think what we're seeing here is converging evidence coming with the same conclusion, different sources. Just want to put that on the record.

DR. JAMES MCMANAMAN: Dr. Popendorf or Pessah?

DR. ISAAC PESSAH: Yes, I just have a question and clarification. We are actually making a recommendation based on one set of data and one set of analyses. Is that correct or incorrect?

DR. ANNA LOWIT: Do you mean one set of data as being the Columbia cord blood? Is that your - -

DR. ISAAC PESSAH: That was my question. It's very straightforward.

DR. ANNA LOWIT: Yes. But to say it like that I think ignores several decades if not hundreds and thousands of chlorpyrifos studies. There are literally thousands of chlorpyrifos studies on many things. This is one piece of a very large puzzle. And we have done a formal weight systematic review and weight of the evidence. So I think to pull

it out as one piece of evidence that is ignoring everything else is a misrepresentation.

DR.ISAAC PESSAH: No. I actually want to include everything else in my mind. So there have been other studies that have made these measurements on chlorpyrifos in a similar cohort?

DR. ANNA LOWIT: No. The Columbia study is unique in that. The other cohorts look at either the TCPy in urine which is not the most specific marker because it's prevalent in the environment and tends to overestimate exposure, and it comes from other pesticides. And the other cohorts tend to look at the dialkyphosphates or what you could call the DAPs or subsets of the DAPs which are definitely nonspecific. So with respect to specificity to chlorpyrifos this is the data set.

DR. JAMES MCMANAMAN: So I actually think that we're verging into additional information coming into us. And I think that we have to -- so Dr. Pessah's question is a legitimate question. It should be addressed to the panel and not to the agency. So I would like other panel members to weigh in on that if they have an opinion. Yes, Dr. Koutros?

DR. STELLA KOUTROS: I guess I have a

fundamental disagreement with Dr. Pessah's perspective that it's our duty as we've been charged here today and that we've agreed to participate in the consideration that the agency is using one study. I believe that our charge has been to help them make the determination about the best way to use this one study. It has been the subject of several technical reviews, previous panel reviews, about the utility and value of using that one study. And that's not what we are here today to judge.

The agency, it appears to me, has already made the determination to move forward with this data based on 10 years worth of review. And they are asking us to help them figure out a good way to do that.

DR. JAMES MCMANAMAS: I think that those are legitimate questions. And I think the panel's charge responsibility is to evaluate the science and the legitimacy and the reliability of these data. How the agency chooses to use that information is up to the agency, but I think our charge is purely about the science.

DR. STELLA KOUTROS: Our evaluation of the reliability of the data was not our charge, it was

the charge of a previous panel. And so I think it would be repetitive of us and completely devalue the scientific panels before us who have sussed already the validity and reliability of this data.

DR. DAVID JETT: Yes. So this is Dave Jett, NIH. So this is actually a little bit different from where my mind was. I was thinking of this as advice on the uncertainty and how that uncertainty -- I mean uncertainty can be used in two actually very different ways. One is you know, to sort of help you guys decide on margin of error in a risk assessment sense. It could also be used you know, to make the argument that there's too much uncertainty to make a regulatory decision.

So I wanted to stay away from that and just report on what we thought -- you know, I identify and quantitate that magnitude of uncertainty. Is that -- you want more than that or is that our charge? I'm just trying to get a sense of our charge.

DR. JAMES MCMANAMAN: So just a reminder that our charge -- our deliberations have to be on materials that were provided to us and on those materials only, and the information that are related to those materials that we were able to find from

public documents. And our charge is superficially related to questions such as reliability of the use of female blood levels as a surrogate for fetal exposure as Question 1. So we are, indeed, being asked to comment and to discuss the reliability of that use. So I think it's totally legitimate that we do so.

And we can include, to the best of our ability, the previous panel's information and the primary data. And let me remind the panel that we are not required to reach consensus. We can have disagreements as panel members and those will be recorded in the written document. But in order to -- this is a difficult question that we are being asked to address so I'd not like to cut off any further discussion about it. But just to reiterate that we are being asked to evaluate the information that was given to us or that was publicly available.

So with that -- and answer the specific charge. So with that, Dr. Terry had his hand up and I'll let him.

DR. ALVIN TERRY: Yes. I had a question for Dr. Lowit. As we sort of --

DR. JAMES MCMANAMAN: No, we can't be going back to the agency. I has to be along --

DR. ALVIN TERRY: Well it was a clarification of something she said this morning.

DR. JAMES MCMANAMAN: Oh, okay, all right.

DR. ALVIN TERRY: Whenever you were talking about the point of departure and the two pg/g threshold value plasma level, you said what is measurable and what is safe may be two different things. And as a research scientist I have a hard time getting my head around that one. I mean if you can't measure it, I mean how do you make any designation whatsoever of what you're dealing with? I mean there are millions of things you can't measure.

DR. JAMES MCMANAMAN: No, that's not a clarification.

DR. ALVIN TERRY: Well, I would like to hear that clarified.

DR. JAMES MCMANAMAN: Well, that's not an issue for now. So I think that's the agency's opinion and it's been stated that's how they're -- you know, what they want to work on. But we have to deal with the science in front of us. And if you disagree with that let's just say that we disagree with that view.

DR. ALVIN TERRY: All right. It'll come up in the point five.

DR. JAMES MCMANAMAN: Okay. Dr. Popendorf?

DR. WILLIAM POPENDORF: Yes. Just to add to the summary of going back to the differences between Spearman and the other sources that we considered. Transparency in Haddis' data was the log-log correlations run by Perrea and Wyatt in Perrea I think 2002, I think Wyatt 2004 which were more quantitative, different tests, parametric, but it definitely showed some nonlinearities with some large differences in some portion of the data.

DR. ANNA LOWIT: Can I just ask a question? Are you talking about the correlations between cord and maternal blood or log-log correlations?

DR. WILLIAM POPENDORF: Yes. That was kind of going back a little bit on the -- I had my hand up but didn't quite get in. But yeah, going back to the cord versus maternal blood, yeah.

DR. JAMES MCMANAMAN: Dr. Fisher?

DR. JEFFREY FISHER: Yes. Jeff Fisher. I think we -- the entire group said yes to 1.a. But

then it's the devils in the details about what that relationship is beyond the text and nonlinearity. But I think we all said yes.

DR. JAMES MCMANAMAN: I don't know whether we all said yes or not but that's -- that will end up in the report, what the views were.

DR. STELLA KOUTROS: And just to ask for a point of clarification. Is it necessary for us to speak our either agreement or disagreement with each item of agency's proposals out loud? Or can we -- you know, for the sake of time I don't want to go back to everything that happened yesterday. Is it sufficient just from the perspective of process for me to just provide those in written comments?

DR. JAMES MCMANAMAN: Well it would be best if we could provide your individual perspectives at the time the question was addressed. But you've raised an issue now that we're happy to consider if you know, you made a point that you disagree with the conclusions then that's you know, there's clearly going to be not consensus on these -- many of these questions.

DR. STELLA KOUTROS: Thank you. And I -- obviously I think we'll have a full day of

opportunity to bring up additional issues.

DR. JAMES MCMANAMAN: So if possible can we move on to the next charge question -- number three?

DR. ELIZABETH HOLMAN: Beth Holman, EPA. Question 3, Pharmacokinetic or PK Time Course Considerations for Labor and Delivery, (see Section 5). Figure 2a and 2b on page 17 to 18 provide an example PK profile for chlorpyrifos for current exposures to pesticide applicators. Similar figures for food, water, and residential exposures are shown throughout the issue paper, (see Section 6 and 9). As shown in Figure 2a, each PK profile shows a consistent pattern of a daily, rapid increase in internal dose during the exposure periods, followed by a rapid decline after the exposure period ends.

The rapid decline of chlorpyrifos after exposure terminates is expected given how rapidly chlorpyrifos is initially metabolized. The periods of rapid increase represent rapid uptake during activities that lead to chlorpyrifos exposures. While the periods of rapid decrease are primarily attributed to distribution from the central compartment circulation into the peripheral compartments, body

tissues lost to metabolism and binding to esterase. For chlorpyrifos the half-life of this initial phase is estimated to be approximately four hours.

Upon cessation of the exposure, the terminal half-life, approximately 120 hours, predominates resulting in asymptotic appearance for the internal dosimetry. As summarized in Section 5 for deriving the proposed point of departures (see Section 7). The agency is assuming the Columbia levels do not represent values within the rapid increase/decrease space. Instead, the agency is assuming the reported values for cord blood and maternal blood are at the low points within the terminal clearance period and thus unlikely changing significantly across several days.

Although part of labor is spent at home where exposure is assumed to occur, some portion was spent in the hospital. Meaning removal from the apartment caused the exposure to cease. This assumption is being made because labor and delivery typically requires multiple hours. Moreover, maternal blood samples for some mothers were taken up to two days after delivery. The agency also notes that the results from the agency's exposure characterization

analysis of the Columbia study, (see Section 6), closely match those from the Columbia study providing further support for the agency's characterization of the PK profile.

Please comment on the agency's characterization of the PK profile and the interpretation of the Columbia biomonitoring data. Please include in your comments the agency's proposal to use the 10 and 24-hour post time points on the PK profiles for assessing risk to chlorpyrifos.

DR. JAMES MCMANAMAN: Thank you. The discussants on this are -- Dr. Sweeney is the lead discussant, Dr. Fisher, Dr. Hayton and Georgopoulos.

DR. LISA SWEENEYZ: Thank you. I additionally had input from doctors Koutros and Popendorf in these comments. And collectively the six respondents to this question submitted about 10 pages of written comments on the issues raised in this charge question. I also had some limited discussions with others who raised concerns that I have incorporated into the summary. Therefore, I have consolidated the comments in such a manner that I hope will facilitate the communication of key points of both agreement and disagreement among the group.

After my summary, which is only about a page and a half instead of 10 pages, I suggest we go to the assigned discussants to provide additional detail if they deem fit, such as issues not mentioned in my summary, issues raised generally by one person. Then the additional contributors and then open it to the rest of the panel for comment. We appreciate the agency's responsiveness to the recommendations of previous SAPs as demonstrated by their willingness to embrace the challenge of applying PBPK modeling techniques to human biomonitoring and epidemiological data.

These are far from routine tests and the agency is to be commended on their creativity, innovation, and the rigor of their efforts. Furthermore, EPA has been transparent in the documentation of their assumptions and their efforts, and displayed openness and candor regarding the limitations of what could be achieved with the chlorpyrifos data set. Multiple respondents noted that PBPK modeling is indeed a valuable tool to interpret the biomonitoring data in circumstances where multiple roots of exposure occur. Especially when it is based on best available information on the

inputs.

Concern was raised, however, by at least two individuals about the following points: use of cord blood at delivery in the CCCEH study as a PoD rather than time-weighted average during pregnancy at peak concentration earlier in pregnancy, or blood concentration at exit from the home residence; the assertion that cord blood measurements in the CCCEH study can be characterized as predominantly corresponding to levels tense 24-hours post-peak.

The lack of justification of an absence of chlorpyrifos exposure between hospital admission and collection of cord and maternal blood; and the absence of a sensitivity analysis that would help characterize the dependence of key model outputs on particular parameters. And two reviewers commented on the level of agreement between the agency's exposure characterization of the CCCEH study and blood measurements from the study.

To address those points in a little bit more detail, three individuals suggested that PBPK modeling should be used to convert the CCCEH blood data test made the higher pre-admission blood concentrations using the best available information on

the exposure scenario. In particular, two discussants noted the CCCEH study specific information on times from hospital admission to delivery and maternal blood collection, as indicated in the Haddis submission -- Haddis (2016), page 50.

Two discussants noted that a measure more indicative of cumulative exposure such as the area under the curve or a time-weighted average blood concentration to be considered more relevant to risk than peak concentration. Respondents were split in their opinions of the agency's characterization of the cord blood data as adequately corresponding to 10 to 24-hour terminal clearance phase. Concurring comments indicated that these panelists found the agency's considerations in this regard to be careful, reasonable, or adequate characterizations of the CCCEH exposure scenarios.

Those disagreeing noted that the initial decline phase of four hours is less than many labors. Whereas the agency cited papers indicating wide variations in the duration of active labor, and average labors of around six hours, with a weighted mean standard deviation of roughly three-and-a-half hours. Placing many deliveries in the initial rapid

clearance phase with a four hour half-life, rather than in the terminal half-life phase. Also, the 10 hour post-exposure assumption could potentially lie in a transition zone between times that are clearly in the initial post-peak clearance phase versus those in the terminal phase.

A number of panelists have questioned whether the study participants were truly unexposed to chlorpyrifos for the period between hospital admission and blood collection. They would urge the agency to provide support for this assumption as none was identified in the current issue paper. The discussants who suggested the use of sensitivity analysis requested global and local sensitivity analyses that would characterize the sensitivity of the model's outputs. For example, blood chlorpyrifos at key times to the model parameters and/or exposure assumptions.

These discussants recommend that the sensitivity analyses be extended to the maternal and fetal compartments of the Dow pregnancy model into the life stage model. While it is true that full evaluation of the modified pregnancy model is lacking, and such an evaluation would in fact present major

challenges, nevertheless it could be used as a valuable risk informing supplementary tool for calculating relevant tissue doses for fetal compartments under the selected scenarios. One panelist notes that, "The exposure characterization provided by the agency in Section 6 closely matches the real human data that the CCCEH study has to offer."

In contrast, another says, "If the broadcast and perimeter exposures occurred as assumed by the agency, exposed mothers would have higher blood concentrations of chlorpyrifos than those reporting in Figure 1. Thus the agency's scenarios appear to exceed the upper end of the scenarios encountered by the CCCEH study participants." As there appears to be disagreement on the particular topic, and that topic is addressed more fully in subsequent charge questions such as Charge Question 4, it might be better to defer that discussion to that charge question where other panelists may have weighed in since that aspect was sort of peripheral to Charge Question 3 and is more generally the subject of Charge Question 4.

So that's my summary of the consolidated comments. I have an additional

individual comment, should I go ahead with that?

DR. JAMES MCMANAMAN: Go ahead.

DR. LISA SWEENEY: I would further add the following: The EPA asked that we comment on, "The agency's characterization of the PK profile and the interpretation of the CCCEH biomonitoring data." EPA does indeed speculate on possible exposure profiles in corresponding pharmacokinetic profiles for CCCEH participants. However, when it comes to deriving the proposed RFD, EPA uses PK and exposure information only to characterize the time from departing the residence until birth and maternal blood collection. I won't speculate on motivations for that choice.

I'll state that while I do not consider myself to be an expert in exposure assessment per se', it is my opinion that exposure patterns timing and magnitude for the study participants probably cannot be known with sufficient certainty to derive measures of internal dose that reflect chlorpyrifos dosimetry throughout gestation Such internal dose metrics, if they could be reliably calculated, would provide a substantially more meaningful reflection of the risk of neurodevelopmental effects than can be captured in a snapshot blood concentration at delivery.

DR. JAMES MCMANAMAN: Thank you. Dr. Fisher?

DR. JEFFREY FISHER: Well, Lisa captured all of my comments in her summary. Thank you.

DR. JAMES MCMANAMAN: Okay. Dr. Hayton?

DR. WILLIAM HAYTON: Yes. I agree with -- I mean I provided all my comments. And I think as I understood it role out from Lisa, I think that's it.

DR. LISA SWEENEY: You had additional comments about blood brain barrier and dermal absorption. Do you wish to bring those up for the agency?

DR. WILLIAM HAYTON: Yes I did. I did, I provided those to you but looking back on it the agency's not seeking comments on the structure of the model. So I think I'll just leave those as marginal notes to myself and they probably shouldn't be incorporated. Thanks.

DR. JAMES MCMANAMAN: Dr. Georgopoulos, can you hear me?

DR. PANOS GEORGOPOULOS: Yes. I do hear you. The summary by Dr. Sweeney covered the most

important points. And I would like to go over precisely the need for sensitivity analysis that I think will basically corroborate the choices that are presented in the report. Because we should not expect some of the outcomes to be very sensitive to the exact time lapse between admission and blood collection and so on. I think it also would be very helpful, it would strengthen the case of the agency, if the data that are reported in Dale's report -- Dr. Haddis' submitted comments regarding the distribution of time periods from admission to child birth to blood collection.

I don't know if the agency was aware of that information and decided not to use it. But using even statistical metrics from those I think would be grounding the outcomes of the conclusions in a more solid way than it is right now. So I think that would be important to really consider and to combine this with a sensitivity analysis. Finally -- and again the comment about using those pregnancy model as a supplemental risk informing tool because analysis of that can address some of the issues of calculating actual target tissue dose.

I mean my -- I understand that the cord

blood measurements are not the only ones that are available. But that's the advantage of having the PBPK modeling tools, is that we can relate them to something that is more risk relevant. And though these numbers cannot be used directly they provide substantial insight. I mean we can calculate total variable dose to tissue over time to the fetus and even the integrated dose, I think, would be very useful under a different scenario. So again I think it will strengthen the case for this.

The other comment that I hear were sometimes about semantics. I mean I think some of the wording could be improved. I mean using words like -- in the charge question saying that the results of the PK modeling closely match the measurements of the study is probably an overstatement. I think the ranges are consistently such that they match each other because you know, given the uncertainty that we have in the calculations that were performed to use words like closely matched, again, it's a matter of semantics but I think it could be stated in a more appropriate way.

Again, I hear some other comments that are more in the low (inaudible) but they are not as

specific to the question. I agree with the summary that Dr. Sweeney provided.

DR. JAMES MCMANAMAN: Thank you. Okay. This charge question is open to the other panel members now. Dr. Popendorf?

DR. WILLIAM POPENDORF: Yes. I did provide some of the comments that Dr. Sweeney referred to and I'd like to spend some time talking about that. Because it actually -- I referred to, yesterday, some of my concerns with the cord blood data. And it will certainly have impacts I think on, at least to me on subsequent questions. And I think these are based on the PBPK simulations that prior SAPs did not have available to them. So it really goes back to the validity of the cord blood data.

And I think the basic problem is that I would disagree with the assumption that the chlorpyrifos in maternal blood collect -- well, excuse me, I would not disagree that the chlorpyrifos in maternal blood samples collected one to two days after delivery is at a low point and stable and somewhat reliable. Which is why I answered yes to Question 1.a. However, the same PBPK predications led me to conclude that the presumption within the issues paper

that the cord blood samples are in a steady state is seriously flawed.

While it's true that some of the samples collected more than 10 hours after admission to the hospital would be or could be stable, are likely to be stable, as stated, most are not likely to be stable. And I'll just, I think it's worthy elaborating on that. By the way, Fred, if you would either pull up Figure -- my slides, or we could -- well anyway. You may recall that within the issues paper the presumption that the cord bloods were at or near their low point was based on the Neal report that looked at a review of other articles that comprised 7,000 women or so and found that active labor lasted an average of six hours.

And they actually, to quote, "Up to 13.4 hours at two standard deviations from the mean." Which is I think probably why the agency said 10 hours it would be stable. However, they didn't have the second quote is, "Perhaps finding the best indicating," this is a quote of Neal's, "Perhaps the finding best indicating that the duration of normal active labor varies widely is that the weighted mean of the standard deviation is three-and-a-half hours."

Now those of you who have some background in statistics, if you've got a mean of six hours with a standard deviation of three-and-a-half it's probably not normal, but that's kind of minor. But anyway, it's very wide.

And further, Neal quotes, "The contemporary practice of most providers aimed to admit women to the labor unit when cervical dilation is expected to be more rapid, i.e., the onset of active phase of labor." Which is really the point of his whole article. So we've got this pretty well known wide variation inactive labor times which means times of admission to delivery. Now the assumption is that there is no exposure in the hospital. So basically once they're admitted they're going into this active phase of -- I think the agency sometimes calls the active or the rapid initial half-life phase with a half-life of four hours.

Now Haddis does a little more work and it's a multi-compartmental model. So it's not a straight half-life of four hours. It starts at maybe three-and-a-half and gets a little longer, but four hours is a pretty good number. So if you just think in terms of four hours, now that every four hours is

half of what was there, so after two half-lives it's 25 percent of what was there, that' seven hours in. We're just about to the average point, we've gone through two half-lives already. So half the population's already gone through two half-lives.

So you've got some spread there and of course the other half of the delivering mothers are going to be spread out. If you include the one half-life above that it's about 78 percent of the people though within the 10 hours are still in this half-life phase where values are changing. You can go to the next slide too, Fred. So the point of that, when you look at these sorts of curves -- and this is a generic curve I found in the issues paper. No numbers on it which is kind of good.

But you can see that you can actually, if you start looking at this in terms of half-lives that it depends really on the time of delivery or the time in the hospital whether you start with a recent low exposure -- I mean you can --

DR. WILLIAM HAYTON: Excuse me, this is William Hayton. Could you tell us what's up there?

DR. WILLIAM POPENDORF: It's a generic one.

DR. WILLIAM HAYTON: But is it the mother or the fetus or do we know what the timescale is?

DR. WILLIAM POPENDORF: It's not the fetus because this is PBPK from Appendix X, it's definitely the mother.

DR. WILLIAM HAYTON: So it's pregnant versus non-pregnant female?

DR. WILLIAM POPENDORF: I think it's a spiked dose. And I don't mean to look at the numbers there you know, it's just representative of the curve. The point is if you look at you know, envision the person walking, the expectant mother walking in the door, at some point they're going to have delivery, the cord will be sampled. There's a whole other question of from the time of delivery I don't think they were right there, they probably didn't take the sample from the cord at that point. So there's some lag time there. Is the chlorpyrifos metabolized after delivery, between time delivery, and sample? Unknown.

But if they're walking in the door you could take any value -- I guess I don't have a pointer, but pick any sort of Y-value there you know, whether you want to be high or low. The point is that

you can get there in multiple ways. You can either have a low recent exposure or you could have started at a high value and come down. The impact of this variation in delivery times means that you could get any value of chlorpyrifos based strictly on delivery times. I mean I've tried to do some calculations, I certainly didn't do a simulation.

You could virtually reproduce the entire spectrum of cord values in the Rauh (2012) article. People walking in the door all at the same level, delivering over a period of plus and minus two half-lives, eight hours, which is within the range reported by Neal, and reproduce that graph. So you can get there by starting at high values, you can get there starting by low values. Technically you probably couldn't if you dichotomize the -- I think on the next slide I actually you know, for what it's worth that is the Figure 1a from Rauh that we've been talking about and you know, they're all black dots.

If you were to dichotomize that distribution to those that were exposed or delivering before 2000, before the cancellation versus those after, I think Figure 1 in the paper puts most or virtually all the high values before cancellation,

some of the lows. But after cancellation Figure 1 says that those low values would be you know, at one and non-detects. So you could actually, if you dichotomize and said okay, those before 2000, before cancellation, if you gave them all one value I could reproduce that I think just based on delivery times.

So I think to me the potential for the short delivery times has potentially -- you can create a small number of relatively high blood values. And if you look at those plots that correlation's really driven by a relatively small number of points. But it's -- you can get there either by you know, again starting low and delivering early, starting high and delivering later. You get to the same you know, you'll have a measurable value. For those that happened to read Haddis, there is some actual data in their records somewhere for at least 133 deliveries of the time between admission and delivery.

He was doing some calculation in Table 25. I think he was trying to come up -- well, I don't know what he was trying to do, he calculated an average delivery time. But if you look at the data in that table there's some glitch. I don't know, I think it had to do with -- well, I won't go into why it may

have been. But anyway, those numbers aren't reliable at all in those times that he reports. I mean the times are valid but what he puts in the table to calculate an average delivery time are not valid. If you see the table I'm sure you'd agree.

