U.S. ENVIRONMENTAL PROTECTION AGENCY (EPA)

SCIENCE ADVISORY COMMITTEE ON CHEMICALS (SACC)

VIRTUAL PUBLIC MEETING

DRAFT RISK EVALUATION FOR DI-ISODECYL PHTHALATE (DIDP) AND DRAFT HAZARD ASSESSMENTS FOR DI-ISONONYL PHTHALATE (DINP)

SACC WEBSITE:

https://www.epa.gov/tsca-peer-review

DOCKET NUMBER:

EPA-HQ-OPPT-2024-0073

ONLINE VIA ZOOM AND YOUTUBE

July 30-August 1, 2024

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OPENING OF MEETING DAY 1

DR. ALAA KAMEL: Good morning. My name is Alaa Kamel, and I will be serving as the Designated Federal Official for the U.S. EPA Science Advisory Committee on Chemicals, SACC. For this meeting, and in my role, I will be opening this public meeting, and I want to thank Dr. George Cobb for serving as the chair of the Committee for this meeting.

I also want to thank the members of the Committee, ad hoc reviewers, and the public for attending this important meeting. We appreciate the time and effort of the Committee members in preparing for this meeting, considering their busy schedules.

In addition, I want to thank EPA's Office of Pollution Prevention and Toxics, OPPT, and my colleagues in the Peer Review and Ethics Branch, PREB, in EPA for their hard work in preparing for this important review of EPA's Draft Risk Evaluation for Di-isodecyl Phthalates (DIDP)

and the Draft Hazard Assessments for Di-isononyl Phthalates (DINP).

I would like to thank my colleagues Steve Knott of the Peer Review and Ethics Branch -- he's the manager -- and from the Mission Support Division of the Office of Program Support in EPA. And I would to thank Tamue Gibson, the executive secretary of the FIFRA Scientific Advisory Panel and the Science Advisory Committee on Chemicals. They are both online this week and will be serving as backups to my role as DFO.

Thanks are also due to Dr. Sharlene Matten and William Wooge, our Assistant Deputy Ethics officials, who are also DFOs and can serve also as backups.

I also thank Ms. Alie Muneer, the DFO in the Peer Review and Ethics Branch. I want to thank the administrative support team, including Ms. Joyce Coates, Ms. Barbara Ewell, and our contractor Kurd Ali from EnDyna.

The SACC is a federal advisory committee that provides independent scientific

peer review and advice to the EPA on chemical-related issues regarding the impact of proposed regulatory actions on human health and the environment. The SACC provides advice and recommendations to EPA. Decision-making and implementation authority remains with the Agency.

The SACC for this meeting is comprised of 15 members who are experts in toxicology, environmental risk assessment, exposure assessment, and related sciences.

The expertise of these members is augmented by eight additional ad hoc reviewers, who are special government employees participating in this SACC peer review providing additional scientific expertise, including terrestrial and wildlife ecological risk assessment, bioaccumulation of chemicals and their fate in the environment, exposure to consumer products, and indoor air. Also liver toxicity, cancer, and peroxisome proliferator-activated receptor alpha mode of action, PPARα, and those response

assessment in order to assist in reviews conducted by the SACC committee.

As the DFO for this meeting, I serve as a liaison between the SACC and the Agency. I am also responsible for ensuring provisions of the Federal Advisory Committee Act, also known as FACA, are met.

The Federal Advisory Committee Act of 1972 established a system that governs the creation, operation, and termination of executive-branch advisory committees. SACC meetings are subject to all FACA requirements. These include opening meetings, timely public notice of meetings, and document availability to the public. All documents are available to the public in the docket at www.regulations.gov, listed in the meeting agenda.

As the designated federal official for this meeting, a critical responsibility is to work with appropriate agency officials to ensure that all appropriate ethics regulations are satisfied.

In that capacity, committee members receive training on provisions of the federal conflict of interest laws and ethics and scientific integrity training. In addition, each participant has filed a standard government financial disclosure report. Our deputy ethics official for the Office of Program Support and their team in consultation with the Office of General Counsel has reviewed these reports to ensure all ethic requirements are met.

The SACC, today and in the next coming days, will review challenging scientific issues over the next four days. We have a full agenda, so meeting times are approximate, thus we may not keep to exact times as noted in the agenda due to discussions and public comments. We strive to ensure adequate time for Agency presentations, public comments, and Committee deliberations.