I don't know, it's just something that he put in and didn't really look at it. Again, maybe it's another example of information we don't have. But when I saw those PBPK values and started thinking about the implication, that variation in delivery time, those cord values to me could easily be -- in fact based on what I just said if you walk in the door, vary the delivery times, I can reproduce that. So to me these are artifacts of delivery time much more than they really represent some recent past exposure.

And because of that transient effect the stability of those data -- the correlations are what they are but I don't -- I mean you can put within a range each of those dots should have like a four X factor, they're each represented by bars. And maybe there's some way to do an analysis, like a sensitivity analysis, but the variability of the chlorpyrifos values, the x-axis values, is huge.

DR. DAVID JETT: Yeah. Since this is something I was going to raise as well. So it would be great to know if we had the time they left the house data. But I know that's going to be just really hard to get. But shouldn't we be able to get the admission times -- days and times for this study to address this?

DR. WILLIAM POPENDORF: You mean like from the hospital?

DR. DAVID JETT: From the hospital records. Oh, and this is Dave Jett, NIH.

DR. STELLA KOUTROS: This is Stella Koutros. I think that it is unlikely that the 2016 FIFRA SAP panel could procure that data.

DR. DAVID JETT: Not we but they.

DR. JAMES MCMANAMAN: Given that we don't have access to the hard measurements it's going to be illogical that we can get that. So Dr. Hayton had his hand up first.

DR. WILLIAM HAYTON: I'd like to inform the discussion a little bit, I hope I'm informing it. We have to remember the fetus is a peripheral compartment, it's still hooked up to the mother. But I don't think we can assume that the profile for --

the simulator from mother's blood is representative of what's going on on the fetal side. My guess is they're quite a bit more attenuated. So I don't think the peaks in the fetus you know, if you could actually measure or use the model to simulate it, I don't think the peaks in the fetus would be nearly as high as they are in the mother is my guess.

I think that could be verified through some modeling but it is a peripheral compartment. The other thing I'd like to say is that it seems to me the Figure 1 which shows the cord and mother's data and the fact that they seem at least at higher concentrations to ratio out about one or close to one, in other words they're about the same. And if we say that the mother's blood is post-distribution, post-peak in the long half-life phase, then it seems to be that sort of -- because the concentrations are the same it sort of suggests that the cords are too.

It's either that or you have a much different pharmacokinetics going on in the fetus than in the mother.

DR. JAMES MCMANAMAN: I think Dr. Popendorf wants to respond.

DR. WILLIAM POPENDORF: I certainly

take your experience on cord and fetus for what it's you know, I don't have any expertise in that per se. But not all of the cord and maternal values are equal, again. So what's driving these is -- we don't you know, have a full appreciation for. So what you say has some validity and has had some impact on this figure. When you said Figure 1 by the way you meant this Figure 1 or the issue paper Figure 1?

DR. WILLIAM HAYTON: Yeah. It's really a table but it's referred to as a figure. The one that has the numbers that are very hard to read.

DR. WILLIAM POPENDORF: Dr. Koutros?

DR. STELLA KOUTROS: It seems to me that the crux of the issues that I heard from Dr. Sweeney and Dr. Popendorf are related to the fact that one measurement of exposure to chlorpyrifos in the plasma is limited with respect to predicting what may have happened over the course of pregnancy and subsequent exposure after delivery. So there's an exposure piece that's missing in our ability to understand the full time course that we're interested in. So --

DR. WILLIAM POPENDORF: Excuse me. Well that's true. I mean I am concerned. My comments

didn't really relate to anything beyond -- I mean this is all short-term information.

DR. STELLA KOUTROS: Sure. So I guess I'm wondering, given that the Columbia study can't provide us with a time weighted average or information about cumulative exposure. And that we don't know exactly when or if the mother's continued to be exposed once they left their house. That information isn't provided in the Columbia study. So it kind of gets back to this fundamental question that I have in that we've been dealt the hand that we've been dealt with and has the agency used that data that are available to us, not what we would like to have to make some determinations downstream for their risk modeling.

I thought that their interpretation of the available information from the Columbia study which has the uncertainties that you noted was very considerate in that it took into account information for pregnancy and labor patterns. And also the simulations show for example that you know, the exposure was probably a lot higher at some previous point in time which was consistent with some of the data from the study. So I guess I'm just wondering if

the panel has any recommendations for the agency given the data that are available and not based on data that we don't have.

DR. JAMES MCMANAMAN: So I'm trying to figure out how to -- does Dr. Popendorf have a response to that? Okay. So, Dr. Rohlman you were next.

DR. DIANE ROHLMAN: Diane Rohlman. I just want to point out that in the Dale Haddis preliminary data that he does -- Dr. Haddis does have information about the time lag between the baby's birth date and time and the date of maternal blood collection. That's found on page 43 in that document.

DR. JAMES MCMANAMAN: Dr. Fisher, you had your hand up?

DR. JEFFREY FISHER: Yes. I think she -- Diane had pointed out the information. But in the simulation world, the modeling world, you could simulate the potential scenarios that we just discussed and not assume you're in the terminal phase. And I think -- or my intention in the summary statement with these measures of exposure can come from simulation. Through simulation you can get area under the curve time-weighted average. You can

reconstruct and calculate these metrics of exposure I know we don't have the data so to me it was from a simulation point of view. And they show up and down plots, that's an exposure.

Those up and down lines can be presented or calculated as a time-weighted average or area under the plasma curve. So those are other metrics of exposure to capture during the exposure phase.

DR. JAMES MCMANAMAN: Okay. I think that unless there's anyone --

DR. PANOS GEORGOPOULOS: If -- sorry to interrupt.

DR. JAMES MCMANAMAN: Yeah. Dr. Georgopoulos, go ahead. It's good to hear from you.

DR. PANOS GEORGOPOULOS: Yes. Just you know, a few years ago in a number of studies we went to this enterprise of reconstructing exposures of chlorpyrifos using sparse data and PBPK modeling, using actually the same models that were available from Dow in 2009, 2010. And it's an extremely complex issue because of the time scales involved in this. Actually in the paper that we published in 2009 the challenges of reconstructing exposures from biomarker

data and PBPK modeling we picked chlorpyrifos as the model chemical that presents these problems in trying to reconstruct long-term exposures from a limited number of points in time.

The point that I want to make is however, in this case we are here to pick the most simplified approach. And that's why a sensitivity analysis of the model is probably going to corroborate the general conclusions of the issue paper. One can do a systematic reversal symmetry get rather wide ranges of possible exposures. Which you know, are going to probably not to be very helpful because it will depend upon a number of assumptions. And the assumptions that the agency is making are quite reasonable. The suggestion that I would have is using the data reported in Dale's report for the time between birth and maternal blood collection and so on, maybe using them in combination with sensitivity analysis confirms that their range of estimate are reasonable.

But I don't think that a systematic reconstruction of exposure using the PBPK model can provide more specific information. Because as I said we're just going to get a very wide distribution of

potential exposures. I mean we don't even know, we are assuming that the marker application and the pattern of exposure is an assumption that leads to reasonable result. And here we can only talk about changes. So maybe -- and I don't want to elaborate into the details of this but because of the (inaudible) wrote this up we've gone through the exercise of trying to reconstruct complex exposures. It was the (inaudible) study and other studies and you get very wide ranges of uncertainty.

So it would not really add to much to this analysis.

DR. JAMES MCMANAMAN: Thank you. Dr. Sagiv?

DR. SHARON SAGIV: Can you go back to the slide before this? Okay. So from what I'm reading from the slide and I'm no PBPK specialist or modeler, it seems to me that the slopes of the reduction due to the half-lives are dose dependent. Is that a correct interpretation of this slide? So from what I'm reading from the appendix, the dotted versus the solids lines are the pregnant mother and the non-pregnant woman. But the curves represent different doses, it depends on where you start.

Right?

And from looking at the slope of each of those curves it looks like the slope is quite a bit higher or larger from when you start. Am I interpreting that correctly? Because if I am then I have another point.

DR. LISA SWEENEY: Are you trying to curve left and right or different colored lines within the figure?

DR. SHARON SAGIV: I don't think it matters but let me be the left line.

DR. LISA SWEENEY: Okay. Well --

DR. SHARON SAGIV: Just the one on the left.

DR. LISA SWEENEY: This is Dr. Sweeney. The y-axis is on a linear scale, not a log scale. So you would expect the slopes to be different. But if it were on a linear scale the slopes would look the same because the half-life is the same. So it's something that you can't pick up as well in a plot with that shape of axis.

DR. SHARON SAVIG: Okay. Thank you for clarifying that. So if we were to put this on a log scale the slopes would be the same?

DR. LISA SWEENEY: Yes.

DR. SHARON SAVIG: Okay.

DR. JAMES MCMANAMAN: All right.

DR. PANOS GEORGOPOULOS: Also if I can make -- this particular slide comes from the (inaudible) report. It's for an oral exposure and a single oral dose of over 24 hours. So it's not directly relevant to what we are talking because of the way the chlorpyrifos. There's a difference between the inhalation dose versus the oral. So it's not the most representative of graphs that we would use. But the main point is that we see something that is dose dependent is a fact.

DR. JAMES MCMANAMAN: Thank you, Dr. Georgopoulos. Dr. Popendorf?

DR. WILLIAM POPENDORF: Yes. And I apologize. And I was just looking for a curve that had enough of a timeframe that you could see the slope. It's not representative -- you know, it's not specific to what I was talking about. All these curves yeah, there's some variations with dosing and the route of dosing, and how much history there is to it but why all have a curve something along these lines. And again, you can start at a low point and

take a -- in my case what I was talking about, starting at a low point, one of the middle curves there and have a short delivery. And there you are going into the Rauh data, Rauh (2011).

Or you could start at a high point and end up with a long delivery and have the same value. So it's just representative you know, all your comments and you know, those are -- yeah, there is --

DR. JAMES MCMANAMAN: So it's just meant to illustrate limitations.

DR. WILLIAM POPENDORF: Illustrative with -- that's all it was chosen for.

DR. JAMES MCMANAMAN: Okay. Thank you. All right. That was a pretty thorough discussion. Does the agency -- we'll take it back to the agency. Any need for further clarification?

DR. ANNA LOWIT: No. We appreciate all the discussion and we appreciate Dr. Sweeney's very careful separation of where people concurred and where there was differences of opinion. I think that was very helpful.

DR. JAMES MCMANAMAN: All right. Thank you. We'll go on to the next charge question then.

DR. ELIZABETH HOLMAN: Beth Holman at

EPA.

DR. JAMES MCMANAMAN: This is Charge Question 4.

DR. ELIZABETH HOLMAN: Charge Question 4. Again, Beth Holman, EPA. Question 4: Evaluation of Columbia Cord Blood Data and Predicted Exposures to the Cohort (see Section 6). The agency has used the PBPK model to predict blood levels in women across several exposure scenarios for comparison with the cord blood levels reported by Columbia (see Section 6). Food exposure is expected to have occurred (see Section 6.2), whereas drinking water exposure was unlikely (see Section 6.1).

Given the lack of specific Columbia exposure information, the agency has developed six possible residential exposure scenarios representing a broad range of residential post-application exposures to chlorpyrifos products available prior to the voluntary cancellation of indoor products in 2000 (see Section 6.3). Two exposure scenarios were conducted using EPA standard residential exposure assessment approaches; these two scenarios represent the high end exposure potential.

To estimate lower exposures, four

additional PBPK model simulations were conducted with use of reported values from the Columbia investigators. These six possible residential exposure scenarios were input into the PBPK model to predict a range of potential exposures for comparison to the predicted internal dosimetry levels reported by the Columbia investigators.

Based on the results of these simulations, the agency has concluded that: 1) the reported higher blood levels in the Columbia study from 1998 to 2000 are likely driven primarily by residential use of the broadcast and perimeter chlorpyrifos products registered for use at that time; and 2) these results further support the reasonableness of the magnitude and distribution of data reported by Columbia. Please comment on the agency's conclusions that these scenarios adequately capture the range of exposure.

Please also comment on the agency's simulations from residential and food exposures and the degree to which the estimates of internal blood levels do or do not match the Columbia cohort results before and after the cancellation of indoor products in 2000.

DR. JAMES MCMANAMAN: Thank you. So the discussants on this are doctors Jett, Koutros, Eric, and Popendorf. Dr. Jett is the lead discussant.

DR. DAVID JETT: Thank you. So yes, I was assigned the lead for this question but we are really fortunate to have experts on the panel with much more experience with epidemiology and PBPK modeling. So what I will do is give my general comments and then just turn the floor over to each one of the people that participated in our group. So first, I guess I wanted to make a small comment on the water exposure piece in the document. And I think that dismissing the drinking water as a major source of chlorpyrifos is probably the right thing.

I am still a little unclear on the significance of the chlorpyrifos oxon expected even if as stated you know, the chlorination and the mixing should take care of that and keep it well below significant levels. With regard to the food, the data and Table 2 in the document support the agency's assertion that food exposure is likely low and that these data are in general agreement with the data from the Columbia study after the year 2000. In terms of the modeling effort -- and by the way, some of my

comments are going to sound a bit repetitive so I'll try to keep them short, because they were covered in the previous question.

So for the modeling, the data for the food seemed to generate realistic data since they are similar to the lower levels reported in the Columbia study. However, the peak blood level is 7.14 which is a little bit higher than the cutoff tertile reported in the report. So the contribution of food is probably relatively small but not absolutely absent. Now with regard to the residential chlorpyrifos exposure scenarios the uncertainty of the time and frequency of the residential exposures in relation to the timing of the cord blood collection is unavoidable and cannot be guided by the Columba study because those data are not available.

But using monthly applications is a good estimation since this was reported to be the case in the literature and is a recommendation for the frequency of the application of this pesticide. It's also possible that chlorpyrifos was applied more or even less frequently, and it would be interesting to see exactly how more or less frequent applications would affect the data generated by the model. In

terms of the simulations themselves, these are the stimulations of residential exposures and then their comparison with the Columbia study.

The modeling effort versus the Columbia study data, in that effort the agency chose to use the 24 hours after the last peak on day 30 as a comparator for the Columbia study. And I'm not sure the significance of the other higher concentrations predicted from the models. And the question, whether they should be addressed even if they are far higher than the values in the Columbia study since those higher values may have been missed due to the timing of the blood samples in the study. Especially if a mother delivered shortly after leaving the home, for instance.

And that's about it and so I will turn it over to our other panel members at this point.

DR. JAMES MCMANAMAN: Dr. Koutros?

DR. STELLA KOUTROS: So my disclaimer is that I don't have a great appreciation for the way that this data has been simulated or the methods used to do that. But the data that the agency has presented with respect to the water and food source exposure are convincing to support the assertion that

it's unlikely that these sources contributed significantly to the observed high levels of measured chlorpyrifos exposure in the Columbia cohort. And the nice range of possible residential exposure scenarios, I thought that was really interesting.

I don't know if it's typical to pick six, I don't know what the significance of that is. But I thought it was a nice range of possible residential scenarios presented and showed and support the conclusion that the Columbia reported values are plausible and similar to the simulations.

DR. JAMES MCMANAMAN: Thank you. Dr. Ehrich?

DR. MARION EHRICH: Okay. We have to go back to some things here. I thought the scenarios and results obtained likely suggested concentrations of chlorpyrifos in exposed subjects. Especially samples obtained after collection of indoor products will in most cases be below levels of detection. And I supposed that's fine for simulation because we've had that before. I think the EPA is put in a hard spot here, because these epidemiological studies are good but they were set up to be research studies and not studies used for regulation, and that only is

something that came later.

And if you're regulating on something like residues -- the proposed mean for determining chlorpyrifos exposure is based on analysis of a parent compound in blood, metabolites, and urine. If this is to be the case it is necessary that precise and sensitive analyses can be reproduced, quantitated in multiple laboratories with data available for scrutiny. And I would suggest a recommendation for the EPA, the scrutiny should be at least as rigorous as that done for the FDA in dealing with residues in milk or in food and feed, and that involves additional laboratory testing.

Now if the Center for Veterinary Medicine wants to close down a dairy facility because there's residues in the milk they send the sample to another lab like ours for testing. We also get the method and see if we can do that type of method. Which is why I was asking so many -- if you don't understand it do you ask questions of the people that did it. Which is why there were so many questions to Dr. Barr who graciously answered those questions. Or you use a method that you have in your laboratory.

So additional lab testing of suspected

samples, method review, and for laboratories like ours we even have right now, this week, they're testing unknown samples from the FDA for residues in milk which are low levels like there would probably be in cord blood here. So I would suggest from review of information provided on chlorpyrifos, questions are raised about basing points of departure for risk analysis on quantitations from a single laboratory with analyses done externally, always at the same laboratory. This adds to putting the EPA in kind of a bad spot when you're trying to defend the data. And so I am trying to provide some suggestions for you.

So what you did with the data that you had in doing the modeling I thought you did a good job. But I question very much that that data -- you're going to have trouble defending that data when you can't have the actual data, it's not done in multiple laboratories. The FDA, if they're going to shut down a dairy facility for example, they do all this. And that's something much smaller than what's happening here. We're having something that has national implications, this is setting a precedent. And you need really rigorous data in order to set this up.

And that's not saying anything against that study because it's probably the best epidemiological study, but it was not set up to provide that type of rigor that you have to defend.

DR. JAMES MCMANAMAN: Thank you. Dr. Popendorf?

DR. WILLIAM POPENDORF: I think I basically agree that the PBPK models do cover a good representative range of exposures. I think we've given some good reasons why the peaks that are predicted by the PBPK model are not found in the Columbia data because of this rapid phase of elimination that I was just talking about earlier. I did note on the other hand that if you look at the time when residential applications were being done the PBPK model doesn't really predict any low exposures. And there were some found in the pre-cancellation phase of the Columbia data.

So that kind of begs the question were people all using -- was chlorpyrifos applied to all of the residence or not? Supposedly I think there was about 15 percent who weren't, or at least self-reported not using chlorpyrifos. So how did they get zero values? And I also -- I don't have any

explanation for this but you may recall back in Wyatt, 2003 they said, 'There was no significant difference in the levels of chlorpyrifos and some other things, in maternal and cord plasma levels among the groups based on self-reported pesticide use.'

So they looked that those that reported use and not, and didn't find any differences. Yet some people ended up with low values and the PBPK model doesn't predict low values. So the low end I guess I have some questions about. But the high end I think is reasonable and all the other routes of exposure I'm comfortable with.

DR. JAMES MCMANAMAN: Okay. This charge question's open to the other panel members at this time.

DR. DAVID JETT: I was just thinking about I may have said PDBKPK modeling. I work in drug discovery and development. So a correction I guess.

DR. JAMES MCMANAMAN: All right. Thank you, Dr. Jett. Okay. Hearing no additional questions I'll turn it back to the agency.

DR. ANNA LOWIT: We don't have any clarifying questions. Thank you.

DR. JAMES MCMANAMAN: Okay. Thank you.

We'll move on to the next charge question then, Charge Question 5.

DR. ELIZABETH HOLMAN: Question 5 - Options for Deriving a point of departure for Neurodevelopmental Outcomes Based on the Columbia Biomonitoring Data. As summarized in Section 7.2, the agency has proposed a PoD for the observed neurodevelopmental effects and offered alternative options based on internal blood concentrations of chlorpyrifos from the results of the Columbia University study.

Question 5.a., Approach to Using the Cord Blood. The agency could consider continuing to use the acetylcholinesterase PoDs and apply additional factors over and above the Food Quality and Protection Act 10X Safety Factor to reflect the level of uncertainty of protecting for neurodevelopmental outcomes when using acetylcholinesterase for the PoD. However, the agency would still need to quantify the difference between effects from acetylcholinesterase inhibition and from neurodevelopmental outcomes, and the analysis to evaluate the appropriate additional factors would again require the agency to make quantitative use of the Columbia cord blood data with

the same uncertainties described above.

The agency has elected to propose to use the cord blood directly as the PoD as the simpler, more understandable approach. Please comment on the agency proposal to use cord blood directly as the PoD.

DR. JAMES MCMANAMAN: Thank you. The discussants on this are doctors Carr, Funk, Pessah, Sweeney, and Terry. Dr. Carr is the lead discussant.

DR. SHARON SAGIV: Can we, before we dive into this, take a five minute break, please?

DR. JAMES MCMANAMAN: Sure I think that's appropriate, yeah. All right. So be back at a quarter 'til.

(Brief Recess)

DR. JAMES MCMANAMAN: Let's get started again. Okay. I think we'll get started with the next charge question. This is Charge Question 5.a., and I think you've read it. You did read it into the minutes? Okay. So the discussants again are doctors Carr, Funk, Pessah, Sweeney, and Terry, and the lead discussant is Dr. Carr.

DR. RUSSELL CARR: This is an attempted summation of all my contributors' comments. It is the opinion of some panel members that the CCCEH

study is a well-designed longitudinal birth cohort research study that provides some of the strongest epidemiological data linking prenatal exposures to chlorpyrifos to developmental impairments later in childhood. And that the longitudinal design and the measurement of biomarkers specific to chlorpyrifos at birth are a major strength of this study.

However, other panel members have an opinion that the CCCEH study, while suggesting a link between prenatal chlorpyrifos exposure and developmental impairments, is plagued by issues that diminish the enthusiasm for this study and create a host of uncertainties. The panel agrees that both epidemiology and toxicology studies suggest there is an evidence for adverse health outcomes associated with chlorpyrifos exposures below levels that result in 10 percent red blood cell acetylcholinesterase inhibition.

However, the panel agrees with the agency that applying additional safety factors to acetylcholinesterase PoD to account for a possible noncholinergic MOA would be problematic because of the challenges in justifying any particular value for such adjustment. The agency has elected to propose the use

of cord blood directly as the PoD as the simpler, more understandable approach. As data accuracy and reproducity have emerged there's major concerns across all fields of sciences. The agency is asking the SAP to judge the weight of evidence based on the results from a single longitudinal study, to make a decision of immense ramifications using the cord blood measures of chlorpyrifos as a point of departure for risk assessment.

As indicated in the response in Charge Question 2 the panel considers the agency direct use of cord blood is inappropriate. The basis for this includes the inability to know or confidently make assumptions about aspects of the exposure patterns, labor and delivery, blood collection, and the uncertainty and timing of the biomarker measurements related to developmental susceptibility. In other words, cord blood measures of chlorpyrifos may be associated with neurodevelopmental outcomes but not causal.

Exposures during periods of other fetal development that might be more causally related to measured health outcomes were not measured and there is an inability to determine the magnitude of the true

magnitude of the exposure. Chlorpyrifos measured in cord blood is thought to represent a period of biomarker stability where chlorpyrifos is not at peak levels or in period of rapid decline. However, there is uncertainty in the use of the PBPK model for extrapolating the chlorpyrifos exposure concentration using the cord blood measures.

This is in part due to uncertainty in the time between peak exposures in cord blood collection. The lack of biological plausibility or animal evidence for how peak cord blood levels of greater than 6.17 pg/g chlorpyrifos can alter Working Memory and produce neurodevelopmental impairment. There's a lack of a dose dependence for adverse biological outcomes, IQ, and Working Memory. These are key issues in the fields of toxicology and pharmacology. Transparency is an issue.

The agency uses 63 pg/g value obtained from Rauh (2011) in the document. This high value as well as four other values were eliminated in the analysis for the effects on Working Memory in Rauh (2011). Behavioral data were available for association with three of the four cord blood values. The lack of information regarding the modified values

of maternal blood used in place of eight percent of the missing cord blood, as Dr. Popendorf has presented a graph, that is not a linear relationship when you make that adjustment.

If such imputations cannot be made with confidence then the cord blood data should not serve as a basis for quantitative human health risk assessment.

DR. JAMES MCMANAMAN: Thank you. Next, Dr. Funk?