For presenters, SACC members, and public commenters, please identify yourselves as you speak into your microphones since this meeting is being webcasted, transcribed, and recorded.

I'd like to note that we have a live video webcast for this meeting through YouTube. To access it, please go to the link in the meeting website listed in the agenda.

Copies of all EPA presentation materials, written public comments, and other documents related to this meeting are available in the public docket at regulations.gov. Copies of presentation materials submitted this week by public commenters will be available in the public docket within the next week.

For this meeting, there are so far 58 registered attendees, 12 of which are registered to give oral comments. Registration to attend this meeting is open until the last day of the meeting.

Members of the Committee and ad hoc reviewers are encouraged to fully consider all written and oral public comments submitted for this meeting. We dedicated adequate time for the Agency presentations, public comments, and peer reviewers to discuss their questions. As we move

through the proceedings, if time allows, we may be able to move to the next agenda item if an item takes less than the anticipated time.

For members of the press, EPA media relations staff is available to answer your questions about this meeting. Please address all questions to Cathy Milbourn at email press@epa.gov. At the conclusion of this meeting, the SACC will prepare a report as a response to all questions posed by the Agency, background materials, presentations, and public comments. This final report also serves as the meeting minutes.

We anticipate the final report and meeting minutes to be completed in 60 days after the meeting is concluded. I wish to thank the Committee, and the ad hoc reviewers, and the public for your participation. I'm looking forward to both a challenging and interesting discussion over the next four days. I now turn the meeting over to our chair Dr. George Cobb. Thank you.

INTRODUCTION AND IDENTIFICATION OF PANEL MEMBERS

DR. GEORGE COBB: Thank you, Dr. Kamel. Welcome, everyone, both the public and our Committee members and EPA staff. Alaa thanked all of the people that I think I would thank, so I'm not going to repeat that, other than to say we are very appreciative of the work that he and his colleagues at EPA have done to help us prepare for this meeting. At this point, I'll simply call the roll for the Committee members and let each one of us introduce ourselves.

I am George Cobb. I am the chair of the Environmental Science Department at Baylor University, and I'm a chemist and an exposure assessment scientist by training.

The next person on the list is Dr. Apte.

DR. UDAYAN APTE: Hi. My name is Udayan Apte. I am a professor at the Department of Pharmacology, Toxicology, and Therapeutics at

the University of Kansas Medical Center. I'm a board-certified toxicologist, and my expertise is in liver disease, liver toxicology, liver cancer. Thank you.

DR. GEORGE COBB: Thank you. Dr. Baker.

DR. MARISSA BAKER: Hi. I'm Marissa Baker. I'm an assistant professor at the University of Washington in Seattle. My background is in industrial hygiene, exposure assessment, and occupational groups.

DR. GEORGE COBB: Thank you. Dr. Chaisson.

DR. CHRISTINE CHAISSON: Hello. My name is Dr. Chris Chaisson, and my beginnings were in toxicology -- particularly chemistry -- but most of my career has been with exposure assessment, including modeling and data statistics. Thank you.

DR. GEORGE COBB: Thank you. Dr. Eick.

DR. STEPHANIE EICK: Hi, everyone. My name is Stephanie Eick. I'm an assistant professor at Emory University at the Rollins School of Public Health. I'm an environmental epidemiologist, and most of my work looks at exposure to chemical mixtures and impacts on health.

DR. GEORGE COBB: Thank you. Dr. Fong.

DR. ALAA KAMEL: I think he would be absent today.

DR. GEORGE COBB: Dr. Gentry.

DR. ROBINAN GENTRY: Hello, everyone. I'm Robinan Gentry. I'm a principal with Ramboll and a toxicologist by training. My expertise is in the area of human health risk assessment.

DR. GEORGE COBB: Thank you. Dr. Graham.

DR. CYNTHIA GRAHAM: Good morning. I'm Cynthia Graham. I'm a PhD toxicologist doing

independent consulting. My expertise is respiratory and dermal sensitization.

DR. GEORGE COBB: Thank you. Dr. Heiger-Bernays.

DR. WENDY HEIGER-BERNAYS: Good morning. My name is Wendy Heiger-Bernays. I'm a professor emeritus and research professor of environmental health. My background and expertise is in molecular toxicology and health risk assessment.