DR. WILLIAM FUNK: Bill Funk. So Dr. Carr summarized most of the main points that I had that he read in his statement. So I'll just reiterate a couple of them that I think are important. And I think that we all were in strong agreement that the evidence is very strong from the Columbia study that the prenatal exposures are strongly associated with the health outcomes. The big question that we had, and I have in particular, is how can these measurements be accurately used to predict the PoD? And that's where some of the -- we warrant --

DR. JAMES MCMANAMAN: Can you put the microphone a little closer?

DR. WILLIAM FUNK: Yeah, sure. Sorry.

So the big question is taking these single measurements from the cord blood, how accurately can you predict the PoD from that? And that is what we -- I would caution with.

DR. JAMES MCMANAMAN: Thank you, Dr. Funk. Dr. Pessah.

DR. ISAAC PESSAH: Just for the record. I want to clarify that I have the highest respect for the group at Columbia. And as Center Director for the Children's Environmental Health System I know of them very well and I know that they hold themselves to high rigorous standards. That isn't the point I'm trying to make by asking whether this is a single study or not. Currently the NIH is facing an amazing uncertainty about replication of data. Not falsified data but data that just isn't repeated and replicated. And so what you're asking us to do is provide you a level of uncertainty or how uncertain we feel as experts in our particular field.

And this work that you've put in front of us goes across many fields by the way. And so I can only speak from not having a biologically plausible target which leads to developmental disorders which is three to four orders of magnitude

below any reported biological effects in vivo in animals, in nonhuman primates, in rats, in mice. What I'd like to see to reduce my uncertainty is replication of the study. Now I know you're on a deadline, but again, given the national and possibly international ramifications of such a point of departure one would at least like to see replication.

DR. JAMES MCMANAMAN: Thank you, Dr. Pessah. Dr. Sweeney?

DR. LISA SWEENEY: I have nothing to add. My comments were well incorporated into the summary statement.

DR. JAMES MCMANAMAN: Dr. Terry?

DR. ALVIN TERRY: So I think most of my sentiments were also covered. And I would just also reiterate that even if we took for granted that this is the best of all epidemiologic studies, it's a single study. And you know, even if you're thinking about this idea of changing the safety factor for cholinesterase, even that takes for granted that you believe that there truly is in fact a neurodevelopmental outcome based on these really small levels. And so for me I mean as a scientist I like to see something like what the lawyers say, preponderance

of the evidence.

And a single study, single point in time, questionable, extremely low values, no biological plausibility -- there's nothing I'm aware of in the literature that would suggest you know, pica moller (phonetic) levels cause some significant neuronal change that could underlie a prefrontal cortex-based memory task. It's very difficult for me to connect the dots with such a -- and make a recommendation on a decision of such magnitude. And it came up before about what was discussed in the 2012 SAP. I was there and a lot of the basic science literature was reviewed and discussed.

And yes there's information out there suggesting neurodevelopmental outcomes in animals. In our own lab we have some interesting data ongoing right now in culture where we're seeing some very low levels CPF concentrations affecting axonal transport. But this isn't a peer review, hasn't been published, it's not ready for primetime. So I just don't feel that as it stands right now and particularly in the information that we reviewed that I would be ready to recommend that there is a change to the PoD.

DR. JAMES MCMANAMAN: Thank you, Dr.

Terry. So this is now open to other panel members. Dr. Sagiv?

DR. SHARON SAGIV: I wanted to acknowledge the challenge here which is that we have polar opposite pieces of information. One using acetylcholinesterase inhibition where the PoD is way too high. And then we have the Columbia study, which I as an epidemiologist also have reservations about using one study, where the PoD is much, much lower. And so it sort of defies logic to stick with a PoD that we know is too high. And also defies logic to go to a PoD that is based on one study. So I think the challenge -- I'm not offering a solution here but I'm just recognizing that it's -- from a logical standpoint how do we come to the middle here?

Because I feel that as a panel we can't ignore the fact that we have an epidemiological study that is suggesting associations with a neurodevelopmental, with a number of neurodevelopmental measures. I want to state again that I have a great deal of respect for the Columbia group, I think their data's good. It's one study though. And so that's where the conundrum comes in. And I just, I don't know, as the agency I think you're

in a very difficult position to bridge that. And as a panel we're in a very difficult position too because we don't have the information to bridge that gap.

So I just wanted to state that I recognize those challenges.

DR. JAMES MCMANAMAN: Thank you, Dr. Sagiv. Dr. Ehrich.

DR. MARION EHRICH: Okay. Just for the record on, Russell on your statement there. There's also uncertainty with the measurements because they were not reproduced in another laboratory, the measurements themselves, the chemistry. So that wasn't on your list. I think that probably even use of one study could be improved if those values could be reproduced, if the chemistry values could be reproduced in another laboratory, even if the epidemiology wasn't done. At least that would be stronger and give the EPA better justification for defense of whatever they decide here.

DR. JAMES MCMANAMAN: Thank you, Dr. Ehrich. Dr. Jett:

DR. DAVID JETT: This is just again quick for the record. I just related to Dr. Terry's comment. I probably, again, don't agree that there is

no evidence for noncholinesterase mechanisms both from in vitro as well as in vivo studies from not just my laboratory, from several others.

DR. JAMES MCMANAMAN: Dr. Koutros. I wasn't sure who had their hand up first. Dr. Popendorf?

DR. WILLIAM POPENDORF: We're flexible. Yeah, Dr. Popendorf. Just a point -- well, actually I want to make a point but a clarification. Did you say something about cord blood was in a period of rapid decline or was not in a period of rapid decline?

DR. RUSSELL CARR: Chlorpyrifos measured in cord blood is thought to represent a period of biomarker stability where chlorpyrifos is not at peak levels or in a period of rapid decline. They assumed that it was asymptomatic.

DR. WILLIAM POPENDORF: Or asyntactic, yeah.

DR. RUSSELL CARR: Asyntactic, that word.

DR. WILLIAM POPENDORF: Yes. Popendorf again. Yeah. My prior point was that I would disagree with that quite strongly. I think it still is in a period of rapid decline in many -- in most

cases. Well more than half of the cases based on the evidence that we have. So that would be certainly a difference in that aspect of it.

DR. RUSSELL CARR: Basically the statement says, "Is thought based on the assumptions that were made." I think that statement was going -- that the assumptions were made in a document that assumed that it was stable and not in period of rapid decline. So I'll make that clear.

DR. WILLIAM POPENDORF: Yeah. So you're reflecting the issues paper position rather than our positon? Yeah, okay.

DR. RUSSELL CARR: Yes.

DR. WILLIAM POPENDORF: That would be important.

DR. JAMES MCMANAMANG: That was Dr. Carr and Dr. Popendorf.

DR. WILLIAM POPENDORF: So, yes. And like I say I would say I would definitely believe that it is in a period of rapid decline. And the other much less important issue was again not having access to the data and the way the Columbia group manipulated the data in a couple of ways to deal with missing samples. Particularly in this case the missing cord

blood samples. And they used the Wyatt formula which was -- we don't know what the data was, they didn't show us the data. They ran that log-log correlation to come up with a formula.

So when they had missing -- they had about eight percent, so 21 cord blood values were missing. They used the formula, applied it to the mother's data, put it into -- well, into the cord blood database to run the correlations that they then used. So we don't know really what was the data to generate that formula. It was clearly non-linear. We don't know where the missing values were and what influence that may or may not have had on the distribution of cord blood and the resulting correlations.

So that's just one more unknown. Then there was the point made about there were initially four sort of outliers that were beyond the scale of Figure 1.a. The memo that we had back from Columbia indicated that they removed two of them. One subject did not have outcomes so they didn't have the Working Memory index value. They took out the 63 with very little -- no objective criteria. This influence was observed -- was confirmed that based on residual

analysis -- misquoting again, start at the beginning.

"Subject with 63 pg/g was a highly influential observation (outlier) and drastically impacts inference." So they took that one out. Then they had two left. When they ran the cubic's blind correlations that they showed in the figure they took the other two out which is why they only went up to 25 on the scale. It wasn't clear when they ran the regressions that gave the slopes whether or not those two values were in. And again no particular criteria other than they had an influence on the stability of the regression whether they were in or not.

So they took them out. And if you look at the data that they left in I mean if you're picking and choosing you can pick and choose other points. If you look at that figure -- Fred, I don't know if you want to pop that one back up again. But just visually looking at the data I mean the numbers are the numbers are those are valid numbers. But looking at the data one can pick and choose other points that probably influence that slope. So it was rather subjective what they did. Which is again, a concern using that as a PoD. It's -- there are several.

DR. SHARON SAGIV: Can I just address

the question of input?

DR. JAMES MCMANAMAN: If he's finished then -- Dr. Sagiv?

DR. SHARON SAGIV: So in epidemiology we do something called influence analysis and it's usually done statistically. So I need to read back and see what they did, but I believe that's what they did, an influence analysis. Whereas if one observation influences the results in an extreme way it is sort of standard to remove that observation. Because one observation should not be influencing an entire curve. So I don't think they picked it out -- what I'm trying to get at is I don't think it was a subjective decision.

I mean maybe using influence analysis could be perceived as subjective but we often do it in epidemiology. And I think it's usually done as a more conservative approach. That usually leads to -- often leads to a lower effect. So I would have to see exactly -- I don't know if they actually mentioned why they took it out. It's in the paper I'm sure but --

[Speaker off microphone]

DR. SHARON SAGIV: It's not in the paper. But did they say that they did an influence

analysis, do you remember? Okay. All right.

[Speakers off microphone]

DR. SHARON SAGIV: So when they say highly influential observation that's a little bit different than being an outlier. An outlier would be that you have a point that's much, much higher than the distribution of exposures. I'm assuming that you're basing this on exposure. An influential observation would be different than that in that that data point would influence the results, the effect estimate, the association, unduly. And I believe when you say highly influential observation that's what they're getting at. That it affected the results.

So if you did the analysis with all the data points, it would look very different than the analysis taking that one observation out which I believe is a more conservative approach to presenting your results. Because one observation should not be influencing your results to that extreme. So that's usually why we do it and it usually leads to -- I'm saying usually because I don't know what they did here, usually leads to a more conservative estimate, an estimate closer to the null

I just wanted to make that distinction

that they're not cooking their data here. I think they're using an approaches that we use in epidemiology to get at a more conservative estimate of the fact.

DR. WILLIAM POPENDORF: And I certainly wouldn't challenge that. Fred, can you go another, I don't know, slide forward the other way? Yeah. I did this, this is just the full graph. And to your point, we don't know where that point was. So you may be right. I mean they may have done exactly what you said. What influence it may have had, as you can see, Figure 1.a. is the upper left and the 63 value that they threw out, I ran the scale up to where, I think it's 60. So you can kind of see what influence, it's way out there on the end of that scale.

And if you look at the slope that they did report without that point and two others, project that slope down, not this slope but the one they ran for regression, it actually predicts an effect below the x-axis that they showed. Which is somewhere around 60 or something. So whether you know, what the influence was, was it an influence to keep it less of an effect or was it an influence that would have made it more, we don't know. It was apparently you know,

based on what they say it had an influence.

And then the other two points -- the next page if you read that. But I mean we don't know, it's just one of those uncertainties that we have here.

DR. STELLA KOUTROS: This is Stella Koutros.

DR. JAMES MCMANAMAN: Okay.

DR. STELLA KOUTROS: I would like to disagree with some of the conclusions that were presented in summary by Dr. Carr at the start of our discussion of this question. Although it sounded to me that many of you said that you appreciate the value of the epidemiologic study, all of the subsequent points devalued all of the information that those epidemiologic studies provided. That's the wealth and totality of the epidemiologic data to support a relationship between prenatal exposure to chlorpyrifos and neurodevelopmental outcomes, number one.

The fact that we do not understand the mechanism by which this occurs does not mean it doesn't actually happen, but that it is a source of uncertainty. There were several other points that I can't even remember to make at this point and I will

include in my written comments associated with this question. However, I do want to say if I did not say before that I would agree with the agency's proposal to use the cord blood directly as the PoD. And one other comment before we move on to someone else or to the next question.

For those of you who have said that replication is necessary and that careful scrutiny of these results is warranted, I totally agree with that. But number one, think about what opportunities we really do have to replicate this data in the real world, number one. And then number two, I wanted to state my really big surprise that this panel of scientists is not willing to accept published, peer reviewed data from the Columbia studies. It seems to me that some of you would not be satisfied until you get to analyze this data yourself.

And I think that's inappropriate. We can't even seem to agree that the Columbia researchers can do a proper consideration of correlation. And that is shocking to me from a group of scientists. I would have expect that from industry and we heard it yesterday but it's kind of surprising to hear from some of the people at this table.

DR. JAMES MCMANAMAN: All right. Dr. Rohlman?

DR. DIANE ROHLMAN: Diane Rohlman. So I've been listening to these comments and I've been having many thoughts going through my head. And I agree with, certainly with Stella's points as well as Dr. Sagiv's -- David's, Alvin's. I mean there's many -- every study has uncertainty in it and as scientists we are reluctant to rely on one study for many reasons because we know of that uncertainty. And we're in this position here that replication of this study is not possible. So we are forced to think outside the box. We're forced to think of ways to replicate it.

And I commend the EPA and the modelers in the room for using those methods to try to take what we do know, things we can reproduce, and to use that to try to replicate this data. And I think that is an approach going forward. I also recognize the animal researchers in the room and the people working with cells who are able to look at other things. And what we're trying to do here is to build a body of evidence to make decisions to protect the health of people. So when we look at this we need to weigh a lot of factors here and I'm torn.

I agree with Dr. Sagiv that the current PoD using the cholinesterase inhibition is probably too high. When we look at you know, the weight of evidence from occupational studies, from the child studies, from the animal literature, we see that there probably needs to be a change. I also recognize Dr. Pessah's viewpoint that a single study is very difficult here. And in the absence of replication we need to find alternatives here. So you know, again, I'm looking for solutions. I recognize the issue, I recognize the impact this has economically on our agricultural producers. I see all of that.

But we have to use our science which is what we're called here to do. And I think Dr. Koutros has a really good point you know, is that these studies were peer reviewed. The Columbia group does have a stellar reputation. They have received numerous grants with federal funding that were peer reviewed from a number of panels. We need to put some faith in their findings there. So no conclusions, just a bunch of statements. And I'll stop here.

DR. JAMES MCMANAMAN: And Dr. Carr?

DR. RUSSELL CARR: You're right, we will never be able to replicate this study because of

the voluntary cancellation of chlorpyrifos because of potential for neurotoxicity. We've eliminated this exposure scenario from our situation by that voluntary cancellation. That almost in itself is kind of a pseudo safety factor move and that move improved the situation and it's evident in the data. And I'm just saying that that's something that we should also consider. That we've made -- APA did a good job and Dow agreed and this exposure scenario should not happen again unless somebody does something illegal.

DR. JAMES MCMANAMAN: Dr. Sweeney.

DR. LISA SWEENEY: I'm a co-author on a paper on the use of PBPK modeling and risk assessment where the lead author is from the EPA and a couple of co-authors are also from the EPA that's titled, "Why Being Published is Not Enough." So it's pretty standard in PBPK modeling that the EPA is not just going to use a model in the form in which it was published for risk assessment because it may not have been developed with risk assessment in mind. And I guess I don't feel too sorry for epidemiologists if someone wants to reanalyze their data. Because I don't think I've ever had a model that the EPA just used off the shelf without checking get out and

rejiggering it and adjusting the parameters.

And that's part of the problem with modeling and data analysis is they can always go back and say, 'Well what about this, what if you changed this, what if you did it a little bit differently?' Whereas, people aren't going to tell you to redo a two year cancer study in animals. So I think that's just part of being in the data analysis world as opposed to the animal study data generation world. That redoing the analyses is something that just comes with the territory.

DR. JAMES MCMANAMAN: Dr. Holman?

DR. ELIZABETH HOLMAN: I agree, Dr. Sweeney, that it is important. And certainly having access to the data and rerunning these analyses would increase our confidence in these findings. So the data is available, is not available, that's not been made clear to the panel. Dale Haddis seems to have more information. I think that all needs to be considered as well. I'd also like to address Dr. Carr's comments here. And he is correct in that the residential use of chlorpyrifos has been eliminated but it is still being used.

I think we need to think about these

future exposure scenarios and think about occupational exposures and take home exposures and really focus on what are the current exposures and how to address those. And that, perhaps, is where the other child study, the CHAMACOS project in particular, could be addressing those as well.

DR. JAMES MCMANAMAN: Dr. Popendorf?

DR. WILLIAM POPENDORF: Question actually, because a couple of people have mentioned the ability to replicate or alternatives to the PoD or the approach. Is there a question where we are actually looking for -- where they are looking for alternatives?

DR. JAMES MCMANAMAN: I think that that was brought out in the --

DR. ELIZABETH HOLMAN: It would be this one because the preamble to Question 5 is basically the alternative approach. And I haven't heard an alternative discussed.

DR. WILLIAM POPENDORF: Okay. So I would like to, if I could, it's not just this panel that has had trouble with this particular question. The previous panels have also had trouble with this. And I'm quoting here in the 2008 -- this is from the

2012 Scientific Advisory Panel. "In 2008 the SAP advised against using data from the epidemiology studies, including the Columbia mother's and newborn study which measures chlorpyrifos directly before deriving a point of departure due to limitations and exposure assessment in these epidemiology studies for the purpose of risk assessment."

And they go on to say, "The panel recognizes the limitations of estimating chlorpyrifos exposures based on exposure measures collected in the three longitudinal children's cohort studies, the Columbia study, the Mount Sinai study, and the CHAMACOS study. Consequently, the panel largely concurs with the EPA that the data generated from these studies alone are not adequate enough to obtain a point of departure for the purpose of quantitative risk assessment." So there has been a long-standing concern about the use of these data because of the problems associated with these data.

Not that they weren't -- not to impute the investigators or that the studies were not done correctly but it's just that they were limited. And to ignore those eliminations has been a problem with the 2008, 2012, and now with this panel. So I don't

think that we are unique in our questioning of the use of these data.

DR. JAMES MCMANAMAN: Dr. Hayton?

DR. WILLIAM HAYTON: Cord blood -- I'm kind of late to the party with the question but is that arterial blood or venous blood? It's mixed?

DR. WILLIAM POPENDORF: It's blood in the umbilical cord.

DR. WILLIAM HAYTON: But doesn't the umbilical cord -- I mean it carries the blood supply to the fetus and a return from.

UNIDENTIFIED SPEAKER: Really no one is qualified.

And unless the fetus is at some kind of steady state they're not the same thing. I have no idea either but --

DR. STELLA KOUTROS: This is Stella Koutros. I just wanted to ask a clarifying question to Dr. McManaman who read a quote from the 2008?

DR. JAMES MCMANAMAN: No. This is from the 2012. That was referring to the 2008.

DR. STELLA KOUTROS: Okay. I thought it was my understanding that subsequent evaluations may have made some updated conclusions based on that.

But maybe the agency can correct us if we're wrong.

DR. JAMES MCMANAMAN: And there were several recommendations from the 2012 that we could read that were related to considering other, for instance, the TCPy metabolites which are mainly present in foods. So I don't know that we can -- can we come up with a help to the agency for using something other than cord blood? I mean that's the measurements we have but we feel there is a real problem with using them because of the uncertainties in what those measurements mean and how they relate to exposure.

And I don't -- I mean I haven't heard anyone, the agency, from public commenter's, to members of this panel come up with anything that gives me confidence that we will ever because the limitations -- I mean the studies are too limited. So I hate to be a negative Nancy about this but it's -- Dr. Rohlman?

DR. DIANE ROHLMAN: Diane Rohlman. So this is maybe moving outside of my expertise but what the heck. I think that you know, I agree that we have heard a lot of information about how the cord blood might not be the appropriate biomarker. That there

are problems with other biomarkers that are out there as far as being nonspecific. But perhaps we need to take a weight of evidence approach with those biomarkers. Cholinesterase inhibition is probably not the best measure because we are seeing it affects below cholinesterase inhibition.

And it's also maybe not a good measure when you think about trying to collect that because there are problems with cholinesterase inhibition in that you need to have two samples. There's a lot of individual variability as well. However, that is a biomarker that can be used. TCPy, although nonspecific and is available in the environment and there's other concerns that have been raised, also could be used as another biomarker of exposures. The DAPs which are widely collected, we have NHANES data, we have a lot of data from the other child studies which are very nonspecific for chlorpyrifos, are focusing more on organophosphates as well.

So is there a way to combine those different types of biomarker to look at the relationship between the cord blood, the maternal blood, the DAPs, the TCPy? And these are things that maybe we uncouple from the Columbia study, we can

model in with animal studies, we can link it with other outcomes. Again, this is not my area of expertise. I know that you know, I think Dr. Lowit did a very good job this morning explaining the situation with our two options as far as developing appoint of departure.

The two options, one is to use the maternal cord blood levels which we've had much discussion about and have expressed concern. The second one is to remain with the 10 percent cholinesterase inhibition but add levels of uncertainty to that. And again, what would those look like and how would we assess that? So perhaps a third alternative is to use the tools that we have to think about combining different measures and coming up with some sort of weight of evidence approach.

And all I can really do is present the big picture and hope that the experts can take it and run with it.

DR. JAMES MCMANAMAN: I think Dr. Jett had his hand up first.

DR. DAVID JETT: This is great tie-in because these are the two things I was thinking about. First was in terms of -- if I were trying to figure

out -- I keep thinking about the deadline. And if I was trying to figure out how to respond to that deadline and if one of the options is you know, to maybe buy some time for lack of a better word, is whether or not there are some studies right now that are ongoing but near finished that could potentially augment the data from the Columbia study. That's one thing.

And I know of a few things that are going on and they're CPF levels, organophosphate levels, as well as biomarkers that could. That was one thing. And Diane just -- let's see, what was the other thing? But yeah, I mean I think that -- oh, the other thing was this idea of uncertainty. And when I was thinking of trying to, as I said before, trying to focus on uncertainty, identify the uncertainty, I never really thought about using that uncertainty for the existing cholinesterase point of departure.

I guess the question that I have -- and I just don't know enough about risk assessment and regulatory, but is it possible to include higher levels of uncertainty than the 10X factor. And if so, maybe that's the approach that we should take. And so I sort of repeated what you said but I just wanted to

add that because I thought about that.

DR. ELIZABETH HOLMAN: If that was a question to the agency the answer is yes, that additional uncertainty factors can be applied.

DR. JAMES MCMANAMAN: Dr. Pessah.

DR. ISAAC PESSAH: There is clear human data that when you alter cholinesterase in the brain you change Working Memory. Now, it's in a different context, it's for treatment of Alzheimer's Disease. You improve Working Memory. But that doesn't mean if that change occurs during development where cholinergic synapses are making and breaking a million a second is the latest estimate that you wouldn't have abnormal development.

And so why can't we use an anchor that's well-known to derive more rigorous points of departure rather than journey into the unknown? Which is the way I have to view this as a molecular and cellular toxicologist.

DR. JAMES MCMANAMAN: Thank you. In response -- this is Dr. McManaman. In response to that, I think that there is evidence emerging, and it's a little bit old now, too, that these agents can have effects on the muscarinic receptors and effects

on other neurotransmitters. And to the degree that these have been explored as modes of action or uses for points of departure I think hasn't really been fully discussed, at least in this panel. But I think it's something that needs to be discussed as an alternative to using a single study, single issue that has a limited reproducibility because of the nature of it as the point of departure.

So I throw that out as an alternative to how we could move forward with the risk assessment on this.