DR. GEORGE COBB: Thank you. Ms. Jenkins.

MS. ALLISON JENKINS: Good morning. I'm Allison Jenkins. I'm a senior toxicologist at the Texas Commission on Environmental Quality. I'm a risk assessor and human toxicologist there -- do a little bit of everything with air, water, waste. Thank you.

DR. GEORGE COBB: Thank you. Dr. Li.

DR. LI LI: Good morning. I'm Li Li, Assistant Professor of Environmental Health at

the University of Nevada, Reno. My expertise is in branch modeling with a focus on environmental chemistry and human exposure signs about chemical substances. Thank you.

DR. GEORGE COBB: Thank you. Dr. Merced-Nieves.

DR. FRANCHESKA MERCED-NIEVES: Morning. My name is Francheska Merced-Nieves. I'm an assistant professor at Icahn School of Medicine at Mount Sinai. My expertise are neurotoxicology and mixtures and cumulative impacts on brain development.

DR. GEORGE COBB: Thank you. Dr. Ottinger.

DR. MARY OTTINGER: Good morning. I'm Mary Ann Ottinger. I'm a professor emeritus at the University of Houston. My expertise is in endocrinology and ecotoxicology with work in neurobiology and comparative biology of aging.

DR. GEORGE COBB: Thank you. Dr. Przybyla.

DR. JENNIFER PRZYBYLA: Good morning. I'm Jennifer Przybyla. I am an environmental health scientist with the Agency for Toxic Substance and Disease Registry. My expertise is in human health risk assessment. Thank you.

DR. GEORGE COBB: Thank you. Dr. Reif.

DR. DAVID REIF: Hi. I am David Reif. I'm chief of the Predictive Toxicology Branch at the National Institute of Environmental Health Sciences. As formerly a professor of bioinformatics at NC State University, my expertise is in computational biology informatics and artificial intelligence.

DR. GEORGE COBB: Thank you. Dr. Sahmel Elliott (phonetic).

DR. ALAA KAMEL: I don't think she's participating.

DR. GEORGE COBB: Mr. Wright also is not participating. Dr. David.

DR. RAYMOND DAVID: Hi. I'm Raymond David. I'm a retired toxicologist -- retired from industry. I have my own consulting business, and I have been a long-time student of phthalate esters since the early nineties.

DR. GEORGE COBB: Thank you. Dr. Fanning.

DR. ELINOR FANNING: Good morning. My name is Elinor Fanning. I'm a public health toxicologist with the Washington State Department of Health. I have training in molecular biology, and my current work is mostly concerning toxics in consumer products. Thank you.

DR. GEORGE COBB: Thank you. Dr. Fenner-Crisp.

DR. PENELOPE FENNER-CRISP: Good morning. I'm Penny Fenner-Crisp. I'm an independent consultant living in Charlottesville, Virginia, formerly an EPA employee -- spent 22 years in the drinking water, toxics, and pesticide program. My area of expertise is all things

toxicology, human health risk assessment, and regulatory science policy and guidance.

DR. GEORGE COBB: Thank you. Dr. Howdeshell.

DR. KEMBRA HOWDESHELL: Kembra Howdeshell. I'm with the National Institute of Environmental Health Science, where I am a health scientist in the division of translational toxicology. My expertise is reproductive and developmental toxicology and mixtures and systematic review.

DR. GEORGE COBB: Thank you. Dr. Martinez.

DR. JEANELLE MARTINEZ: Hi. Good morning. My name if Jeanelle Martinez. I'm a board-certified toxicologist, working as a principal scientist at B. Braun in the pharmaceutical chemistry research division. I have over 25 years of experience with state, local, and national agencies doing human health risk assessments. Currently, I do human health

risk assessments for pharmaceutical containers and medical devices.

DR. GEORGE COBB: Thank you. Dr. Shuman-Goodier.

DR. MOLLY SHUMAN-GOODIER: Good morning, everyone. I'm Molly Shuman-Goodier. I'm a research scientist with the Washington Department of Fish and Wildlife. My expertise is in ecotoxicology and environmental endocrinology. I'm serving as an ad hoc reviewer, and I've spent time working at EPA with the hard-working folks in OPPT as an eco-assessor. Thank you.

DR. GEORGE COBB: Thank you. Dr. Spade.