DR. DAVID JETT: Yeah. This is Dave Jett, NIH. I was going to say that comment made me feel young again because I actually did that for my dissertation and was publishing in the eighties on direct action of LPs on muscarinic receptors. So, yeah. And the other thing that I would add relative to Dr. Pessah's comment is there is a clear morphogenic role for acetylcholinesterase in neurodevelopment that has nothing to do with the active binding site. And we've shown and others have shown that indeed these you know, cholinesterase can have this effect.

So this is what I meant earlier about

these non-cholinesterase mechanisms -- well, in that case it's cholinesterase but non-catalytic -- it's more morphogenic than catalytic. So yeah, I think that you're right. I mean these are -- potentially we could revisit the idea of using cholinesterase in a different way as a point departure.

DR. JAMES MCMANAMAN: I'm going to interrupt just for a second here. So this is Dr. McManaman again. This is from the 2012 SAP, "The panel concurs with the agency's position that the acetylcholinesterase data continue to be the strongest resource of data for deriving points of departure for chlorpyrifos." So there has been a change since 2012. The panel agreed with the use of acetylcholinesterase as the strongest evidence for point of departure.

And I have not heard anything -- I mean we can't ignore the epidemiological data but I have not heard anything that really refutes that, you know. The levels are much below the cholinesterase inhibition but they're much below anything that we can imagine in terms of biological effect. So it makes it very difficult to assess what should be used as a point of departure and risk assessment since we're in a kind of a limbo area in terms of our knowledge. Dr.

Popendorf had his hand up.

DR. WILLIAM POPENDORF: Thank you. Just a couple of points here. Just kind of going back to linking the 2008, 2012 reports to their concerns. I mean that's one of the things that drove the PBPK development that we're now looking at today that I think has some added benefits. I think the comments we made yesterday in the recommendation to Question 1.a. was to look at -- I mean we felt looking at maternal blood, not cord blood, was a viable alternative. It hasn't been explored, they didn't publish on it, it presents its own set of problems.

But maybe for various reasons we all seem to agree, or at least the primary reviewers, and there was maybe some others that didn't, that it has potential to be looked at much like they did with the cord blood as a point of departure. Probably in conjunction with the PBPK because obviously you're looking at the terminal data. So we don't know you know, what happened barely a week ago, let alone what happens months ago during gestation. Perhaps as an aside, but comments have been made, they were in the issue paper made today, about effects well below the change in cholinesterase or inhibition of

acetylcholinesterase.

I was wondering about that and I took the citations that were in the issues paper, Index 3 perhaps -- Dawson, Derone and Howard, et. al (phonetic). And went back to look at their levels of cholinesterase inhibition and their exposure. These were in vitro studies. They actually did measure cholinesterase inhibition and we're talking about in vitro in the pg to below pg range and they aren't that different. They were seeing at the lowest level -- and I've got a presentation we could spend some time looking at but the lowest level they looked at that saw effects was about a two percent cholinesterase inhibition.

Now clinically two percent isn't anything but -- and everything else was the cholinesterase inhibitions, this was in vitro and brain cell. So we're looking at basically brain cell acetylcholinesterase. But they aren't as different as I think some comments have been made and was in the issues paper. And third, as a potential alternative epidemiologic study we can't replicate certainly what was done.

But if someone did have questions about

the differences in pre- and post-outcomes there are opportunities to go to look at basically cross-sectional studies in residents in the same buildings, the same facilities, under the same exposure. Potentially using aged children who were at early ages at school if there were any standardized tests, looking at people who were born the cancellation -- mid-1990s versus let's say post cancellation. You could get thousands of people, you could get super on your p-values.

DR. STELLA KOUTROS: Not blood samples.

DR. WILLIAM POPENDORF: No. No blood samples but in terms of with cholinesterase inhibition and without. This is simply the question of use without -- I mean we had some data that showed differences before and after, people had questions about that. That part could get replicated very, very readily by cross-sectional studies with data that's probably available.

DR. STELLA KOUTROS: This is Stella Koutros. What you're proposing is a significantly more crude epidemiologic study than the one that has been provided to us for consideration. And because of that and because of Dr. McManaman's comments about not

having any comments to support the validity of the cord blood measurements I will provide some comments on that. But I just want to say a few things about the value of that data. First of all, we have blood samples collected from a prospective cohort that show a quantitative measure of exposure to chlorpyrifos.

This is an amazing piece of information and some of you have doubted the reliability of that information. Which, I understand that it hasn't been replicated at another lab. However, it has been compelling to me that we observe a temporal trend in the decline of those measurements of chlorpyrifos in the blood directly associated with the residential cancellation which gives me confidence in the observed measurements in those data. Second, it is extraordinarily unique that there is a study that has even timed this blood collection to the specific exposure that occurred.

I believe that it's a bit crude but we know that these people were living in a place, based on the data provided by the Columbia study, where chlorpyrifos was applied in their home. And that is a really unique piece of information. Not a lot of studies have been able to characterize that. So I

don't think we should take it for granted and throw it away because we think we can only bound it by about 30 days.

DR. JAMES MCMANAMAN: Yes, Dr. Carr?

DR. RUSSELL CARR: I was going to address this a little later. But the people were living in a place where also nine to 10 organophosphates were detected -- five carbamates in addition to other compounds. The level of Diazanon in the air samples ranges from anywhere -- if you take the mean it's 7.5 fold higher and if you look at just the high values it's almost 31 fold higher. And what I'm saying is there are issues as far as not just chlorpyrifos. We can detect chlorpyrifos in the blood because it's lipophilic, Diazanon is not that lipophilic.

It's not going to do what chlorpyrifos does in a pharmacokinetic model. But the point is it was present in the environment at seven times higher concentrations than chlorpyrifos.

DR. STELLA KOUTROS: And what you're describing is actually another strength of the study in that there is detailed characterization of known co-exposures that are relevant to our consideration.

And which have been considered as co-variants and as confounders of the associations that we have been looking at and they've been carefully considered. I actually think that's a huge strength of what we've been able to look at.

DR. JAMES MCMANAMAN: Thank you, Dr. Koutros, Dr. Carr. Dr. Sagiv?

DR. SHARON SAGIV: I have a -- I feel like this is sort of a little bit of a brainstorming session so I'm going to put this out there. And people might hate it but I have a little bit of an idea. So I have a lot of faith in the Columbia study. I will state again my reservation about this being one study and I think that more epidemiologic studies need to be done. But wait, I'm not done yet because I know that's not going to be a popular sentiment in this room. There are a number of longitudinal epidemiologic studies that have banked blood, I don't know banked cord blood, banked maternal blood during pregnancy at delivery.

I don't know how stable chlorpyrifos is in that blood so that's maybe something we need to think about but there are -- and they also have existing measures of neurodevelopment. So I feel like

this is actually something that could be done and replicated pretty quickly and easily if the funding's there. But hear me out, I'm not done. I am not saying that we wait for that epidemiologic evidence for more than one study to come out. I'm saying that's the long view, that we can replicate this study, it's possible to do this.

But we can't wait until those studies are done and I agree with you on that. So it feels like if we can make a -- and the thing that feels a little bit smoke and mirrors to me is this acetylcholinesterase inhibition. What does that really translate into? What is the uncertainty around that inhibition translate to in terms of a reference dose? Like what does that look like? If there's enough uncertainty in that acetylcholinesterase inhibition does that bring the level down, the PoD down enough that's reasonable?

Because I think that the PoD now is way too high. But to bring it down using those uncertainty factors based on those data, those uncertainty factors, what does that look like? Anybody in the room know what that would look like or how that would even translate into a PoD based on cord

blood? So that's what I'm offering. And this is just a thought and offering as a way of compromising so we don't wait too long but then we, at the same time, have other longitudinal studies looking at this question. And then down the line the PoD gets adjusted again. It's just an idea so feel free to attack me now.

DR. WILLIAM POPENDORF: Is that different than the right hand or the left hand side of the figure that was talked about earlier by Dr. Lowit in the --

DR. ANNA LOWIT: What she's suggesting was my left side.

DR. SHARON SAGIV: It was the left side but with the idea that we have other epidemiologic studies going in the meantime that could maybe inform the PoD better.

DR. JAMES MCMANAMAN: Well, this has been an interesting conversation. Dr. Popendorf, do you have another comment to make?

DR. WILLIAM POPENDORF: Just slightly. I mean what I was proposing was not -- I mean I think the opportunities to show, to confirm even more strongly the effect of chlorpyrifos. Not you know,

I'd expect there to be an effect. And so if someone were questioning the small sample size in the Columbia data there are opportunities to expand the sample size and to show that -- if this effect is true I'd expect that to be much more significant.

DR. JAMES MCMANAMAN: Okay. Thank you, doctor. This is Dr. McManaman and that was Dr. Popendorf. We have a situation where there's got to be variability in the exposures of certain populations of people ongoing at the current levels. The issue is that there's no safe level for chlorpyrifos, that's what I heard. That the level of point of departure is going to be to the point where it's going to be revoked because there's really no safe level of doing that. And maybe I'm misstating that, so correct me.

But given its widespread use, and given the variability of exposures, if there is a relationship we should be able to detect that now at these levels. If these current levels are still toxic to human populations or still have adverse effects on human populations then we should be able to detect that. So perhaps additional studies are needed with the current populations to see if there is any correlation between the level of chlorpyrifos and

neurologic changes.

DR. STELLA KOUTROS: This is Dr. Stella Koutros. It's difficult for me to understand your suggestion given that we know from the Columbia study that contemporary measurements of chlorpyrifos are likely to be below the limit of detection.

DR. JAMES MCMANAMAN: Well if they're below the level of detection for that study then that, in my mind raises an issue with the validity of that study. If it's below the level of detection and we see correlations drawn between whole IQ and chlorpyrifos levels, then I don't see how you can -- you can't be sitting here arguing it both ways. So if the levels now are still toxic then we should see that there should be an association between toxicity and the levels.

DR. SHARON SAGIV: Sharon Sagiv from UC Berkeley. I would recommend using an existing longitudinal study that recruited participants before 2000.

DR. STELLA KOUTROS: And what would that be exactly?

DR. SHARON SAGIV: Well because we would have more detectable values and we could

replicate our findings.

DR. STELLA KOUTROS: I didn't know if you had one in mind.

DR. SHARON SAGIV: Oh, no. That's the question. I mean there is this new ECHO mechanism that's going to be recruiting a lot of different cohorts, up to 50 I understand. And maybe that effort will produce a longitudinal study that started pre-2000 where we have banked cord blood or maternal samples. That's one of the criteria for recruiting that cohort. And then neurodevelopmental outcomes you know, those kids will be old enough to have some neuro outcomes.

DR. JAMES MCMANAMAN: Dr. Pessah?

DR. ISSAC PESSAH: I think these are all great ideas but from what I understand I think we have to come up with answers to the questions. And so I heard one possibility that actually could get done within -- actually if there was concerted effort and cooperation, within a month. And that is to take the banked samples that Columbia has, send them to an independent certified lab and just make the measurements again and rerun the analysis.

I can't imagine that the amount of

resources that we've poured into the modeling, and that we've poured into the epi study over the last 12 years couldn't afford to just reanalyze those samples and make sure.

DR. JAMES MCMANAMAN: Okay.

DR. SHARON SAGIV: Is it that simple? Is the solution to this that simple, this replication of the existing samples?

DR. JAMES MCMANAMAN: It's a good question but can you ask that after the deliberations have ended? We'll come back to you. So, Dr. Koutros?

DR. STELLA KOUTROS: I just wanted to comment on we do not know if the investigators have existing plasma available to even do such a thing. Secondly, I don't know that the EPA should be undertaking that research or scientific effort, I don't know. And I don't know who owns these samples and whether this would be the appropriate use as determined by the investigators for those samples, if they even remain.

DR. ISSAC PESSAH: So there was a response from the analytical lab that they either returned the samples to Columbia or if Columbia did not want them they destroyed them.

DR. JAMES MCMANAMAN: All right. Yes, Dr. Funk?

DR. WILLIAM FUNK: I just wanted to comment that normally that does go in the opposite direction for studies. You analyze your samples and if you want to validate you send them to the CDC. They have a very high reputation for analyzing samples.

DR. MARION EHRICH: This is Dr. Ehrich. And nobody would have to do all of them. Even 10 or 20 of these done again would strengthen the -- because all we have is this Figure 1 that doesn't even give data on any of them. It would strengthen the data. I agree with you, the CDC should have high levels and they shouldn't be worried about somebody -- but USP has really high levels too, FDA has really high. But they never said on here if this is an iso-lab. It would have been verified for that particular type assay.

DR. JAMES MCMANAMAN: This is Dr. McManaman. As Dr. Ehrich pointed out, this study was not done for risk assessment initially. So the way the samples were handled is subject of some concern. Even though they may have done their best in handling

they you know, it wasn't done for this specific purpose. And the other is that there is -- I don't think that anyone on the panel is questioning the measurements per se.

But what I'm questioning, what other panel members are questioning is how can you draw conclusions -- a dose response saying that there's a linear relationship between neurological damage and levels of chlorpyrifos when the levels of detection were below the analytical levels. So it's that relationship.

DR. STELLA KOUTROS: That is not true. What you just said is not true.

DR. JAMES MCMANAMAN: Well that's you know, the analytical levels were in parts per billion and the levels measured were in parts per trillion.

DR. STELLA KOUTROS: Dr. McManaman, what percentage of the samples had values below the limit of detection in the linear regression analysis associated with prenatal exposure to chlorpyrifos and neurobehavioral outcomes in the Rauh (2011) paper?

DR. DAVID JETT: Could I just -- real quick before this thought goes away. I was struck by Dr. Lowit, something she said earlier about -- when

you were asked about are you basing this whole thing on one study. And I think that that's what everybody is struggling with. But isn't that not true? Because I think that we have to look at this as a piece of a larger picture.

DR. JAMES MCMANAMAN: You can't ask Dr. Holman **[off microphone]** the panel.

DR. DAVID JETT: Oh. I was just, I was asking the panel. I'm sorry.

DR. SHARON SAGIV: Can I make one just additional comment?

DR. JAMES MCMANAMAN: Dr. Sagiv?

DR. SHARON SAGIV: That in my epidemiologic opinion I don't think that reanalyzing the Columbia samples would be my next step. My next step would be to look for a cohort, and they are out there. You would be shocked at what cohorts are out there, and I think ECHO will reveal this, that have pre-2000 banked samples and neuro measures or neuromeasures could be conducted on those participants. So I think it's important to do this in another study.

And I don't have -- this is not stating that I don't have faith in the Columbia study. This

is my reservation about using one epidemiologic study. And I just feel that in order to use a point of departure based on cord blood I would feel more confident with having another epi study conducted. So I don't think that reanalyzing Columbia samples is -- I mean maybe if you did like Dr. Ehrich said, maybe 10, fine, but I don't know that that's the best use of resources.

DR. ISAAC PESSAH: Isaac Pessah. I absolutely agree with you. I was just trying to come to a consensus.

DR. JAMES MCMANAMAN: All right. Dr. Carr?

DR. RUSSELL CARR: I also think -- this is something I just thought of, that maybe we could -- you have 71 to 72 pregnant mothers who wore the backpacks that you have air samples from and that's data that you have and you have the behavioral data. Maybe it's possible to look at it using that. Because there you would have a range of chlorpyrifos and a range of Diazanon and you could have the range of how the neurological outcomes fall within those. Because those are actually measurements of what was in the household.

DR. STELLLA KOUTROS: We have measurements of what was in the blood too. I don't know how it's different than what you're proposing.

DR. JAMES MCMANAMAN: All right. Well I think this horse has been beaten to death. And unfortunately I'm certain that we can't give you a consensus answer to that question. I hope that we've given you any kind of insight. So I will go back to the agency and you can ask for clarifications.

DR. ANNA LOWIT: Given the importance of this question would it be possible for us to ask clarifying questions after lunch and let the team get together and think about what those might be to be most useful?

DR. JAMES MCMANAMAN: That would be fine. So we'll break for lunch. How long will you need?

DR. ANNA LOWIT: We've been at this along time. I don't know if 30 minutes is going to help.

DR. JAMES MCMANAMAN: Will an hour be sufficient?

DR. ANNA LOWIT: Sure, an hour.

DR. JAMES MCMANAMAN: Yeah. Several

years? Try to get started as soon as we can get all the members. Hope the agency has had a chance to get nourishment and I know the panel was happy to get their nourishment. Okay. So as we left it, we asked the agency if the panel's deliberations were clear and you were coming back to us with clarifications.

MS. DANA VOGEL: Hi. This is Dana Vogel. Dr. Lowit will be out for a few hours but she'll be back. So I'm standing gin right now. Just one thing in the vein of clarification. First, we'd like to thank you for all the thoughtful discussion this morning. We recognize these aren't easy questions to answer. We've grappled with a lot of similar issues that you're talking about over the past decade and as you have noted in this current paper as well. And a lot of what your discussions are echoes what we've struggled with and what we've grappled with.

So what would be most helpful to us is if it seems -- I guess from our perceptive if a consensus cannot be reached, if a synthesis of the common themes that the panel has come up with could be written in the report as well as the range of the divergent opinions. That would be most helpful for us

in that synthesis of ideas and how we go forward and make our science-based regulatory decision.

DR. JAMES MCMANAMAN: Okay. Is that clear to the panel then that we should emphasize where there's agreement and where there's disagreement and the reasons why in detail. Okay. So we can move on then to Charge Question 5.b.

DR. ELIZABETH HOLMAN: Beth Holman, EPA. Question 5.b., Point of Departure Options. From the Columbia publications, there are two general options that EPA has considered for deriving a PoD for extrapolating risk to chlorpyrifos: 1) Lower limit of the top tertile greater than 6.17 pg/g cord in blood derived from Rauh et al (2006) and repeated in other Columbia publications; or 2) Benchmark Dose estimates derived from linear regression reported in Rauh et al (2011) for deficits in Working Memory.

Rauh et al (2011) reported that for each standard deviation increase in exposure 4.61 pg/g there is a 1.4 percent reduction in Full-Scale IQ and a 2.8 percent reduction in Working Memory. The agency has decided to use the BMD approach. Please comment on the PoD options considered by agency.

DR. JAMES MCMANAMAN: Thank you. So

the discussants on this question are Carr, Funk, Pessah, Sweeney, and Terry. Dr. Carr is the lead discussant.

DR. RUSSELL CARR: These are the summarized comments of the associate discussants and myself. And I'll read them and if they have anything to add they can. If the agency were to decide to use cord blood chlorpyrifos to determine PoD the agency's decision to use BMD derived from linear regression for deficits in Working Memory is valid. This method has been developed, reviewed, and vetted previously for methyl mercury used in multiple studies. However, in this case using the single study, neither the use of BMD or the lower limit of the top tertile greater than 6.17 pg/g cord blood as a point of departure could be justified by any scientific evaluation.

The BMD for IQ and Working Memory is directly related to the cord blood values. And the same concerns as noted above in Charge 5 and Charge 2 related to the uncertainties relying on cord blood levels of chlorpyrifos must be considered. And there were additional comments. The high low dichotomization in the analysis is not satisfying and the differences in interpretation when the non-detect,

low, mid, and high-range groups are compared is also cause for concern when considering the Rauh (2006) as a possible key study.

For the point of departure based on Working Memory index there is no discussion of the biological or functional significance of any benchmark level of Working Memory index reduction. No precedence in IRIS for use of Working Memory index was found by the panel members. As indicated in the 2012 SAP report, the environment in which the exposure occurred contained nine to 10 organophosphate insecticides and five carbamates. In air samples in Wyatt et al (2002) Diazanon was found in every sample and was 7.5 fold higher than chlorpyrifos, which was also found in every sample.

The differences if you compared just the high dosages could be as much as 31 fold higher. Diazaonon is not as lipophilic as chlorpyrifos so it's not surprising that it only appeared in 50 percent of the umbilical blood samples as compared to 75 for chlorpyrifos. However, the greater levels of the Diazanon present in the pregnancy suggest the concept of mixtures and additivity. When an individual is exposed to two or more chemicals that possess the same

mechanism of action, the resulting toxicological outcome will be greater than if the individual was exposed to only one of those chemicals alone.

Following exposure to such a mixture it would be impossible to separate the independent effects of each chemical on a neurochemical or behavioral outcome, regardless of the model used. As I was stating earlier, if we could just possibly use the air sampling data. We know who those mothers are, they were pregnant, and if we had neurobehavioral data on those kids maybe it could be used as a confirmation of sorts on the presence of chlorpyrifos on neurobehavioral outcomes.

In addition, the environment of the pregnant mothers also continued multiple chemicals that have been demonstrated by the CCCEH to effect the same parameters, mainly Bayley scores and IQ that chlorpyrifos has been demonstrated to do. And those effects of different chemicals were all found in the same cohort of the 725 children.

DR. JAMES MCMANAMAN: Thank you, Dr. Carr. Dr. Funk?

DR. WILLIAM FUNK: Bill Funk. I agree with everything that Dr. Carr said. He summarized a

lot of our statements in that we agree with the decision to use the BMD approach.

DR. JAMES MCMANAMAN: Thank you. Dr. Pessah?

DR. ISAAC PESSAH: I agree with Dr. Carr's summary.

DR. MCMANAMAN: Dr. Sweeney?

DR. LISA SWEENEY: In addition, I would like to note that perhaps different shapes of dose response could be fit to the cord blood data, although there are certainly concerns about how well we know what the concentrations really are. But in any dose response data fitting more than one shape would be helpful. And that's more the standard in the NIRUS type assessment where they use a suite of dose response models to consider the data. Dale Haddis' 2014 evaluation of the data on page 105 they assumed a linear response at lower doses and then a saturating effect.

When I look at the data it's not intuitively obvious that this is better than a strict linear. But I think having 321 points in their data analysis reduced to nine points with y error bars and missing x error bars it's a little hard to tell. If

more of the original data could be recovered a more rigorous dose response analysis with a suite of models could possibly be conducted.

DR. JAMES MCMANAMAN: Thank you, Dr. Sweeney. Dr. Terry?

DR. ALVIN TERRY: I believe that Dr. Carr covered all of my comments. Thank you.

DR. JAMES MCMANAMAN: Okay. This charge question is now open for comments from the entire panel. Dr. Popendorf?

DR. WILLIAM POPENDORF: Yes. I just had a few other comments. One, looking at the options and just remind us that in Charge Question 1 we recommended looking at the maternal blood data. Of course to do that would require access to the original data that we don't have. Again a reminder about the influence of the delivery time and the influence on the correlations being proposed to use. Two technical things on the way they did their calculations. One, was I think the way they used their average standard deviation of the slope and the confidence interval of the regression is a function of the x-axis basically.

So the average confidence interval is not you know, it gets bigger as you go higher and

smaller as you go lower. So you're overestimating and using a larger confidence interval than would be appropriate for the very low doses that you're trying to evaluate. So I think you may be able to do a calculation with the information you have but you shouldn't use the confidence interval that you're starting with. And then the other, I'm not 100 percent sure exactly how you're doing that calculation.

But I think -- you know that saying some people use a lamp post the way a drunk uses -- some people use statistics the way a drunk uses a lamp post, more for support than elimination. I actually looked that one up. It actually goes back to a quote by an Andrew Lang in 1910 and the someone was politicians. So 100 years ago it's still the same issues. That wasn't even in the U.S. for that matter. Anyway, we're kind of doing both. and personally I use both. I use statistics more for support than elimination but there are some differences.

And I think you actually would end up -- when you try to find out what the variability is of the dose, or the exposure in your terminology, that you want to use -- because you're going to go to your

two percent effect and then back calculate to the 95 percent confidence interval, you're going to use that confidence limit. And you actually get a different slope and confidence intervals if you regress y against x as compared to x against y. It's not a simple algebraic transformation. So there's going to be some differences there as well.

That one I think you actually would need data for. So you're making an approximation by doing what you're doing. But I think you can get a different confidence interval in the range. If you want to use 2.8 percent effect you'd want a different confidence interval in that range.