DR. DANIEL SPADE: Good morning. I'm Daniel Spade. I'm an assistant professor in the department of pathology and laboratory medicine at Brown University. I am a toxicologist, and my area of expertise is male reproductive toxicologies.

DR. GEORGE COBB: Thank you. Dr. Wolf.

DR. DOUGLAS WOLF: Douglas Wolf, veterinary pathologist by training. I retired from both U.S. EPA and Syngenta Crop Protection, independent consultant with expertise in toxicology, toxicologic pathology, and carcinogenesis.

DR. GEORGE COBB: Thank you. Is there anyone whose name I did not call? Please raise your hand, if there is. I think we got through everyone. So, now we can move on to our introductions of the other folks from EPA.

At this point, I turn the floor over to Dr. Elissa Reeves, who is the director of OPPT within the Office of Chemical Safety and Pollution Prevention. Dr. Reeves.

INTRODUCTION AND WELCOME

DR. ELISSA REAVES: Great. Thank you, Dr. Cobb. Good morning, everyone. I want to welcome our new members of the SACC, and, of course, welcome back those of you who have been

with us for a while now. We are pleased to have you back with us this week to review our first two phthalate risk evaluations.

My name's Elissa Reeves. I'm the director of the Office of Pollution Prevention and Toxics. I've been in this position since late last year. I came over from the Office of Pesticide Programs, where I had over 20 years' experience in toxicology, risk assessment, and risk management.

This morning, I have the pleasure today to welcome Dr. Michal Freedhoff, the assistant administrator for EPA's Office of Chemical Safety and Pollution Prevention, to give some opening remarks. Michal began her tenure as the AA in June of 2021. Prior to that, she joined the EPA as the principal deputy assistant administrator for OCSPP in January 2021. Dr. Freedhoff has more than 20 years of government experience, most recently as the minority director of oversight for the Senate Environment and Public Works Committee.

She began her congressional service in 1996 in then Congressman Ed Markey's office as a congressional science and engineering fellow after receiving a PhD in physical chemistry at the University of Rochester. Dr. Freedhoff has also served on the staffs of the House Science Committee, the House Select Committee on Energy Independence and Global Warming, the House Energy and Commerce Committee, and the House Natural Resources Committee.

With environmental expertise spanning a range of policy areas, her legislative work includes the 2016 reauthorization of TSCA -- the Toxic Substances Control Act -- 2019 legislation to address PFAS contamination, the fuel economy provisions in the 2007 Energy Independence and Security Act, and a law requiring the creation of an online database of potential consumer products' safety defects.

It's my pleasure this morning to welcome Dr. Freedhoff to give our opening remarks. Dr. Freedhoff.

WELCOME AND INTRODUCTORY COMMENTS

DR. MICHAL FREEDHOFF: Thanks so much. Hello, everybody. I'm happy I could be here today to help kick off the meeting. I'd like to start by welcoming our new Committee members. We've had four new members join the SACC -- Dr. Arthur Fong, Dr. Robinan Gentry, Dr. Li Li, and Dr. Jennifer Sahmel. We also have some folks who've signed up for another go-around with our merry band -- Dr. Udayan Apte, Dr. Marissa Baker, Dr. Christine Chaisson, Dr. Wendy Heiger-Bernays, Dr. Jennifer Przybyla, and Dr. David Reif.

I want to give you all a very warm welcome to the Committee. The SACC has done invaluable work for us for many years, and we're excited to have you on board and look forward to your insights and contributions.

We've also had to say goodbye to two of our SACC members -- Dr. Carmen Messerlian and

Dr. Charles Vorhees. Our thanks to them as well for all of their work.

Thank you all for being virtually here. I also just want to say that I am sorry we can't meet in person. Unfortunately, we continue to be underfunded, and so we've had to move to virtual SACC meetings. Since TSCA was amended in 2016, it's been a continual struggle to get the resources we need to do the critical work that needs to be done, and we didn't even come close to getting what we need from Congress this past year.

We told Congress we'd need an increase of about $48 million over our FY 2023 funding levels to meet many of the statutory deadlines in TSCA, and instead, our toxics budget was cut by $5 million. This is a serious blow. It endangers our ability to do what TSCA tells us we have to do to protect human health and the environment in the time frames the law requires.