DR. JAMES MCMANAMAN: Thank you, Dr. Popendorf. Dr. Hayton?

DR. WILLIAM HAYTON: Thanks. Bill Hayton. Just to get a little more information perhaps from Dr. Carr. You mentioned something about backpack air sampling and that would be a way to get around confounding exposures to other chemicals? Or am I totally missing that?

DR. RUSSELL CARR: I don't think necessarily it would be a way to get around confounding exposure to other variables. But I'm just

saying that they have data varying the amount of chlorpyrifos and varying the amount of Diazanon that certain mothers were exposed to and those mothers were 71 or 72 mothers that were in the cohort. And if they had matching neurobehavioral data maybe we could just look at how the residue analysis of exposure during pregnancy compares to the neurobehavioral outcomes.

There were other things in there that backpacks didn't pick up, but those were just two of the most prominent things that were in everything.

DR. JAMES MCMANAMAN: So instead of what's being done now is just using some kind of exposure modeling assessment. Is that the point? I mean you'd actually measure -- you'd have measured exposures versus hypothetical?

DR. RUSSELL CARR: From my understanding that is correct. Those are actually measured exposures. Now I'm not sure about the timing. I think the timing varied from six weeks to one month prior to birth. It's in the Wyatt (2002) paper. But as far as those two chemicals, I know chlorpyrifos was found everywhere and Diazanon was found everywhere.

DR. JAMES MCMANAMAN: Yes, Dr. Sagiv?

DR. SHARON SAGIV: I think that the power for that study would be very low. I mean you'd have to see what the range of exposure was but an N of 77 to look at those tests I think would be underpowered.

DR. RUSSELL: I agree but it's all we got. I mean I'm just trying to get some conformational type support for or against.

DR. SHARON SAGIV: Yeah. My guess is that it would muddy the waters more than clear them.

DR. JAMES MCMANAMAN: Yes, Dr. Rohlman?

DR. DIANE ROHLMAN: Diane Rohlman. I agree that it's nice to have confirmation evidence and certainly that's one way to do it. But I would caution, just because it's in the air, we really want to make sure what gets in the body and the cord blood helps to move us closer to that. So just be mindful of the types of exposure and metrics that we're combining. But again, for confirmation purposes that could be appropriate.

DR. JAMES MCMANAMAN: Yes, Dr. Sweeney?

DR. LISA SWEENEY: Depending on the sensitivity of the methods you might not have as large of a percentage of non-detects as you do in the cord

blood studies. So it's possible that you might get a little more information about the lower exposures if you were actually able to quantify them in air. So there could be advantages of -- plus in a sense misclassification because you just don't know where to draw the line on non-detects. You might have continuous data for a larger fraction of your population even though, as you know, there would be a smaller group.

DR. JAMES MCMANAMAN: Thank you. Other comments? Okay. Back to the agency.

MS. DANA VOGEL: No clarifying questions. Jeff, do you have anything?

DR. JAMES MCMANAMAN: Okay. We'll move on to Charge Question 5.c.

DR. ELIZABETH HOLMAN: Beth Holman, EPA. Question 5.c., Agency's Proposal for the Point of Departure. The agency proposal applies the BMD approach to the Rauh et al (2011) study, and the agency has selected a two percent change in Working Memory or an internal dose of 2.16 pg/g as the point of departure. This agency proposed value is quantitatively near the value reported by Rauh, 2.8 percent reduction in Working Memory, and thus

supported by the existing data, but is still health protective and conservative.

Please comment on the analysis/calculations used to derive these estimates as described in Appendix 6 and the selection of a two percent response level.

DR. JAMES MCMANAMAN: Thank you. The discussants on this are doctors Carr, Pessah, Sweeney, and Terry. Dr. Carr is the lead discussant.

DR. RUSSELL CARR: The discussants focus were mainly more concerned with the two percent response level. The analysis calculations basically used to derive these estimates are from the model. And I don't think we have any issues with those calculations or the procedures used to derive those estimates. As noted in the response to Charge Question 5.b., a two percent response level is of questionable biological significance. A two percent change in Working Memory would likely be much lower than one standard deviation in any population of participants in a behavioral study.

Basically, going along with 5.a. and 5.b., the panel's current opinion is the agency has provided insufficient justification for this policy

choice.

DR. JAMES MCMANAMAN: Okay. Thank you, Dr. Carr. Dr. Pessah?

DR. ISAAC PESSAH: Again, I think that one could make an argument for a two percent change, especially at the tails. But at the mean I think, again, one would probably have to question the significance of that small change.

DR. JAMES MCMANAMAN: Thank you, Dr. Pessah. Dr. Sweeney?

DR. LISA SWEENEY: I concur. Nothing to add.

DR. JAMES MCMANAMAN: Thank you, Dr. Sweeney. Dr. Terry?

DR. ALVIN TERRY: Same here.

DR. JAMES MCMANAMAN: Okay. This is now open to the panel. Dr. Sagiv?

DR. SHARON SAGIV: You knew I was going to respond to this. So this is Sharon Sagiv from UC Berkeley. So this is something we discussed yesterday a couple of times. And I wanted to make it clear, Dr. Pessah alluded to this, but I wanted to make sure that it was understood the impact of a two percent change in IQ. For a single individual I agree -- say we're

looking at two IQ points, for a single individual moving down two IQ points doesn't sound like a -- I wouldn't think it would be such a big deal. On a population level, going down on a population level two points is a very different thing.

If you think about a normal distribution of IQ scores, and here is the bell shaped curve, if you were to shift that curve over, think about the tails. So if you have five percent of people falling under intellectually impaired in normal distribution, you shift that distribution over by two points, you can have 10 percent of people in that tail. That is a big deal. So on a population level going two IQ points is a big deal. And there is a lot of supporting evidence. I would refer you to David Bellinger's paper.

He's written at length about this in a few different papers. That's David Bellinger at Harvard School of Public Health and Children's Hospital Boston. I just want to make sure that's clear. That two IQ points in a population level is an important thing.

DR. DAVID JETT: And that's for lead, not chlorpyrifos.

DR. SHARON SAGIV: Yes. But it's for lead in IQ. And they have found with lead decrements in IQ points and it's, I think, very transferable to this question. So IQ is different than --

DR. DAVID JETT: No. I'm just clarifying this so they won't think that this is a chlorpyrifos paper.

DR. SHARON SAGIV: Yes, yes. These are lead studies. Sorry, yes but the principle applies.

DR. JAMES MCMANAMAN: Dr. Rohlman did you -- oh, sorry. Yes?

DR. STELLA KOUTROS: This is Stella Koutros. I agree with the panel members that the methods used to calculate the estimates were appropriate. I disagree with the other discussants about the lack of their utility for our purposes. And I will elaborate in my written comments. And I think that using the two percent change is entirely appropriate because it is derived from the human data in the Columbia study.

DR. JAMES MCMANAMAN: Dr. Terry?

DR. ALVIN TERRY: So I'd like to ask a question about this analogy about the bell shaped curve. Because the Columbia data set that I've seen

doesn't have a normal distribution, most of those values are skewed to the left. So just for clarification, how do you grapple with that?

DR. SHARON SAGIV: IQ scores in general are normally distributed with a mean of 100 and a standard deviation of 15. This is Working Memory Index so it's not exactly IQ. It's a subscale of the Full-Scale IQ and it has a mean of 10 and a standard deviation of three. I think that's what we established yesterday. And what I'm hearing from you is that the Columbia population may have fell in the lower end of, maybe a mean score IQ or Working Memory Index that's below the norm, correct?

However, that should still be normally distributed in that population. And I don't know, they didn't necessarily give us that data, but that's usually the assumption, that those scores are normally distributed within the population even if they are maybe skewed a little bit to the left. So maybe your mean would be a mean of 95 instead of 100 but you still move the population mean two IQ points down, that's still the same principle, you're moving the distribution down an IQ. And maybe their IQ is lower because of chlorpyrifos.

I'm just kidding. But the same principle would apply is what I'm saying.

DR. ALVIN TERRY: And I hope I'm not conflating two different things. But when you look at the data set where the extrapolations were made and you see either the Working Memory score or the IQ on the left and the concentration of chlorpyrifos on the right, there's so many values to the left. And then as you go higher in concentration there are very few values, it's like 80 percent to the left and 20 percent to the right. So then there's this fit. And then if you look up and down the x-axis there's a really wide range of that Working Memory score. So that's where I get confused.

DR. SHARON SAGIV: And you would expect a range in IQ scores. The fact that there is more sparse data at the higher end of the exposure distribution has no bearing on the fact that you still have a range of IQ scores that probably approximates normal distribution. I mean there are some neuro outcomes that are not normally distributed but IQ is not one of those outcomes.

DR. ALVIN TERRY: Part of these numbers, like a 2.8 percent change or something, come

from an extrapolation (inaudible) [off microphone] that's driving. Is that not right?

DR. SHARON SAGIV: I think that what they're doing is that when you look at the effect of moving one standard deviation away that that's what the change is related to. So it's not extrapolation, it's the statistical measure. And I'll defer to my epi friends to say that in more technical terms.

DR. DIANE ROHLMAN: Yeah. I think that Dr. Terry, what you're describing is what the statistical approaches that we are offered allow us to estimate these changes.

DR. WILLIAM POPENDORF: Excuse me, Will Popendorf. I'm wondering, Dr. Terry, when you're saying skewed to the left, literally you're referring to the x-axis and they're talking about the y-axis. It's the distribution of the behavioral scores, the Working Memory. And that, if you look at it from the y-axis, it is bell shaped, just like it should be.

DR. STELLA KOUTROS: This is Dr. Stella Koutros. I think that Dr. Terry was thinking about both. And that his question is really just rooted in the statistical models used for the conduct of this epidemiologic study. And perhaps a statistician would

be better suited to explain the merits of those to you.

DR. JAMES MCMANAMAN: Okay. This is Dr. McManaman. So I need some help with clarifying this then too. So the choice of the two percent response level was not based on the slope of the line related to the Working Memory and chlorpyrifos levels. Because the graph that I see looks like that there is more variability at the lowest level of chlorpyrifos than there is at the higher levels. And if the slope of that line is a basis for a LOD or a decision about what should be allowed then I have some question about the relevance of that line or the reliability of that line or the accuracy of that line actually.

Is the line drawn correctly? Maybe I don't even need to worry about the line. But that's where --

DR. SHARON SAGIV: The line is a spline. So it doesn't impose a linear association on the data. I think that the representation of a spline here was very appropriate for that reason. Because if you just do a linear regression and you represent the line from the linear regression, you're imposing a linear relationship between your exposure and outcome.

DR. JAMES MCMANAMAN: Dr. Sweeney?

DR. LISA SWEENEY: But the spline was not used to derive that, the linear regression was what was used to derive the slope that's used for the RFD.

DR. SHARON SAGIV: Yes. Though it's showing that --

DR. LISA SWEENEY: You can't actually have a plot of the regression used to derive the RFD but we can sort of imagine what it would be like.

DR. SHARON SAGIV: From the spline. It's basically showing you that it's pretty linear but it's going the extra step of not assuming linearity. They wanted to say this looks pretty linear but we're going to show you with a spline that it looks linear.

DR. STELLA KOUTROS: Dr. McManaman, I understand what you're asking. You are fundamentally asking how linear regression works given the exposure information we have and the outcome data that we have and how the slope is derived in the linear regression. It's associated standard error and 95 percent confidence interval which is very easily back calculated from one or the other. And so perhaps then you're interested in a discussion about how the linear

regression allows us to estimate the slope given the data that we have.

DR. JAMES MCMANAMAN: No. I know how a linear regression is derived. It's in the interpretation of this. Because if you were to eliminate some of the points on the lowest end then that would change the slope entirely, it would change the point of departure, I guess, for how to use that information. Is that not correct?

DR. STELLA KOUTROS: Yes. If you remove some of the data the results will change.

DR. SHARON SAGIV: Yeah. I don't think I understand, what do you mean by eliminate some of the --

DR. JAMES MCMANAMAN: Well, so the greatest variability in Working Memory is at the zero level of chlorpyrifos. So if that --

DR. SHARON SAGIV: It might be that there's the most data there. I think that when you get to more sparse data it's hard to see variability because you have more sparse data.

DR. JAMES MCMANAMAN: So then that goes back to the reliability of that line. What does it mean? I mean if we're only limited to that data but

that data's really not reflective of reality then I don't know how to deal with it.

DR. SHARON SAGIV: Well that's why we do our regressions. And that is maybe a good reason why they decided to eliminate those two points that were way above the distribution. Because as you get to higher values, you get to more sparse data, and the model doesn't fit quite as well at the high, high levels. So you use the data from the entire distribution to generate a regression coefficient and generate the spline, knowing that you're going to be doing a worse job of that, which the confidence intervals reflect, at the higher end of the exposure distribution because you have less data there.

DR. JAMES MCMANAMAN: Okay. Dr. Sweeney?

DR. LISA SWEENEY: Dr. Haddis used some of the same data to develop another curve that uses a lot of the same data. But it uses a standard error rather than standard deviation. It's on page 105 in his comments. And other than the non-detect group, they're in equal size groups of 22. So you can compare the standard error bars and you know, ignoring the non-detect group which is larger, the error bars

are -- I wouldn't say there's any particular trend on the size of the error bars for the eight groups where there were detections.

I'd have to do some math to try to figure out whether or not the error bar on the larger group of non-detects is similar in size. But at any rate, it seems like the data that are closer to the end of the x-axis, the left data, are going to control the intercept much more than they're going to control the slope. It's going to be the data that are further to the right, the larger x values that are going to control the slope, not so much the non-detect data.

DR. JAMES MCMANAMAN: Okay. Any other comments?

DR. WILLIAM POPENDORF: Bill Popendorf. And I kind of thought the same thing. And I had to really go back and think about it and I think I've got a little -- if more clarification is needed I can explain I think in a little different way, maybe a little clearer way. If you go back to the other slide, Fred, the regression line is trying to explain the most effect of the x-axis on the y-axis. And the R-squared is basically the fraction of the variance of the y-axis explained by the x-axis.

And as a result, the confidence interval does not reflect the variability in the data, it's the confidence of the regression line itself. And so that gets smaller as you approach the intercept and bigger as you're trying to predict the influence of the x. So the linear regression would have something similar to that except it would be straight lines instead of curved lines.

DR. DIANE ROHLMAN: Diane Rohlman. I don't agree with that. I think we're -- I don't know where we're going with this but if you have concerns about this model I would encourage us to consult with a biostatistician. This you know, it's not -- go ahead.

DR. SHARON SAGIV: I want to be clear about this. The confidence interval around that line is not the confidence interval from a linear regression, it's a confidence interval from a spline. A confidence interval from a linear regression will be completely parallel from a linear regression. Well, it might not be but it's not a linear regression.

DR. WILLIAM POPENDORF: Yeah. It's influenced by the confidence of the intercept and the slope itself. And they're somewhat independent.

DR. SHARON SAGIV: But from a linear regression you'll be getting one beta coefficient and one confidence interval.

DR. WILLIAM POPENDORF: Right. Well, no. I mean one --

DR. SHARON SAGIV: Well, if you do the predicted probabilities -- are you talking if you plotted the predicted probabilities for each of those points that you would get --

DR. WILLIAM POPENDORF: You could do that or just looking at the -- if Y equals a Plus BX and there's a confidence interval in A, and a confidence interval in X, if you look where X equals zero you're going to get a different confidence interval than you're going to get for any value of X greater than zero. So they're not equal. It would look like this except that it would be straight instead of curvy.

DR. SHARON SAGIV: Okay. But this confidence interval is not for a linear regression.

DR. WILLIAM POPENDORF: It would be a similar pattern but they'd all be straight lines not a spline. Yeah. It wouldn't look much different. I'm saying it's still going to look kind of like that but

you wouldn't expect the confidence interval near the x-axis to expand out to match the data that's obviously dispersed at that point.

DR. SHARON SAGIV: But if you were to look at splines for other data they usually look similar to this. That when you get to the higher end of the exposure range where there is more sparse data the spline confidence intervals will increase, the widths of them will increase at that point.

DR. WILLIAM POPENDORF: I think that would even be true if there were more data out there. It would be less variance but it still would probably be -- well, it depends on the R-squared value, I'll bet. If the R-squared is one then -- well, look at the extremes.

DR. JAMES MCMANAMAN: So I don't know that -- did we help any? It helped me but I think that we went off on a tangent a little. Sorry.

DR. SHARON SAGIV: We did.

DR. WILLIAM POPENDORF: Yeah. If it helps, but if it doesn't --

DR. SHARON SAGIV: We have to figure out what that number's going to be and there seems to be low confidence in that number for some people.

DR. JAMES MCMANAMAN: Yes. Okay. Other comments, discussion? Dr. Pessah?

DR. ISAAC PESSAH: I promise it's not a statistical question. I just was wondering, is this common to have so many zero values in an exposure type of study?

DR. SHARON SAGIV: Yes.

DR. ISAAC PESSAH: I mean 80 percent of --

DR. SHARON SAGIV: It depends on the exposure, yeah. Usually you have a lot of people that fall either in the non-detects or pretty low.

DR. JAMES MCMANAMAN: Dr. Carr?

DR. RUSSELL CARR: Sharon, you made the comment that the reason they may have eliminated those two points is they didn't fit the model or they -- I'm not sure exactly what the justification for eliminating data is unless you do outlier tests. Because I mean if I look at the data, on just their data presented, the very highest exposure level has an average IQ. And if I look at that entire set of data, I see one guy down there at the bottom that could possibly be an outlier just looking at the rest of the population.

And I don't understand how you can pick your really highest exposure, which should be your one of your most important, to establish a dose response relationship. But they eliminated that value. I mean I'm having a little issue just coming from the lab science down into you know, trying to relate to how it relates.

DR. SHARON SAGIV: Yeah. That wouldn't necessarily be an outlier, that point, because it's falling within where most of the data is. But it does seem like it's a bit of a -- it might be an influential variable or observation because it's certainly far away from that regression line. And splines are you know, they will be influenced by those kinds of points. To get back to your original comment, they got rid of the two that fell way above 25 because I think they said they made the model unstable. And I guess it's possible if you have -- I mean it's double the highest value here. I think it was 63.

DR. RUSSELL CARR: It was 63.

DR. SHARON SAGIV: I mean it's really high.

DR. RUSSELL CARR: So then basically if

it was say, up at 4.6, just hypothetically --

DR. SHARON SAGIV: What was up at 4.6? That dot was up at 4.6

DR. RUSSELL CARR: Say that 63 value was a little bit elevated.

DR. SHARON SAGIV: Oh.

DR. RUSSELL CARR: Or if it's a little bit down it was have dropped it, made the model go steeper down. If it was up a little bit it would have changed the trajectory of that slide.

DR. SHARON SAGIV: It could have, yeah.

DR. RUSSELL CARR: Okay.

DR. JAMES MCMANAMAN: So again are we talking about limited amounts of data, trying to extrapolate, or is this sufficient?

DR. SHARON SAGIV: No. Well I think it was appropriate for them to omit those two points. I mean I'd question them quite heavily in their influence on the spline. What I would have done is I would have compared it with and without those points and hopefully it wouldn't have changed. But if it had I would have had a lot of pause. Especially if it made the slope steeper and suggested more of an effect. I would have said that's really not the most

conservative way to present these data.

Especially because they're so -- I mean epidemiologists are always trying to find alternative explanations for their results. That's kind of what we're taught when we do epidemiology. So as standard of practice I think if you do have values that are really high that are influencing unduly the slope, I think omitting them was the right thing to do. But we don't know what they did because they didn't say.

DR. JAMES MCMANAMAN: Okay. Everybody clear on the statistics here? All right. Okay. So I will then go back to the agency.

MS. DANA VOGEL: I'm just going to summarize what I think I heard. The panel agreed with the methods used for calculation but not necessarily -- there are some differing opinions on whether or not the two percent -- on the two percent. I thought that's what I heard. I was just trying to summarize.

DR. RUSSELL CARR: The calculations are fine. I mean that's just basically good model calculations. But there are differing opinions on the two percent.

MS. DANA VOGEL: On the two percent. Right. Okay.

DR. JAMES MCMANAMAN: Okay. Next charge question, Charge Question 6.a.

DR. ELIZABETH HOLMAN: Beth Holman, EPA. Question 6 - Assessing Extrapolation/Uncertainty (see Section 8). In typical risk assessments, point of departures are derived directly from laboratory animal studies and inter- and intra-species extrapolation is accomplished by the use of default 10X factors. In the case of chlorpyrifos, the proposed PoDs are derived from human information obviating the need for the inter-species extrapolation.

However, the agency still needs to consider intra-species extrapolation of the PoD from the Columbia epidemiology data across the diverse human population (see Section 8.1). Moreover, the agency must consider the statutory requirement of the FQPA 10X Safety Factor for "potential pre- and postnatal toxicity and completeness of data with respect to exposure and toxicity to infants and children" (see Section 8.2).

Question 6.a., Intra-species Extrapolation. For chlorpyrifos, the agency proposed to use a 10X intra-species extrapolation factor. This

10X, apportioned equally between 3X for PK variability and 3X for PD variability is consistent with that used previously by the EPA IRIS program for methyl mercury (see Appendix 8). Please comment on the agency's scientific rationale of the proposed use of a 10X intra-species extrapolation factor.

DR. JAMES MCMANAMAN: Thank you. The discussants on this are doctors Jett, Funk, Koutros, Rohlman, and Sobrian. Dr. Jett is the lead discussant.

DR. DAVID JETT: Oh, I'll do the same as I did before if you have a question. I'll read my general comments and then turn it over to our discussants. So with regard to the intra-species extrapolation you know, it's clear that many factors effect differences in population studies. And PK and PD variability is almost certain to exist and will affect the point of departure estimate.

And using the precedent or the methodology set by the methyl mercury study is one approach. But it may not be sufficient because of differences in the toxicology of the two chemicals, the kinds of the exposures, and the populations exposed. So it's probably a minor source of

uncertainty just using that methodology, but very minor. So in terms of the uncertainties, the uncertainties listed in Table 5, I think it was from the methyl mercury study again, are definitely relevant to the Columbia study.

And also because any given behavioral manifestation of the toxic effects of any neurodevelopmental toxicant depends on several types of nervous system damage and location of this damage, and the temporal matching of exposure to this damage. This is likely a source of uncertainty as well. And that's been covered several times now. So for that question I think that's it for me. There's a couple other things but --

DR. JAMES MCMANAMAN: Thank you, Dr. Jett. Dr. Funk?

DR. WILLIAM FUNK: Bill Funk. I have a lot of overlap which was, Jett, what you said. So I won't go into a lot of details on that. Just I'll summarize that the agency's proposal to use 10 time intra-species extrapolation factor is reasonable, it's consistent with other methods that have been employed. And this was used with methyl mercury. And then I go through and I list a lot of things about process

uncertainties which you've already gone through.

DR. JAMES MCMANAMAN: Thank you, Dr. Funk. Dr. Koutros.

DR. STELLA KOUTROS: I have nothing to add beyond what Dr. Funk said.

DR. JAMES MCMANAMAN: Thank you, Dr. Koutros. Dr. Rohlman?

DR. DIANE ROHLMAN: I agree with the previous reviewers.

DR. JAMES MCMANAMAN: Thank you, Dr. Rohlman. Dr. Sobrian.

DR. SONYA SOBRIAN: I agree also. I have a list of uncertainties that make the use of the 10X factor reasonable. But using that factor though the one issue that comes up, if you calculate what it would be it's below the level of detection of many of the assays used. So the question would be how is the agency going to regulate an exposure level that may not be able to be measured?

DR. JAMES MCMANAMAN: Thank you, Dr. Sobrian. This question is now open to the other panel members. Yes, Dr. Hayton?

DR. WILLIAM HAYTON: Well this is just kind of right off the top of my head. But three times

for pharmacokinetics, is the idea there that if you give the same dose to a population of people that the exposure, say the area under the curve, would fall within a range of three? Because if that's the thought there I think that's -- experience would show with drugs anyway that you would get a much bigger range of exposures for pharmacokinetics.

And then if you add a particular plasma concentration in a population of people I think you would get more than a 3X range of effect you know, quantitative measure of effect. On the other hand you know, I know that the agency very commonly uses the three by three and 10. But I think that's a very -- would you call it, not conservative but liberal application, I guess, of the safety factor.

DR. JAMES MCMANAMAN: Thank you, Dr. Hayton. Other comments? All right. Hearing none, I'll go back to the agency.

MS. DANA VOGEL: No clarifying questions. Thanks.

DR. JAMES MCMANAMAN: Okay. Thank you. We'll move on then to Charge Question 6.b.

DR. ELIZABETH HOLMAN: Question 6.b., Pre- vs. Post-natal Exposure. Numerous

epidemiological investigations have observed a link between prenatal exposure to chlorpyrifos or OPs and adverse effects on neurodevelopment through age seven years, with additional more limited evidence up through approximately age 11 years. By contrast, epidemiological evidence is more limited for associations between postnatal exposure to chlorpyrifos or other OPs and neurodevelopmental effects, and the Columbia study has specifically not assessed those associations.

Therefore, given that the extensive experimental laboratory animal database suggests that the postnatal period is a potential susceptible time, the lack of postnatal exposure assessment in the Columbia study and other similar cohort studies is a source of uncertainty in the epidemiology database. Please comment on the agency's conclusion that the lack of postnatal exposure assessment in the Columbia study is a source of uncertainty in the epidemiology database.

DR. JAMES MCMANAMAN: Thank you. The discussants on this question are doctors Jett, Funk, Koutros, Rohlman, Sagiv, and Sobrian. Dr. Jett is lead.

DR. DAVID JETT: Thank you. So yes, I agree that in general the postnatal period is an important period to consider. It's likely that postnatal exposure to chlorpyrifos in my opinion contributes to the developmental neurotoxicity. And the lack of such data in the Columbia study is probably another source of uncertainty that should be considered. Also, the single time point exposure assessment when cord blood was taken does not reflect the dynamic nature of exposures. Again, we've talked about this.

I think that even if we did know exactly when the developing nervous system was exposed to chlorpyrifos it's still very difficult to link back to a specific event during neurodevelopment that results in a specific phenotype such as ADHD. And actually that's where I'll stop.

DR. MCMANAMAN: Thank you, Dr. Jett. Dr. Funk?

DR. WILLIAM FUNK: Bill Funk. Just a couple things to add to that. I had on here, looking at the animal studies versus the epidemiology studies there is some strong evidence to suggest there are some effects postnatally. However, I think a lot of

that has to be cautiously looked at because of the differences between the experiments that have been done with epidemiology and toxicology where there's higher doses and different endpoints they've been looking at. So while there is some evidence from the tox data, I think, it's definitely uncertainty in the Columbia study.

I did want to note one other thing that, I don't know if it has been looked at, but looking at the data from Columbia one way that, at least you could look a little at postnatal exposures, if you look at the exposures in preborn to newborn exposures, 1999 and 2000, that have the highest doses -- I noted on these there were 138 children in 1999 and 111 in 2000. And if these children were to have exposures postnatally before the volunteer cancellation of chlorpyrifos then there would be potential in the 1999 cohort to have these postnatal exposures where you would most likely not see these occurring in 2000.

So you could potentially look at the exposures in these two groups and the health effects, and if there's differences that could possibly show some -- prenatal exposures could be a part of that

explanation.

DR. JAMES MCMANAMAN: Thank you, Dr. Funk. Dr. Koutros?

DR. STELLA KOUTROS: I'll just briefly add my affirmation that the consideration of this aspect of uncertainty in the risk modeling process is an appropriate interpretation of the epidemiologic data in my opinion.

DR. JAMES MCMANAMAN: Thank you, Dr. Koutros. Dr. Rohlman?

DR. DIANE ROHLMAN: I agree that this lack of postnatal exposure assessment is a source of uncertainty. The brain continues to develop through infancy, childhood, and adolescence. Furthermore, we know that young children are not as efficient in metabolizing chlorpyrifos as adults. For example, lower PON1 activity. Infants return home from the hospital to virtually the same conditions of exposures that were in the environment during the prenatal period. Furthermore, we know that dietary exposure to chlorpyrifos has been demonstrated to be higher in young children.

Therefore, it's necessary to look at the impact of postnatal exposure on neurodevelopmental

outcomes. However, this data is not available in the Columbia cohort, which we've discussed at great extent. I would encourage using the body of evidence from other birth cohort studies, other human studies, examining the impact of postnatal exposure and neurodevelopment as well as the animal research and the modeling data.

DR. JAMES MCMANAMAN: Thank you, Dr. Rohlman. Dr. Sagiv?

DR. SHARON SAGIV: I concur with the panel. And I just wanted to highlight that brain development continues through early childhood into adulthood. Particularly the frontal lobe development which doesn't really mature until later, until adulthood. And that is where they're seeing some of their effects on Working Memory, executive function, attention. So I would think if those structures, those functions, are sensitive to chlorpyrifos, there is no reason to expect they wouldn't be sensitive in the postnatal period when those structures are still developing.

DR. JAMES MCMANAMAN: Thank you, Dr. Sagiv. Dr. Sobrian?

DR. SONYA SOBRIAN: I agree with what

the panel has said. I'm just going to read my short remarks. I think that postnatal assessment should be done for the following reasons: The fact that some of the cognitive neurobehavioral alterations do not appear until 36 months of age and others persist or appear between seven and 11 years of age suggest a need for postnatal assessment. Animal data report, it's been said, neurobehavioral alterations with only early and/or postnatal exposure. There's one in which animals are exposed between approximately one and 21.

So there's no gestational exposure at all and they do find changes. The last, the fact that no critical developmental window has been identified in animal research is suggestive of an ongoing adverse process that might involve also a second hypothesis that involves an environmental trigger which of course you might be able to look at by postnatal assessment.

DR. JAMES MCMANAMAN: Okay. This question is now open to other panel members. If there are no additional comments I'll turn it back -- Dr. Carr?

DR. RUSSELL CARR: I'm in agreement that the postnatal period is an important part of brain development. In animal models typically your

first week to eight days of life is considered gestational. And so we actually have studies starting at day 10 to where we're seeing effects just trying to mimic a toddler exposure. And so that period is maybe as equally as important as prenatal.

DR. JAMES MCMANAMAN: Thank you, Dr. Carr. Other comments? If not --

DR. DAVID JETT: Except that I can confirm with any of us who have had teenagers that that delayed frontal lobe thing, yeah.

DR. SHARON SAGIV: Especially the boys.

DR. JAMES MCMANAMAN: Yeah. I think it even extends into the twenties now you know, the Millennials. So I'll send it back to the agency.

MS. DANA VOGEL: This is Dana Vogel. No clarifying questions. Thanks.

DR. JAMES MCMANAMAN: All right. So we'll do 6.c. and then we'll take a break.

DR. ELIZABETH HOLMAN: Question 6.c., Impact of Sample Size on Columbia Findings. Associations with neurodevelopmental outcomes were consistently identified with respect to the number of abnormal reflexes in the neonatal period. The presence of mental and behavioral issues as well as

gross motor delays were pronounced especially in at ages 24-36 months, and the observation of intelligence decrements at age seven years were seen across the three U.S. children's cohorts using different measures of prenatal chlorpyrifos exposure.

However, with regards to dose-response, the modest sample size in the Columbia study make it difficult to say that the dose-response relationship between exposure to chlorpyrifos and neurodevelopmental outcomes in the overall U.S. population has been fully characterized. The magnitude of the PoD in the general U.S. population of infants and children may be higher or lower than that estimated using the Columbia study results, and the shape of the dose-response curve may also be different.

Please comment on the agency's conclusion that the moderate sample size of the Columbia study is a source of uncertainty, given that the agency is proposing to use the Columbia study data directly for setting a PoD.

DR. JAMES MCMANAMAN: Thank you. The discussants on this are doctors Jett, Funk, Koutros, Rohlman, Sagiv, and Sobrian and Dr. Jett is the lead

discussant.

DR. DAVID JETT: So I think the answer to the question is an easy one. And that is, is it a source of uncertainty, and that's yes. The question is the degree of uncertainty. And I think I've been educated by some of my new epidemiologist friends and probably could be educated more with some statisticians, as you mentioned before. But in general I think you know, modest sample size is a source of uncertainty especially given the heterogeneity of the U.S. population. But you know, I know that's a big picture kind of thing.

And it also limits statistical power and covariant analysis and confounding and things like that. But there's two caveats: One is the sample size requirements depend on the questions being asked. And two, a large scale focused on the neurodevelopmental toxicity of chlorpyrifos has not been done and probably will never be done. So this is the data we have.

DR. JAMES MCMANAMAN: All right. Thank you, Dr. Jett. Dr. Funk?

DR. WILLIAM FUNK: I have nothing to add to that.

DR. JAMES MCMANAMAN: Thank you. Dr. Koutros?

DR. STELLA KOUTROS: Okay. So I'm just going to read a little bit of my written comments first. The adequate sample size needed to have sufficient power to detect a given exposure disease association is based on several factors including the study design, the prevalence of the disease, the prevalence of the exposure, the magnitude of the effect, and the error rate. We actually have the ability to calculate -- we have all these inputs for this study. So I'm hesitant to say that -- so I disagree with what Dr. Jett said about this being a source of uncertainty because we probably can just calculate it.

Your friendly statistician down the block who did your standard error calculations or whatever could actually just calculate it from each study given the inputs that we have. And we could have a real value to reassess the power of the given studies to detect the observed associations. So I'm hesitant to speculate whether the sample size is a source of uncertainty. Because I think it's been commonly -- I heard over the last couple days that the

low sample size is an issue. It is not a requirement that -- so if the magnitude of an association is really strong, you do not need a large sample size.

And I don't think a lot of people understand that.

DR. JAMES MCMANAMAN: Thank you. Dr. Rohlman?

DR. DIANE ROHLMAN: Sample size certainly can impact the interpretation of study findings. And in general we prefer to have more rather than few participants. However, as Dr. Koutros has pointed out that the number of participants doesn't indicate much. It's a bunch of other factors that go into it. However, I do not feel that the sample size for the Columbia study was particularly small. And I would also recommend a power calculation to provide the information about the magnitude of the effect.

I do want to comment that the study population is not representative necessarily of the entire U.S. population and this could limit generalizability.

DR. JAMES MCMANAMAN: Thank you, Dr. Rohlman. Dr. Sagiv?

DR. SHARON SAGIV: It's so funny we should be talking about power curves. Diane and I met over dinner and we did one. We did a power curve and we inputted the standard deviation of the exposure, the standard deviation of the outcome, the number of participants, the alpha, and some choices for a beta. And what we saw -- and I'm glad to include this in the report, I'm not sure if it's necessary, is that this study had the power to detect reductions in Working Memory Index as small as 0.1 per one pg/g increase in CPF, in chlorpyrifos, which is much lower than the reductions they reported in Rauh (2011).

Which they reported percent change but they also reported a range -- and I didn't convert this to percent change, they reported a range of .35 to .81 for the beta. So the study clearly has enough power to detect this effect. The sample size may have limited the study's ability to investigate effect modification and that should be noted. And that could contribute to the uncertainty if we are interested in looking at more vulnerable subpopulations in a study. So that's one of the few ways that uncertainty might come into play to look at for example, racial minorities, lower SES individuals.

Though this study was looking at mostly those vulnerable populations. So maybe that isn't as much of a concern. But if there was another effect modifier in which we were concerned that would explain a vulnerable population then that would be something to consider. I actually was kind of confused by this question because I didn't really understand the reference to the dose response. I think it seems unlikely that the dose response would be a concern because I think the range in exposure was pretty large in the study. So I guess I didn't --

DR. STELLA KOUTROS: I tried to ask Dr. Lowit this question about -- I couldn't understand why this particular issue was relevant. And she said that it had something to do with the language that was written in that was a quote, a specific quote.

DR. SHARON SAGIV: In the white paper. I found it and I didn't understand it in the white paper either.

DR. STELLA KOUTROS: You know what, so I don't understand why this particular source of potential uncertainty is more relevant than perhaps any of the other ones --

DR. SHARON SAGIV: Yeah. I don't

think this is a concern for -- this doesn't concern me in terms of uncertainty. The only thing that concerns me might be effect modification and I think that's actually a low concern as well.

DR. STELLA KOUTROS: I agree with you. Thank you for doing some of those power calculations. This is the first time I'm hearing them and if those are reproducible then I also agree that the sample size then is not a source of uncertainty although there are other sources of uncertainty.

DR. JAMES MCMANAMAN: Thank you. Dr. Sobrian?

DR. SONYA SOBRIAN: I'm just wondering why the sample size question also. I think that, as Dr. Jett said, it's going to limit how you can generalize what you have because of the homogenous population. I found though even with a small sample size, finding effects that were -- at least for the behavioral domain, some consistency between that in the epi study and in the animal data I found that even a small sample size still gave you that. That was sort of impressive. There's not much talk about false positives and false negatives and if one is more affected by the limited sample size.

And I think that with this particular case the false positives would be less troubling than the false negatives. I mean, let me take that back. Yeah. While false positives are an issue with a limited sample size, they are less troubling than false positives with a vulnerable population.

DR. JAMES MCMANAMAN: Thank you, Dr. Sobrian. This is now open for the remaining panel. Go ahead.

DR. ALVIN TERRY: This is Alvin Terry. Just like to comment on a few aspects of what was brought up before about dose response. I mean you'll hear the basic research scientist come out in me. But dose response is a fundamental concept in pharmacology and toxicology and I see it twice in this charge question. And I would argue that an observed association is not a substitute for a dose response.

DR. JAMES MCMANAMAN: Thank you, Dr. Terry. Dr. Jett?

DR. DAVID JETT: Yeah. I just wanted to sort of -- it was interesting, your power calculation. So in that calculation I guess it doesn't really address the issue of whether you can do other covariant analyses, or does it?

DR. SHARON SAGIV: No, it doesn't. It's a pretty standard power calculation that does not take into account confounding. So if you had a confounder that was limiting your precision or you had missing data on a covariant it would not account for that. So that's a caveat of our standard power curves. There are power analyses you can do to account for those factors but I didn't want to do that at 10:00 pm and I actually don't know how to do them to be honest. But there's one other thing that I wanted to address because generalizability came up.

And this is a perhaps not completely representative sample of the U.S. population. So generalizability might be a question. But in epidemiology we're steeped in this from day one that internal validity is much more important than external validity. So you first want to get a good effect estimate that's valid and free of confounding and bias. And if you have a more homogenous population, which this is pretty homogenous in terms of being mostly African-American and Dominican, you will have less confounding and therefore more internal validity. So you've gotten a good estimate.

Whether or not it applies to the U.S.

population as a whole, that's another consideration. If you have strong reason to believe that the U.S. population would be -- the effect on the entire U.S. population would be different than the effect in this population then that concern might come up but I don't see a reason for that. I don't know why chlorpyrifos would affect, say, whites more than they would African-Americans.

DR. JAMES MCMANAMAN: So comments from other panel members? Okay. Oh, well, Marion -- Dr. Ehrich?

DR. MARION EHRICH: Marion Ehrich, Virginia Tech. Just a question. Since the dose response they're going down to the limited detection the chances of false negatives actually goes up. Is that going to be a problem in using dose response? I'm asking some of the people with epidemiology background on this. I'm going to add to the uncertainty.

DR. SHARON SAGIV: So you're saying because here are more people in the low exposure range that there would be a higher likelihood of a false negative?

DR. MARION EHRICH: That was also a

statement made by Dr. Barr in her responses.

DR. SHARON SAGIV: Okay. I don't know. I mean I think of false negatives when there's a lot of exposure misclassification. So if there was a lot of exposure misclassification maybe this non-detect issue could do it. Then you might have more false negative. I mean you might attenuate your effect, so you might be underestimating your effect.

DR. DAVID JETT: And this is Dave Jett again. I was thinking about that as well. So this intercept point there's some associated variability with that estimate, right? Wouldn't that variability go down if you had a larger sample size? I'm not sure how that works.

DR. SHARON SAGIV: Your variance will always go down with a larger sample size and the conditions being equal.

DR. DAVID JETT: So I think that was what I was getting at when I said there is some uncertainty associated with the sample size. The power, I know, is important as well but isn't there other considerations that could influence the uncertainty?

DR. SHARON SAGIV: Yeah. If you had a

population of 1,000 it would be better. It would always be better to have more.

DR. JAMES MCMANAMAN: This is Dr. McManaman. So for the epidemiologists on the committee, are there examples where analyses have been done with a relatively large population, say a couple hundred individuals, and a conclusion was arrived at related to any kind of an effect that when the population was expanded to thousands of individuals that an opposite conclusion?

DR. SHARON SAGIV: I think the simple answer is yes.

DR. JAMES MCMANAMAN: Okay. I thought so.

DR. SHARON SAGIV: Yes.

DR. JAMES MCMANAMAN: So that gets to the point of whether this is -- I mean this may be a statistically population to be powered correctly but it may not be powered sufficiently to get the full population effect.

DR. SHARON SAGIV: Yeah. And I mean I think this comes back to the replication question in that you could have a spurious effect in an epidemiologic study. And that's why we usually want

to conduct more than one epidemiologic study.

DR. JAMES MCMANAMAN: Yeah. But given the impact of our conclusions regarding the validity of these in relationship to potential harm to the American public, to the human population, not just Americans but to human populations, and the potential impact on the use of this agent for positive then I think this is an important consideration. And the possibility that there may be uncertainty is an important consideration regarding the actual definition of what a point of departure is.

DR. SHARON SAGIV: Okay.

DR. DAVID JETT: This is Dave Jett. I think the question really in my mind was you know, is this study underpowered relative to your average "epidemiology study?" And from what I hear the answer is no. And that's why is said the uncertainty is there but it's relatively low.

DR. JAMES MCMANAMAN: Yes?

DR. STELLA KOURTOS: I just wanted to add that with respect to the specific issue of uncertainty regarding the sample size of the Columbia study, power calculations suggested to us today make that not a reasonable source of uncertainty for me.

However, there are other factors that I believe do. I was going to say something with respect to your comment that has escaped me at the moment. Forget it.

DR. JAMES MCMANAMAN: That was Dr. Koutros. We'll come back to her in a moment. Dr. Sagiv?

DR. SHARON SAGIV: I just wanted to add that it is not a particularly small population when it comes to an environmental epi question. It is probably an average size population. Not particularly high either but not low that you'd have concerns. I think the biggest concern is that it's one study. I keep coming back to that.

DR. STELLA KOUTROS: Oh, I actually remember what I was going to say. One thing that we could recommend to the agency is, I don't know what approach you used. It sounded like you used the reported beta from the study, right?

DR. SHARON SAGIV: I started with it.

DR. STELLA KOURTOS: Right. So you can use the information provided by the 95 percent confidence interval which is supposed to include 95 percent of the true values in that range. So with the different ranges of the magnitude of effect you could

also calculate the power. And if you're not comfortable with what the power is at the lower end of that range then maybe you could make another consideration.

DR. JAMES MCMANAMAN: Okay. So that would be then an agreed upon area of uncertainty regarding the agency's question.

DR. STELLA KOURTOS: No. It's still a knowable quantity.

DR. JAMES MCMANAMAN: No, no, no. But I think the question was is it a source of uncertainty. So there is --

DR. STELLA KOURTOS: So I think my interpretation of what the group has just repeated in the last 10 minutes is that we do not believe that the sample size is a source of uncertainty. However, we believe that there are other sources of uncertainty which we do not know how might be relevant to the current risk assessment modeling process.

DR. JAMES MCMANAMAN: Okay.

DR. SHARON SAGIV: And the power curve that I generated only went up to .2. It didn't even get to .35 which was the lower range of the beta that was in the paper. So we are very sufficiently

powered. This part does not put uncertainty in our heads. I think we talked about maybe effect modification being one of the few sources.

DR. JAMES MCMANAMAN: So there could be another source within a broader population that could lead to a different conclusion if we were to expand it out to 1,000 or 10,000 individuals. Is that the point?

DR. SHARON SAGIV: I don't understand the question.

DR. JAMES MCMANAMAN: Well, so because --

DR. WILLIAM POPENDORF: I think you're looking -- I mean are you thinking in terms of the homogeneity of the population and --

DR. JAMES MCMANAMAN: Yes. I'm thinking that if --

DR. WILLIAM POPENDORF: -- it needs to be more diverse rather than a simple statistical question then.

DR. JAMES MCMANAMAN: Right. Well so why would there be a changing conclusion using my hypothetical question where there's a -- have a population of 200 and you get one conclusion, you

expand it to 10,000 you get a different conclusion. So is that not a statistical question or is that more of a population and change in population question?

DR. SHARON SAGIV: It could be either.

DR. JAMES MCMANAMAN: Okay. Other comments, questions related to this question? Okay. Oh, Dr. Terry.

DR. ALVIN TERRY: You can stop me if you think I'm out of line on this. But the analogy you just brought up of taking one study with X number of patients and then deciding whether or not you could extrapolate that to a much larger population, this happens all the time obviously in clinical trials for new drugs. You have -- and there you know, can be double blinded perspective and have all the controls in them. If you test you know, 100 schizophrenia patients, you go to the next study and expand it to 1,000 and it doesn't work, you know. So it is an appropriate analogy.

I think it's back to the reputability in letting one study drive your decision making process.

DR. JAMES MCMANAMAN: Right. Thank you. Yeah, Dr. Jett?

DR. DAVID JETT: Would it be appropriate to sort raise this -- not now, raise this as a point of clarification of this question when we have our time with the agency? Are we going to have a time to speak to the agency again, I don't know.

DR. JAMES MCMANAMAN: Oh, we'll have -- at the end.

DR. DAVID JETT: Right. Would it be possible to get clarification on this question during that period from the agency? I don't understand why that's a crazy question. It's a simple question.

DR. JAMES MCMANAMAN: No. The question is the question. Well what we can do now is that if there are no other comments we can go back to the agency and ask if there are additional clarifications needed.

DR. DAVID JETT: Well let me set that up by not asking a question. But just -- so I think one of the things I was trying to struggle with is you know, there's big uncertainty and there's specific uncertainty to this. And the reason I asked the question about the reference dose, I was trying to figure out if the issue of sample size here effects the big question of the reference dose. And that's

why I asked the question about you know, if we had more people in the study would the error around that reference dose shrink.

And just a little -- I guess the question -- well I won't ask a question but that's what I would say.

DR. JAMES MCMANAMAN: But that would be a question for the panel.

DR. STELLA KOURTOS: I think I can articulate if we want to ask the agency for a point of clarification. Although I don't think it would have any bearing on our conclusion for this question. So I guess I don't need any more clarification so I will ask if others --

DR. DAVID JETT: Well I think we do have some discrepancy in our conclusion. I mean I'm hearing on one side this has zero uncertainty, on another side I'm hearing there's some uncertainty. Or is that not significant enough to even worry about?

DR. DIANE ROHLMAN: So the question is, is the moderate -- this is Diane Rohlman, that the moderate sample size of the Columbia study is a source of uncertainty given that they're proposing to use it as a point of departure. And I think our -- I'll

speak with Stella and Sharon, is that there is information there to specifically look at the effect size, the power based on the sample size. So that is no source of uncertainty for that.