So, one of the ways we're making up our budget shortfall is by making our FY '24 peer review meetings virtual rather than offering an

in-person option. Just as an example, by having a fully virtual four-day SACC meeting for formaldehyde, we saved about $100,000. I know some of you have noted that there can be benefits to having meetings in person, and we completely agree and hope that our resources' picture changes sometime soon.

The thing is, whether you're online or in person, some of the most significant changes we've made during this administration have been, in part, a response to feedback from the SACC. And the solutions to many problems that you noted over and over again in your reviews of the first ten risk evaluations, were incorporated into our final risk evaluation framework rule, which frankly has SACC written all over it.

For example, when the SACC reviewed the risk evaluation for 1,4-dioxane -- done under the previous administration -- you had some strong critiques and noted some glaring holes. So, first the risk evaluation didn't look at potential exposures through the water we drink or the air we

breathe, which has clear implications for the general population and especially for fenceline communities. And the risk evaluation also assumed that everyone who worked with the chemical always properly wore personal protective equipment. The SACC questioned those decisions.

Our final risk evaluation rule says that EPA can't exclude exposure pathways or conditions of use from the scope of a risk evaluation. And it also says we have to accurately consider risks to workers.

We've also incorporated a consideration of risk to fenceline communities. The SACC reviewed our fenceline community risk screening approach in March of 2022 and provided valuable feedback, which we've started to incorporate into our subsequent risk evaluations.

Another improvement we've made thanks to feedback from the SACC is in systematic review. We updated our systematic review protocol in 2021, following recommendations from both your

reviews of specific risk evaluations and the National Academy's.

In 2022, you reviewed our revised protocol and provided additional recommendations, which we've also started to incorporate. We've also gotten helpful feedback on specific chemicals, like NMP, which we just proposed a rule to address. During that review, you identified issues with our PPPK exposure modeling and our consideration of aggregate exposures, which we've revised using your advice.

Today, we come to you again to ask for your expertise. We've provided some specific charge questions to guide in the next few days, and we look forward to hearing what you have to say. You'll be considering DIDP and DINP, two phthalates used to make plastic that's found in everything from flooring to furniture to children's toys.

Just two weeks ago, the Biden-Harris Administration released the first comprehensive government-wide strategy to target plastic

pollution. Plastic production and waste doubled over the past two decades, littering our ocean, poisoning the air of communities near production facilities, and threatening public health. This new strategy specifically mentions using TSCA to review chemicals used in plastic production.

The Administration also announced that we aim to phase out federal procurement of single-use plastics from food service operations, events, and packaging by 2027, and from all federal operations by 2035. Since people use all kinds of different plastics every single day, and since exposure to many phthalates -- including DINP -- cause the same health effect, we're also looking at cumulative risk. The SACC reviewed our draft approach for cumulative risk assessment last year.

As you know, we've given you the full DIDP risk evaluation to review but only the hazard assessment for DINP. This is another way we're making our risk evaluation process more efficient and sustainable for the program. We're

hoping to focus your efforts on work that is truly novel and for which we really need your review. And in this case, the exposures for DIDP and DINP are very similar, but the hazards are different. So, we're asking you to look at both chemicals' hazards but to review our approach to exposure to both chemicals based just on what we've provided in the DIDP evaluation.

I know you've got a lot to talk about, so I'll end here. We really look forward to your valuable input. And it really does make a difference and improve the way we do things. Thank you, again, for all the work that you do.

DR. GEORGE COBB: Thank you very much. It's very good to hear from you, and I appreciate you taking the time to come speak with the Committee today. I will say that, just as a chair -- and I've been ad hoc and then a full member for while -- we did take notice of the efforts that EPA took to incorporate the SACC's comments into the risk assessment process. And

I've tried to highlight that in at least our executive summaries when we are reporting out.

So, I do appreciate that and duly note that the EPA is making strides to take into account the types of recommendations that we're making. So, thank you very much.

DR. MICHAL FREEDHOFF: Thank you.

DR. GEORGE COBB: I think at this point we move to our presenters from EPA. We'll be hearing from -- our first technical presentation will be from Dr. Beachum, Dr. Luz, from the Existing Chemicals Risk Assessment Division. And they're going to be talking to us about the overview of the Draft Hazard Assessment.