DR. DAVID JETT: That's the small one. I was talking about the bigger one.

DR. DIANE ROHLMAN: That's the small uncertainty. The bigger one which actually isn't stated there is the kind of extrapolation of the general population. And that's in the setup to the question if you read through that there. And that's where there is some uncertainty. So Dr. McManaman said if we go from the 200 participant study to a 2,000 do we expect to see the same results, and we don't know. We could see different results and Dr. Terry gave us an example as well.

DR. STELLA KOUTROS: I just wanted to reiterate that it was merely just that we didn't understand why this particular source of uncertainty was pulled out here as opposed to other aspects of uncertainty. And if that is somehow relevant to some aspect of the risk modeling process that we haven't appropriately comprehended.

DR. JAMES MCMANAMAN: Dr. Koutros, I

think -- let me take a shot at answering that. I think the reason why is because this was brought up in both the 2008 and 2012 as having a relatively modest sample size. And that's why the agency was using that language and asked the question of this particular panel. And the agency can clarify that if --

MS. DANA VOGEL: This is Dana Vogel. Correct. Jeff, do you want to add anything?

DR. JAMES MCMANAMAN: Okay. Dr. Pessah?

DR. ISSAC PESSAH: The way I understand it, and I may have it wrong, but the point of departure -- the whole point of coming up with a new point of departure is to protect the bigger uncertainty, right? I mean in other words that you're protective of everyone or most people, right? More than just the women in the study. No? Okay.

DR. JAMES MCMANAMAN: Well that's kind of what I thought. This is Dr. McManaman. What's the point of a point of departure if we don't -- I mean who are we trying to protect? We're not trying to protect the people who have already been affected, we're trying to protect people in the future or now, the present. And we're trying to come up with a

logical estimate of what is a safe level of this particular agent.

DR. WILLIAM POPENDORF: Okay. I'm looking at the past versus the future. So I'll pass on this one.

DR. SHARON SAGIV: I think this gets back to the issue of effect modification and effect modification as it applies to generalizability. If you have a specific population that is different from the U.S. population, and you believe that the effect in U.S. population is different then that's not sample size, that's a different issue. It's external validity, it's effect modification, and there is uncertainty with that.

DR. JAMES MCMANAMAN: Dr. Pessah? That was Dr. Sagiv.

DR. ISAAC PESSAH: Isaac Pessah. Do you view this population as representative of the U.S.?

DR. SHARON SAGIV: No. I think I said that, that it's not, it's a minority population.

DR. ISAAC PESSAH: So that doesn't actually fit in trying to attain uncertainty for this question?

DR. SHARON SAGIV: No. That's what I'm

saying. That's what Stella was saying. We're not sure why the sample size itself is a source of uncertainty, we don't see it as a source of uncertainty. We see the sample population as a source of uncertainty. The source population may be a source of uncertainty. The source population is this northern Manhattan, I think Bronx or northern Manhattan --

DR. JAMES MCMANAMAN: South Bronx.

DR. SHARON SAGIV: South Bronx? And that population, as you know, is not representative of the entire U.S. population. But it doesn't get back to the agency's original question which was about sample size. It's a different issue. Though, you know -- no. I will stop there.

DR. JAMES MCMANAMAN: I think we're getting it. All right. So any additional comments related to this charge question? Okay. With that I will turn it back to the agency with the question if additional clarification is needed.

MS. DANA VOGEL: Hi. This is Dana Vogel. No additional clarifications. We would welcome the power analysis to be part of the written report. Thank you.

DR. SHARON SAGIV: I will be checking that with a biostatistician before I send that to you.

DR. JAMES MCMANAMAN: All right. Thank you. Then at this point I think let's take a 15 minute break.

[WHEREUPON A BREAK WAS TAKEN]

DR. JAMES MCMANAMAN: Well, shall we reconvene? Okay. Welcome back. We are about to address Charge Question 7. So I'll turn it back to the agency -- our last charge question.

DR. ELIZABETH HOLMAN: Question 7, Proposed Approach to Deriving Internal Dose Estimates: Integration of Exposure Assessment & PBPK Modeling (Section 9). The agency has proposed to input exposure estimates for chlorpyrifos into the PBPK model to assess internal blood concentrations from current exposure patterns. Several case examples were provided in the draft issue paper representing food exposures (see Section 9.2), drinking water (see Section 9.3), and worker exposure (see Section 9.4). Note: Exposure assumptions used in these examples have been previously reviewed by other SAP panels. Please comment on the implementation of the PBPK model using such exposure inputs and interpretation of respective

simulated blood levels.

DR. JAMES MCMANAMAN: Thank you. The panel on this are doctors Hayton, Popendorf, Sweeney, Fisher, and Georgopoulos. Dr. Hayton is the lead discussant.

DR. HAYTON: Thanks. I'm going to try to incorporate all the comments that I received from the associates as well. So I've broken this up into pieces and so the first part is about implementation of the model. And we say about that that using dose rate theory you would expect a continuous input whether it's intermittent, or like an infusion over a period of time. That would lead to a steady state level and you would expect the average steady state blood concentration. It would be constant, it would be the ratio of the input rate to the average steady state clearance.

And so the issue of whether dose rate and concentration are the same. What it really comes down to is the clearance independent of dose. And so we looked at that from the standpoint of the Michaelis constants that are in the model for metabolism. There's two of them, one at 1,000 and the other one at 8,400 nanograms per mil. And so if you take 10

percent of the Michaelis constant value as the concentration where you might start seeing saturation of metabolism, the simulations that are being done with the model are way below that, they're down in the pg/g level.

So we didn't see that there was any issue with linearity. And the assumption that internal concentration would be linearly related to external dose, we thought that was highly appropriate. The other consideration was time for the simulated concentration to come to a steady state. And the model predicts a terminal elimination half life of about 120 hours. And one would expect 3.3 half lives would bring you to 90 percent of steady state. And that would apply to the more slowly equilibrating tissues in the model. So you got 3.3 half lives, that's 396 hours, that's quite a long time, but that would probably apply more to tissues like fat.

The more blood and the more rapidly equilibrating compartments would come to a steady state much sooner than that, probably within a couple of days, and the simulations show that. I mean the peak level you know, after day one is not much different from day two, three four, right across. You

do have the rising bottoms but the peaks and the average is pretty constant. So the input durations for these simulations in this section were 21 days for food, 120 days for drinking water, 14 days for worker handler exposures.

And so for all three inputs the blood concentrations would be very close to steady state and accurately depict concentrations except over longer exposures. So we had no issues with that part. As far as the exposure inputs, for food the chlorpyrifos ingestion rates was taken from food consumption data compiled from reported food consumption of more than 20,000 individuals over two nonconsecutive survey days during 2003 to 2008. And this was subdivided into different age groups, too.

So I don't want to read all of that but just to jump to the bottom line here is that basically the dietary input rate was based on the food that people eat in the United States and the residue content of that food, all of which had been quantified, it seemed like a very robust way to calculate input. We called it a reasonable data driven approach to establishing chlorpyrifos intake rate in food. And I noted that oxon, CPF oxon, is not

present in food above the limit of detection. So that seems not to be an issue.

Similarly for drinking water the daily consumption volume for the adult female was 1.7 liters divided four times a day. For a formula fed infant it was .69 liters divided into six times a day. Chlorpyrifos concentration came from a simulated chlorpyrifos concentration timed profile after exposure, not exposure, I guess, application of chlorpyrifos to an onion field at a rate of a pound per acre. And we've seen those profiles already, what the profile looks like over a period of a year. The other source was the -- if I can get the spelling here, the Orestimba Creek, which was actually measured.

It wasn't simulated concentrations but measured concentration. So these were input into the model. The model was run for several weeks. And so bottom line here was that the scenarios for drinking input of chlorpyrifos to both the adult female and infant appeared to be reasonable and realistic. We didn't have any issues with that. For worker handlers exposure specific inputs included an eight hour work day, two five day work weeks, separated by two

nonexposure days. Usage rates typical for the agricultural crop from currently registered product labeling.

It included both dermal and inhalation exposure assuming exposure of 100 percent of the dermal surface area and then a day to day shower. So there was no day to day carryover. So these are all elements of the worker handler exposure. This is a little bit outside my expertise but to me the input scenarios seemed to be reasonable and representative of exposure that a worker handler would encounter. I wasn't quite sure about the 100 percent of dermal surface. I'm not sure how consistent that is with use of personal protective measures in clothing but it's conservative in that it would not lead to underestimation of input certainly.

So the inputs all seem very sound and realistic. As far as the results of the three exposure modalities the worker handlers produced by far the highest chlorpyrifos venous blood concentrations. The average maximum peaks for the seven scenarios that were investigated was 393 pg/g of blood ranging from 194 to 954. For the food scenarios venous blood concentrations were much lower than for

worker handler's average peak concentrations during the 120 day simulation being .67 pg/g of blood at the 50th percentile and 7.14 pg/g at the 99.9 percentile.

And peak blood concentrations for drinking water scenarios were similar at 7 pg/g. The onion crop scenario, 2 pg/g for the Orestimba Creek scenario. In terms of interpretation of the simulated blood levels the inputs of chlorpyrifos into the PBPK model from drinking water, food, and worker handler exposure appear to be appropriate and defensible. The inputs are well informed by a considerable amount of data relating to expected drinking water concentrations and dietary contributions.

Worker handler inputs are informed by highly developed occupational exposure methodologies and exposure data sources that have been extensively peer reviewed. The assumptions made in the development of the exposure scenarios have been reviewed previously by other SAPs. And in my group there are no compelling issues with regard to suitability of the inputs. Dr. Fisher is not here, he had to leave a little bit early. And so he had a little piece that I'll read into the record for him.

He says, "The exposure scenarios are

idealized based on generalized knowledge without the benefit of specific analytical measurements of plasma or the sources of external exposure. This approach is a reasonable exercise from a modeling point of view. Because of the uncertainties in both the external exposures and the resulting internal exposure, to gain added support and confidence for the PBPK modeling predictions requires the use of Monte Carlo methods to predict five, 50, and 95th percentiles for a population." So that's sort of a recommendation from him, seems reasonable.

"These hypothetical simulations are informative but without data probably lack the necessary validation (data sets to compare simulation versus observation) for use in a quantitative risk assessment." So that's from Dr. Fisher. Dr. Sweeney had some comments. I can read them or you could read them, Dr. Sweeney.

DR. LISA SWEENEY: I guess I'll make some of my own comments. And if there are any things that I summarized better for you.

DR. WILLIAM HAYTON: I think Dr. Popendorf is next though.

DR. LISA SWEENEY: Okay. I can do that

after you've finished all of the summary comments.

DR. WILLIAM HAYTON: Okay.

DR. JAMES MCMANAMAN: You're finished then, Dr. Hayton?

DR. WILLIAM HAYTON: I'm finished, yes.

DR. JAMES MCMANAMAN: Okay. Dr. Popendorf?

DR. POPENDORF: Yes. I don't have a whole lot to add. I believe your comment about the 100 percent dermal exposure is correct as you know, no personal protective equipment. So it would be a conservative assumption. That's the way I interpreted that piece of information. I think in general the parameters chosen in the situations were good. Being familiar with the California Central Valley, I think you probably maybe -- or they maybe misrepresented a bit of chlorpyrifos in the creek. Which is you know, in the coastal range, very seasonal, relatively low flow, it's not a source of water.

In fact, where it flows into the San Joaquin River, I don't believe that there's anybody uses the San Joaquin below that as a source either. I'm not 100 percent sure of that. But you know, most of those rivers flow out of the Sierra Nevada's and

they're dammed up and used for irrigation and drinking water at that point but not on the other. It is what it is and its good data. So used appropriately in the simulations I think are fine. The only other comment was somewhat beyond probably the scope of where we are right now, but in the drinking water side I think there's a lot of evidence that says oxons are formed and it really hasn't been addressed.

And some of the data shows oxons to be a lot more toxic. So we're just sort of missing that component.

DR. JAMES MCMANAMAN: Thank you, Dr. Popendorf. Dr. Sweeney?

DR. LISA SWEENEY: Part of that charge question is the interpretation of the respected simulated blood levels. And to a certain extent there wasn't a lot of interpretation by the EPA, but my understanding is that it is the simulations of 10 hours after the last peak that are going to be compared to the RFD. And I want to remind people about the definition of the RFD from the IRIS glossary which is that, "An estimate with an uncertainty spanning perhaps an order of magnitude of a daily oral exposure to the human population, including sensitive

subgroups, that is likely to be without an appreciable risk of deleterious effects during a lifetime."

And it goes on from there. So to a certain extent when I heard EPAs sort of orientation presentation this morning where they talked about wanting to make sure the RFD is low enough, well the idea of the RFD is it's supposed to be within an order of magnitude of what they think is supposed to be a risky number. So yes, lower would be safer but it is supposed to be bounded within the realm of what is believed to be within an order of magnitude of risk.

And usually with an RFD and when you're talking about a threshold effect you can't say as much about, well what about exposures above the RFD because it just talks about a cutoff. But in this case they're actually talking about using a value that's based on the linear slope. So in that case you can attempt to make calculations of what sort of risk you would have for people with exposures above the RFD. So if you look at Table 11 for the worker exposure scenarios and you look at the 10 hours after the last peak on day 12, and you see that these estimated concentrations are in the teens and twenties which are a factor of 1,000 above the RFD.

And you're thinking about my goodness -- - the slopes on the Working Memory derivation that we've discussed at length today, you have to think about my goodness, if these people are truly being exposed at levels that, based on these comparisons are a factor of 1,000 above the RFD, why doesn't every pregnant woman who has done this activity -- shouldn't we be seeing massive effects in their children? How could we not have seen this before? So to me it give pause as to -- well for one thing, the linear relationship that was derived, how well that holds.

And also just in general whether assuming a sort of working backwards with one peak value as opposed to considering the possibility that the Columbia cohort was particularly affected by a longer term exposure. Rather than a perhaps shorter duration worker exposure which could be more intermittent. Just makes me wonder whether everything that's gone into the RFD, does this make sense just based on these type of exposures. Which we're told these scenarios are very well vetted and very well established.

And I just have to wonder are these really what the exposures are or are these you know,

biased high in order to be protective. Since I am not an exposure assessor it's hard for me to vet that and I'm willing to accept that the agency methods are well vetted and well accepted. But I just sort of did the math and think wow, this is 1,000 fold higher. And are there effects, have people looked? And if they've looked and not found it what does that mean for the context of this RFD?

DR. JAMES MCMANAMAN: Thank you, Dr. Sweeney. Dr. Georgopoulos, are you there?

DR. PANOS GEORGOPOULOS: Yes, I am here and probably you can hear me, I pressed the unmute button. First of all, there are various issues and Dr. Sweeney brought up some of them regarding the interpretation which is -- there is not much of it. But if we focus on the specifics of the question of the implementation of the PBPK model with the inputs there are some issues. So overall I agree that the overall premise is reasonable and defensible for the scenarios that are described. There are various imitations that should probably be outlined in a more clear way.

And there is this section of the issue paper needs some careful editing because one needs to

go forth and back to try to understand a few things and some statements can be misleading. So I have made a list of examples in my written comments but maybe I can go over one or two. The most important thing, and I think it was properly brought up, so these particular scenarios are reasonable, represents closely of all cases. There is a big difference between performing an individual based exposure analysis that could be for a real individual, we have data, activity, diets, and so on.

Or for a virtual idealized individual as is the case for the simulations performed for this particular analysis. Or if you do a population based analysis, which is Monte Carlo distributions of input that try to capture both the variability within the population and the uncertainty in the knowledge of variables. So the 2014 revised this (inaudible) and used the population based approach, a probablistic approach. While the new calculations that are shown here are individual based and so they claim to offer an improvement in terms of specific scenarios.

They cannot capture viability within the real population although they were focusing on the entire population of United States. So this is a

distinction that sometimes doesn't come up specifically in the figures. Maybe if I give you an example it would be -- I look for example on the table, very small Table 10 on page 67. The title of the table is, "Summary of PBPK model estimated maximum property for blood concentration falling to the defend the drinking water exposure scenarios." Now the problem here, we know in formula six of population it identifies two populations.

One is infants formula fed with water and the problem is it's -- in this one value given, 29.6 pg/g, that supported the model simulated scenario of exposure, and the other is 624 for a measured scenario of exposure. Now, the reality is that there is no measure of exposure. In both cases it's a modeled exposure. In one case we start with a concentration in water of the Orestimba Creek and there is an assumption about how much water is to be consumed. I mean we should not confuse one particular maximum environment that was intentional industrial exposure. So the exposure is also modeled, it is not (inaudible) per see.

And then, we cannot -- to me if I see this table and somebody can see this table without

reading the entire narrative of the report and the appendices, one would assume that these values are somehow representative of the entire infant population of the United States, they are not. The first one particular scenario for one particular virtual infant that was simulated. The second line says females of child bearing age 13 to 49 years old. Now, that's a very wide age range. And then this one value, one estimate given, again, says model estimate is 699 pg/g, the other is measured 197.

Again, it is not measured, it is based on a value from water concentration. And today's modeling to assume exposure was changing assumption regarding the consumption of water. But this is a value, again, for an idealized adult female, 73 kilograms weight, with specific body mass. And it's by no way representative of the population 13 to 49 years old. I mean we never in exposure calculations use a single value for such a wide population. A 13-year-old maybe is still a child. I feel very uncomfortable having a statement or a table like this. And I know it was shown also in the slides today.

Maybe you know, it should be clarification that this data, one, represents one

adult individual from this population. But in no way -- you cannot define an average person in the population of 13 to 49. And the dosimetry, and the pharmacokinetics, and the exposure, they all depend on behavior, on physiology, on individual biochemistry. And this will be very different of the population. And as you go to the extreme ranges of the edge of the 13-year-old, the 49-year-old, they are different dramatically.

So we have a table that if you look at it without reading every sentence this report can be very misleading. So that's an example of something that needs some very careful editing. And another example -- and I'll stop at this Table 3 on page 32. I think it came up yesterday in the discussion. The title of the table is, "Summary of PBPK model run for analysis or validation of Columbia study blood levels." To me this is totally confusing. That just means that the model they're asking you to validate measured blood levels.

I mean you cannot even use the existing blood levels to evaluate the model they are so sparse. And so it doesn't make any sense to me what this -- the title can be very confusing. A column should be

added to this table showing blood concentrations they are now shown to the highest peak so one could make a consistent comparison for time points for the highest and the lowest peak and so on. These are examples of editing because this particular section is confusing. There are multiple references to the distribution of probablistic modeling that was done for the 2014 risk assessment which has been previewed which just you know, follows the standards and so on.

And it is a lot of information in the appendix but it looks like it was copied rather hastily. Because in the references and that information in Appendix 2 don't appear, some of them, in the list of references in the issue papers. So it looks like it has not been fully integrated in this document. But it is an issue when some scenarios, no matter how representative they are of cases, they don't capture the extremes. They would be exposed to much higher potentially than this.

So even whether they are representative we need to have a better understanding of what do they expect. Yes, they are reasonably conservative scenarios, we often use them, but I think there will be a lot to be gained by careful editing of this

section of the report to identify some of the limitations and to explain the use of selected scenarios. And I would very much point to the fact that we are talking about idealized virtual individuals in these cases. They cannot be extrapolated or assumed to be representative of this large population samples.

DR. JAMES MCMANAMAN: Thank you, Dr. Georgopoulos. Okay. With that I'll open this question to the other members of the panel. Any comments? Yes, Dr. Popendorf?

DR. POPENDORF: Yeah. Two comments that I can add on a couple of comments made previously. I think Dr. Fisher asked about the exposure. And being pretty familiar with what's called PHED data base, it's a pesticide handler exposure database. There are a lot of exposure studies where they've looked at people doing various jobs. They have measured how much pesticide is used and they find out how much pesticide gets on the surfaces of the person.

Air concentration and they use a breathing rate and do dermal monitoring to find out what the exposure level is on to the skin. So then

they can extrapolate using for instance, like a PBPK model to figure out what goes inside. But that's the database they used presumably. I'm not intimately familiar with the numbers within it but generally for each task, like the various handlers that were used here, we'll have a range of values that have been collected or you know, studies done. And they don't specify what percentile of what's called the unit exposure coefficient they used but they'll have a range of values.

And we don't know what they used. So they might consider what they used in light of everything. Hopefully it was maybe 50 percent, it could have been the 95 percentile. They don't say, we don't know. But again, I was familiar with that and pretty comfortable with it. And just to perhaps clarify the previous speaker on that page 67, yeah. The modeled estimate column is the bulb onion data from Georgia. So the concentrations in water were estimated versus the measured values were the Orestimba Creek in California.

So the labeling could be better but that's what he was talking about.

DR. JAMES MCMANAMAN: Other comments?

Okay. Well then turn it back to the agency.

DR. JEFF DAWSON: Reminding me to say my name. I was actually going to do it.

DR. JAMES MCMANAMAN: This is Jeff Dawson.

DR. JEFF DAWSON: Right.

DR. JAMES MCMANAMAN: I'll help you.

DR. JEFF DAWSON: It's hard to remember after all this. So I don't think we had clarifying questions. But some of the discussion -- maybe if I can provide some additional information that would help clarify in the report. Just given some of the topics that have been discussed.

DR. JAMES MCMANAMAN: Has it already been presented?

DR. JEFF DAWSON: Well they were talking about it and I think there was a little bit if misinterpretation about what we actually did. And I wanted to just provide a little bit to clarify so the report --

DR. JAMES MCMANAMAN: If it's clarification but we can't allow new information.

DR. JEFF DAWSON: It's clarification.

DR. JAMES MCMANAMAN: Okay.

DR. JEFF DAWSON: So to follow up on Dr. Popendorf's comments about the occupational exposure estimates and the loading across the entire skin surface. So basically we did use the database and now some of these scenarios have gone beyond the pesticide exposure database to the ATTF database at this point. I have to check the exact ones to make sure. But basically they represent the exposures to the skin and they're actually monitored, not modeled under the work clothing and protective equipment for those scenarios.

So it's not just like it's you know, you're wearing nothing or something. So it's reflective of actual occupational exposures. And these scenarios in here are representative of what we could include our regulatory process. We would look at the whole set of allowable label conditions when we did an actual risk assessment. This is just a very small subset of the allowable uses for chlorpyrifos and set it kind of the lower -- you know, it's a big continuum of exposures associated with the use chlorpyrifos. These are kind of the lower values.

Because when we were working through these as far as application of the model we were

thinking that you know, we don't want to do any more work than we need to so we can kind of ratchet up as we go along to see where this kind of a threshold issue. The other question was that the RFD. So because we're working under the context of the Food Quality Protection Act it's 10 plus the FQPA factor which is in play here. So, hence it's 100 and not 10. And then the PBPK model removes the inter-species factor as well.

DR. LISA SWEENEY: It's on human data so how can you have an inter-species?

DR. ELIZABETH HOLMAN: There's no -- the inter-species reduced to one.

DR. JEFF DAWSON: Right.

DR. ELIZABETH HOLMAN: Right. There is no -- because if you're using a PBPK model.

DR. LISA SWEENEY: Is that a good thing to do with the --

DR. JEFF DAWSON: So they eliminated it I think is what they said.

DR. ELIZABETH HOLMAN: Right. That's because we have the model.

DR. LISA SWEENEY: Right. Not the usual PBPK, you're right.

DR. ELIZABETH HOLMAN: We were just clarifying what our -- what we used as uncertainty factors in this case because of --

DR. JEFF DAWSON: Right. It's a factor of 10.

DR. ELIZABETH HOLMAN: The Food Quality Protection Act is a 10X class.

DR. JEFF DAWSON: Correct. So 10 plus the FQPA factor of the additional 10, that's why it's 100 and not 10 like the RFD methodology.

DR. ELIZABETH HOLMAN: There's an intra-species factors and then the FQPA factor on top of that.

DR. JAMES MCMANAMAN: Okay. Thank you. Yeah. So it's -- we can't be engaging in -- the discussions got to be amongst us. So if it's --

DR. WILLIAM POPENDORF: I mean it's not controversial, it's just clarification.

DR. JAMES MCMANAMAN: Okay.

DR. WILLIAM POPENDORF: Two things you said was not crystal clear. So when the document said 100 percent dermal that was another way of saying full body exposures assessments were conducted. But it doesn't mean that personal protective clothing was

left out of this model? Her usual clothing was worn? Correct?

DR. JEFF DAWSON: Jeff Dawson. Yes. So its reflective of loading across the body when normal work attire per that scenario was included.

DR. WILLIAM POPENDORF: That's definitely useful because I didn't interpret it that way. The other one's -- the document said PHED was used rather than the newer data. So if that's incorrect that should be clarified or fixed.

DR. JEFF DAWSON: Yes. Jeff again. Yes, we could do that.

DR. JAMES MCMANAMAN: That was Dr. Popendorf asking the questions. Okay. So back to the agency. There are no additional clarifications?

MS. DANA VOGEL: So this is Dana Vogel. No additional clarifications.

DR. JAMES MCMANAMAN: Okay. Well then I think that ends the charge questions. So now we're on to the closing remarks. And for the panelists this is a time in which you can make additional comments to the agency and to other panel members about concerns that you might have or questions that you might have. It's not a time for remarks that you might have, it's

not a time for back and forth. But its conclusions and summary comments related to these charge questions. So I guess I will start.

So I want to start by going back to the 2012 panel and quoting a quote from them. Saying, "The panel from 2012 additionally notes that studies evaluating neurodevelopmental effects entailed experimental designs that do not permit an efficient means of determining a point of departure for chlorpyrifos." I still can't say that. I don't know why after -- it's like, I don't know, dentures or something. I don't know. So the point is there was -- I mentioned this before is that there was a lot of uncertainty. And there were a lot of questions about the use of this data, the three neurodevelopmental studies, in terms of setting a point of departure.

And I think for myself and for, I think for many other panel members, I'll let them speak for themselves, but I think that this panel also continues to have questions about the use of this data to set a point of departure. In fact, the 2012 panel which included a number of epidemiologists as well as toxicologists who are on this panel, advised the agency to continue to use the cholinesterase data as

the most sensitive life stages for dose response analysis and deriving points of departure.

While it may be true that the acetylcholinesterase data may be not the most sensitive, I think that that panel clearly recognized that the neurodevelopmental studies were -- the experimental designs of those studies were not appropriate for setting a point of departure and I concur with that. I think that this panel's heard a variety of data both from the agency and from public commenter's that lead us to believe that there is a lot of uncertainty in terms of using the neurodevelopmental data as a point of departure as proposed.

I think that there is additional concerns about whether this is a representative population. Think there are concerns about whether the measurements are -- the validity of the measurements in terms of deriving a linear dose response curve, and a number of other factors have been discussed at length I think, by this panel. So I do not envy you. I think that you're in a tight spot in terms of having to address the court order.

But I think that additional information

is needed before you can derive a point of departure, an effective point of departure that both protects the human population and is not overly burdensome in terms of using an important agent for pesticide management. So good luck. It's a tough problem and I really don't envy you. But I fully think that additional information is required. And I encourage you to try to design experiments that -- and some of those experiments were provided in 2012 and I think that the panel will provide some additional experimental approaches that might be useful and we've discussed some of those.

So I will, at this point, I will end my concluding comments and I'll turn it over to Dr. Jett.

DR. DAVID JETT: Well I guess I don't have a lot to add to that except to say you know, the word chlorpyrifos has been in my head for 20, 25 years now. And you know, I think first of all, I think pest control is important in our modern civilization, there's no way around it. And I think our job is to see that we do that pest control safely. And I think you know, I certainly want to commend the EPA. I mean it's obvious you guys think really, really hard about this and have done a tremendous amount of work. Like

someone said earlier, it's not just for the past couple years, it's been for the past couple decades.

So I think for this particular question, and we are sort of at a cross road with this insecticide, but for this particular question I think the approach is the right approach. And that is to just sort of identify these areas of uncertainty and make the best possible decision you can. The one thing that I will say and then I'll stop, and that is you know, this whole idea of this decision being you know, hinging this decision on this one study. The question is you know, is that really the case first of all, and I don't think that's true.

And there's a whole body of work that goes beyond this one study that contributes to this decision. So that's one thing. And then when we were talking about alternatives I was also thinking -- and this may be sort of far out there, but is there some way -- you have a lot of smart people who know how to you know, model and do things, is there some way that you could have some sort of hybrid solution. Where you know, you use both acetylcholinesterase and these chlorpyrifos levels in the Columbia study to somehow come up with a reasonable point of departure estimate.

So at least explore -- you know, I would recommend, suggest, at least explore opportunities that aren't either/or. But other than that I think that's all I had.

DR. MARION EHRICH: Marion Ehrich, Virginia Tech. Just a general comment. In order for a registrant to put a new pesticide on the market or to re-register a pesticide the data has to be very rigorous. Now we're looking at something the opposite. Maybe the data doesn't need to be quite that rigorous but it needs to have rigor in order to put the EPA in a position of defending their decisions. You have to defend your decisions to allow registration, you have to defend your decisions to have certain cutoffs or restricted uses, you certainly have to have enough data, enough strong data, in order to think about a cancellation.

So if we're basing this on one study where it's not been reproduced, you can't get the actual hard data, there's lots and lots of points below levels of detection, one has to give that really serious thought. And I really enjoyed the discussion when people came up with all kinds of other ideas

about using the urinary data and combining it with some of this. Putting some of these types of information together, using more of these epidemiological studies, using banked blood samples, and so forth. So you can increase the rigor of your data that will help you make the decision.

So that would be my encouragement on you. Because you have to defense what you decide to do and you need rigorous data, good reasons in order to do that.

DR. SONYA SOBRIAN: I certainly agree with what has already been said and I'm sorry I wasn't here for this morning's discussion. I do like the idea of a possible hybrid solution. I think incorporating neurobehavioral end points is important. But I don't think -- I mean to do that though I think if you want to use epidemiological data I think there should be some scheme for systematic evaluation of the strength of the different studies so people can see how you chose to use study one versus study three. But that's not -- I mean that hasn't been presented to us here. So I think using both neurodevelopmental data, but also trying to look for some kind of mechanism. I think that will be important down the

road.

So -- I mean I think you've done a lot of work but I feel -- I think there are a lot of uncertainties in the data that have been presented to us that I would feel uncomfortable trying to make regulations or policy on that because I don't think the data are very strong.

DR. ALVIN TERRY: Alvin Terry, Augusta University. I'd like to first thank the EPA for inviting me to serve on a committee that I think has such an important impact. I mean it's kind of daunting when you go through the reams of material. And I did my best to do that, to go through all of the material, including all the public comments. And you know, I go back to think about the last one of these committees I served on and some of the things we discussed about mechanisms of action. And I think everybody in this room would agree that organophosphates are poisons. I mean they're not you know, trivial compounds.

But we take prescription drugs every day that are also poisonous depending on the dose you take. And so the other comment I'd like to make is I have great respect for the discipline of epidemiology.

And in fact, I use published papers all the time in my intro to the papers that I write and I quote people like Dr. Rauh. And I think they're a gold mine for driving hypothesis testing and basic research studies. But I don't believe epidemiology alone should drive the decision of such magnitude like this. Neither would I say that basic research in animals should drive the decision alone.

I think it should be a combination of the two. And like I mentioned before, what does a preponderance of the evidence suggest? And even to go further, to take only one epidemiology study that may or may not have the different limitations that we covered, I don't think that's sound scientific practice in my own judgment. And so I think most of the other comments that Dr. McManaman covered most of my other sentiments. So my opinion is that there's not enough evidence to change the current PoD guidelines.

DR. LISA SWEENEY: Dr. Lisa Sweeney, Henry M. Jackson Foundation. I'm more familiar with integrated risk information system type risk assessments that use some of the same principles. And in IRIS assessments they sort of limit the number of

uncertainty factors of 10 that you can apply. After a certain point they say if you have to apply that many uncertainty factors, you really don't have enough data to do an assessment. It's harder with an epidemiology study like this where some of the questions are things like how we link back to the exposure.

Because the cord blood is a snapshot in time and I'm concerned that it's not meaningful in terms of birth being the key window of exposure. So the linkages that you have to take back with the uncertainty about labor and delivery, the uncertainty about where you might -- how long since a pesticide application occurred, I think the you know, if you had uncertainty factors for those steps, you'd have too many uncertainty factors. And you'd just have to say this is not something we can use for a quantitative risk assessment even though it might tell us important things about hazards, what the hazards are, what some of the particular issues are with this chemical. But that doesn't mean that you can use it for quantitative risk assessment.

DR. SHARON SAGIV: This is Sharon Sagiv from UC Berkeley. So I want to highlight how, I think it's been said already, how important epidemiologic

data is in this process. Yes, we don't design epi studies for risk assessment, that is true. And they're fraught with error as has been demonstrated over and over again during our discussions. But when it comes down to it, we're not rats. And there is no animal model for some of these neurodevelopmental end points. So animal studies can take us just so far.

And I usually liken neurodevelopment, and I said this earlier to someone, as the canary in the coal mine. And these are sensitive end points and I think we need to use a sensitive end point to find a safe level of exposure in risk assessment. So I think that epi studies are extremely important to risk assessment. I'm not concerned about using them for risk assessment. What I'm concerned about is using one epi study for risk assessment. That really gives me a lot of pause. So I think in terms of setting a precedent here I think we need to value these studies in doing risk assessment, I really do.

I will push back on anyone who says that we should only use animal studies to do risk assessment, especially when it comes to neurodevelopment. But as I said over and over again, I think that using one study does set sort of a bad

precedent. So that's what I have to offer. And I guess I do feel that the PoD right now is too high. We have to figure out a way to lower it. But I don't think that using cord blood from one study is the way to do it. I think that consideration of the uncertainty around the established mechanism might be the better choice.

And really trying to come up with a PoD that makes sense using that mechanism.

DR. DIANE ROHLMAN: Diane Rohlman from the University of Iowa. So I come with a broad perspective here. I understand the benefits of pesticides, the need for them for agricultural crops, for vector control, for making fruit look nice so we eat more and we don't develop cancer as much. So there's many benefits to pesticides. But I also know that they have risks associated with them. And Dr. Terry pointed out that so does our prescription medicine.

And one of our focus is to really try to you know, balance the safe use of these pesticides with the hazards that come with that. And that can be done through a number of different ways. Chlorpyrifos is something we have been looking at for many years.

We have recognized that there are health effects associated with this. EPA has done numerous reviews and has identified that these effects are occurring at low levels. And this is been found in both animal and human studies as well. I think that we've had a lot of discussion today about moving the point of departure to a much lower level than it currently is.

I think that is appropriate, I think it is too high, I agree with Dr. Sagiv. But the concern is using one study. I have no problem with using epidemiological studies. I think the Columbia study is a well done study. It has been peer reviewed and panel reviewed many, many different ways. Every study will have uncertainty and could be done better and different decisions could be made. However, it is a valuable piece that needs to be included as well. It has been proposed that maybe we need to come up with a hybrid approach and also that we perhaps need more evidence from these human studies.

Different things have been suggested today. Looking at databases that might exist, trying to get a subset of examples and reanalyzing them to provide more information to go into this, using an approach that incorporates other biomarker measures,

perhaps weighting those depending on their certainty for how they reflect chlorpyrifos exposure. There are mechanisms, we have to stretch ourselves. In the meantime, when we started this conversation the EPA presented us with two options and we really only have focused on one today. The one we have focused on has been using the Columbia data to lower the PoD.

The other option, which we haven't spent too much time talking about, is sticking with the current PoD but adding in uncertainty factors. And that could be a mechanism to reduce that to a more acceptable level that feels more comfortable to us as far as protecting our children and our workers. So I think that those could be other options. You know, one point of uncertainty about that level has been the reviews that have been done by the EPA and others that have been peer reviewed. And that could be enough evidence to indicate adding an uncertainty factor to that existing PoD.

I'm sure if we put our heads together we could think of other options as well. Thank you. It's been interesting. I've learned a lot.

DR. WILLIAM POPENDORF: Dr. Popendorf here. And these comments are getting more challenging

as one goes around the room, right? And I agree broadly with basically everything that's been said. One of the things that I learned is, the reviews that were done -- I'm sure at the time of the publications of the raw data, for instance -- in the SAP in 2012 we didn't have the kinetic model. And you know, having seen that and having learned the things that it does in terms of fast rates of metabolism, it just led me to really reject that cord data. I just can't say it strongly enough.

It's full implications from an epidemiologic perspective, we've had some discussions, and I'm not enough of a statistician to really appreciate the fact that if you put variability into you know, uncertainty -- this is more uncertainty than misclassification, that you will always end up with a less relationship. That may be true in general, but it's really hard to believe given the fact that in this case if you're looking at three half lives it's a 16-fold potential reduction.

So the data point that you have has very reasonable reason to be 4X in either direction. One could -- well, you don't have the data, but I could envision pulling the data from the graph. I've

done that when I didn't have any other reasons to and sort of access that data and run some simulations with a 4X variability, see what the outcome is. Do you still get the same kind of correlations? If you do then my concerns would be greatly relieved. The other way to relive them was going with the maternal data. But I also support the further explorations with acetylcholine.

So I think they're all potential options. A real challenge right now because you don't have -- more work to be done. So I appreciate the work. Appreciate the opportunities to be here. It's always a good group to be with. Thank you.

DR. STELLA KOUTROS: I don't have that much to say other than I thank the agency for inviting me here and I enjoyed meeting all the panel members or seeing some of you again. And please feel free to contact me if you're ever in D.C., or I understand if you want to run the other way as well. But I just wanted to say that despite the fact that we cannot perhaps all agree, I think that just the attempt to consider the human data, regardless of our conclusions, is a really positive thing. Thank you.

DR. WILLIAM HAYTON: I don't have

anything very profound to add to all this. These are great comments. I've enjoyed working on the panel. I think as far as the pharmacokinetics the PBPK model, we heard from doctor, is it Hinderliter, who made the presentation yesterday, his public comment. I think that was a good comment. I think that the model building hasn't focused very much on chlorpyrifos and there's not very much validation data out there. So I think that could use some focus. Thanks.

DR. WILLIAM FUNK: Hi, Bill Funk. First, I just want to thank you for having me on the panel. It's been really informative for me. My background isn't specifically in pesticides, over the past couple of weeks I've learned a whole lot. And I will say it's been a challenge going back and forth as I've learned more from the past SAP and from the literature with directions I thought I would go when I was -- what my recommendations would be. I know this is a very difficult situation. I think it's very exciting that epidemiology data is being included in risk assessments and I think that the Columbia study and the other ones that we saw were very strong studies.

I personally felt that the cord blood

data is strong evidence that prenatal exposures are associated with health effects we saw several years out. I think my biggest challenge was taking a single study but also taking a single biomarker with such a short biological half life and using that alone to derive the point of departure. But like everybody else, I think the levels do need to be lowered. So I hope we can find a way to do that.

DR. RUSSELL CARR: This is Russell Carr, Mississippi State University. Last but not least. You can't say anything else, man. I want to thank the agency for the work. And basically, I know a lot of effort went into this and I'm sure there will be some good to come out of it. I think that I agree with Sharon that epidemiology studies are important. And I think that searching other databases and especially pay attention to the databases which are basically associated with the current uses of all pesticides.

I mean we've been talking about the Columbia study and you know, like we all said that that really -- unless somebody does something wrong, that won't happen again because it's been eliminated from that use. And I understand that we use that as a

benchmark. But if we're going to use available data you need to try to access populations that are probably likely to be exposed to these compounds and see what type of work is going on in those areas, and see if there is any databases there. And I think that would really help us you know, help us in the lab, too.

I mean it would help us design things to better answer your questions. And I think that's part of the problem, when we design these epidemiology studies and when we design our lab studies, we really don't have PoD and RFD in our mind. I mean we're trying to answer a question, and usually -- sometimes that doesn't help you. And I know reading these -- every time I read in these papers about the amount of variability between the methodology and you know, that's just the nature of the beast, we're all answering different questions.

And I think maybe if we start trying to focus on answering the same questions. I might actually even put red cell cholinesterase in my assay from now on.

DR. JAMES MCMANAMAN: Well, thank you. Before I turn this back over --

DR. PANOS GEORGOPOULOS: I don't know if I --

DR. JAMES MCMANAMAN: Oh, Dr. Georgopoulos. Good, thank you.

DR. PANOS GEORGOPOULOS: First of all, I want to apologize for doing this thing remotely. I know how it is inconvenient. And remote connection, my accent, and my allergies make it, I'm sure, make it very difficult for some people to follow. So I really apologize for this. But just a couple of comments. First of all, I would like to commend the agency for really doing thoughtful work. I mean the EPA is facing a very serious challenge here. And the quantitative information is currently very uncertain.

They're having to decipher the singer from the noise here, it's quite a task. I mean this is something that definitely requires to take -- maybe it requires a paradigm change, I mean a paradigm shift in this case in how human health risk assessments are done. And clearly the timeframe for -- the legally enforced timeframe, its own, presents challenges that are insurmountable. But in the long run I think we are learning a lot of things from this enterprise. I guess people were talking about the issue of

epidemiology. Clearly for the quantitative or in order to get the numbers there we have one study.

But there is a multiplicity of other studies. And they have just been accumulating over the years. That should be taken somehow into account eventually in health risk assessment. And I kept thinking as we were going through these days oh, EPAs human health risk assessment strategic research action plan for 2016 -- 2019, I don't think the word epidemiology appeared in there. But certainly there were concepts of integrating information from multiple sources -- human, animal, mechanistic.

And the concept of multi-criteria decision analysis is integrating multiple sources of information, qualitative and quantitative, in order to strengthen risk assessment is fundamental in there. So I know this is a new research strategy plan, 2019, and here where EPA is facing the need to make decisions in a very short time frame. But definitely the situation we are facing today probably is going to be relevant to a number of other situations.

And taking into account the new tools that are evolving both in terms of modeling, data analytics, the multi-criteria decision analysis will

be essential eventually in bringing together epidemiology data with in vitro data, qualitative data. And strengthening how do you do this when you need to get one specific number for PoD and RFD, I mean that would be a challenge. But certainly I'm glad that EPA at least in the longer term strategic thinking is thinking of multi-criteria decision analysis for risk assessment.

Specially for the case of chlorpyrifos, it was mentioned just by one of the previous speakers that those model for chlorpyrifos was discussed yesterday. Some of the issues of limited evaluation were brought up. But I think -- I personally probably have more faith in Dow's model related to chlorpyrifos metabolites than the research which was developed initially which was used in a couple of studies and appears to be consistent with available data.

But definitely there is a need to improve upon the framework and to start including alternative (inaudible) pathways. Pharmacodynamic models that are exploratory but they may provide information for end points other than the acetylcholinesterase inhibition pathway. And you know, this is not something that can happen in the

short term. But establishing an open framework with different people in the community can develop their own modules, test different pharmacodynamic models, do in vitro, do in vivo extrapolations.

And start utilizing, you know, make use of the variety of in vitro data related to numerous pathways that keep showing up in the literature. That will be very useful. The fact that there are practical difficulties in the wider community using the original model for chlorpyrifos for the platform and so on can be overcome. I think it would be a valuable investment on EPA staff in that respect. Again, as well as the EPA, there are a number of tools that are coming out from the ToxCast and ExpoCast program and even more refined models that really tie together PBPK modeling and exposure of characterization.

And that could be useful eventually. I know that some of these tools are much more refined than the models that have been used for this particular assessment of exposure in the 2014 health risk assessment. But again, these are things that are evolving and can be very useful in the next couple of years. How EPA is going to address the challenges

that they are facing for 2016 is another issue and I wish you the best for this. I mean it's a major challenge and I commend you, again, for the effort that you are putting on this.

DR. JAMES MCMANAMAN: Thank you, Dr. Georgopoulos. Okay. Before turning this back to the agency for their final comments I would sincerely like to thank my fellow panelists. This has been one of the more interesting panels that I've had the pleasure of serving on and I've learned a lot. And actually it's been a lot of fun. I mean, it's been you know, fun in a very interesting way. And so it's quite a pleasure to serve as the session chair. Also like to thank the agency for all of their hard work in this.

I know that they are under a lot of pressure to try to come up with a solution to this question and I appreciate the complexity of it and how hard it is to do this. And really thank you for all your presentations. They were quite good and quite informative. And finally, I'd like to thank the public commenter's. For this particular panel session or this particular session the public commenter's often times have important, but scientifically their comments are not strictly related to the scientific

questions that we're addressing.

But in this particular instance they provided a lot of scientific background and a lot of scientific analyses that were helpful to this panel in coming up with our deliberations. So I really appreciate all the hard work that the public commenter's have put into this. And so with that I'd also like to thank Fred and his staff and all the help that they've given us in terms of getting all the information and getting it to us in a timely way in which we could evaluate for this problem. So with that I'll turn it over to the agency.

MS. DANA VOGEL: Thank you. Yes, we just want to thank you for all the time and effort you've spent. Not just in this meeting room but how you've taken time out of your busy schedule and busy lives to be here and to review documents. And it's clear to us how much time and effort you've spent thinking about or reviewing the materials both in this meeting and outside of this meeting before you came here, during the meeting, at night doing power analyses and other things. We really appreciate the discussion and hearing all the differing perspectives and all the time and effort.

It is a challenge for us and we're sharing our challenge with you. And we appreciate what you've brought to us. So thank you. And I'd also like to thank Fred and the SAP staff for putting this meeting together. I know a lot of work goes into it from their side as well. Thanks.

MR. FRED JENKINS: So I'm going to give the closing remarks. First of all, I want to thank our FIFRA SAP session Chair, Dr. Jim McManaman. You did a masterful job chairing this meeting. Thank you so much. It's always a pleasure working with you. Thank you so much to this panel. Thank you for accepting the invitation. Thank you for your commitment, your enthusiasm, your hard work throughout this entire process. And again, that goes with the sentiment of thank you for the sacrifices you made in your personal time in coming here to help the agency address this important issue.

Thank you to the Office of Pesticide Programs under the leadership of Jack Housenger. Thanks for all your support and hard work and leadership in preparing for this SAP. Thank you to Rick Keigwin, Dana Vogel, Director of ACD, Jeff Dawson, Anna Lowit, Dana Friedman, Elizabeth Holman,

Cecilia Tan, Wade Britton, Rochelle Bohaty, Danette Drew.

Bear with me, some other team members that supported their work I want to acknowledge. Ginger Moser, Danelle Lobdell, James Nyugen, Mark Dyner, Jim Hetrick, Dana Spatz, Jim Cowles, Yu-Ting Guilaran, Kevin Costello, and Anita Pease. And a special thanks to all the agency staff and scientists and managers that supported their work. Thank you very much for the public commenters for your participation in this meeting. Thank you to our contractors for your support in this meeting. And thank you to all the public who attended and also listened on our worldwide webcast.

And I cannot close without thanking the FIFRA SAP staff under the leadership of Laura Bailey. And all of my colleagues which are a tremendous pleasure to work with. Donald Wood, Scott Lynn, Shirley Percival, Joyce Coates, Steve Knott, and Barbara Ewell.

And the last important note that I needed to just remind you all FIFRA SAP report will be ready within 90 days at the close of this meeting. This meeting is officially adjourned. Everyone please

have a nice evening and a good weekend.

(Whereas the meeting was adjourned)