EPA TECHNICAL PRESENTATION 1

DR. COLLIN BEACHUM: Thank you, Dr. Cobb. I appreciate it. Collin Beachum, here, U.S. EPA. Thanks for the introduction. I also wanted to thank the other members of the SACC as well for their participation and the feedback that

we'll receive shortly. And I also want to thank the public commenters that we'll be hearing from later today as well.

Today, as you've heard, we'll be talking about DIDP's Draft Risk Evaluation and the Draft Hazard Assessment for DINP.

Next slide, please. First, I want to say thank you. It takes a small army of people to get us to this point in the process, including the authors and contributors to the Risk Evaluation and the Technical Support Documents, our technical support staff contractors -- who make much of this work possible -- and then also technical experts from within other offices within the EPA.

Next slide, please. The outline for today will be first for the SACC presentations -- the technical presentations from the SACC. We have those broken into four parts. Part 1 is the introduction to TSCA and an introduction to DIDP and DINP. Part 2 will focus on the DIDP in human health hazard and exposure. Part 3 will be the

DINP human health hazard. And then Part 4 will be DIDP environmental hazard and exposure and the DINP environmental hazard.

Our charge questions are directed at our two different chemicals. For DIDP, our charge questions will focus on the exposure analysis, the ecological hazard, and the human health hazard. For DINP, our charge questions will be focused on the ecological hazard and the human health hazard.

Next slide, please. So, in order to connect the dots here, we've given you a road map. On the left hand of this table, you'll see Parts 1, 2, 3, and 4 that correspond to the various presentations. In the middle column here are our presentation sections by title. And on the far right, you'll see the charge questions that are directed at these various parts.

Next slide, please. Now then, we'll start with the Introduction to TSCA.

Next slide, please. To set some regulatory context here, TSCA Section 6(b) requires the EPA to conduct risk evaluations to

determine whether a chemical substance presents an unreasonable risk of injury to human health or the environment. In order to do that, we're not supposed to consider the cost or other non-risk factors, including an unreasonable risk determination to potentially exposed or susceptible subpopulations identified by the EPA as relevant to the risk evaluation under the conditions of use.

TSCA section 6(b)(4)(C) directs the EPA to establish the "form and manner" and "criteria" that govern manufacturer requests that EPA conduct a risk evaluation on a substance that they manufacture. So, this is the portion that directly corresponds to DINP and DIDP as manufacturer-requested risk evaluations.

The EPA has broad discretion to establish these criteria, but relatively less discretion over whether or not to grant those requests that comply with the EPA's criteria. So, in other words, EPA must grant any request if it determines that it complies with EPA's criteria,

until the statutory minimum of 25 percent has been met. What that portion means is that the EPA must grant MREs that meet the criteria if they are 25 percent or less of the total number of risk evaluations under consideration.

Continuing that line, assuming EPA receives requests in excess of that 25 percent threshold, the EPA interprets this provision to grant EPA discretion to determine whether to grant further requests, up to a maximum of half of the total risk evaluations under consideration.

In such circumstances, EPA has the discretion to give preference to the manufacturer requests for which EPA determines that restrictions imposed by one or more states have the potential to significantly impact interstate commerce or health or the environment. In other words, we must grant MREs that meet the criteria up to the 25 percent threshold, and then between the 25 and 50 percent -- up to 50 percent -- so half of the total risk evaluations under consideration.

Next slide, please. U.S. EPA Requirements under TSCA. What are they? We have to evaluate the existing chemicals with clear and enforceable deadlines. In this case, we have three to three-and-a-half years to complete risk evaluations after the final scopes are published. So, we must use the best available science using reasonably available information and make decisions based on the weight of scientific evidence. We'll talk more about those later.

We have to develop a risk-based chemical assessment without consideration of costs or other non-factors, and we must consider risks to potentially exposed or susceptible subpopulations determined to be relevant to the risk evaluation. And, finally, we have to address those unreasonable risks identified in the risk evaluation.

Next slide, please. TSCA Risk Evaluations. The risk evaluation considers the exposure and hazards to determine whether a chemical substance presents an unreasonable risk

to human health or the environment under the conditions of use. The risk evaluation is our primary science support document that the Agency uses if it is necessary to issue regulations to address unreasonable risk.

And then, finally, to the extent that the Administrator makes a decision based on science, the Administrator shall use scientific information, technical procedures, measures, methods, protocols, methodologies, or models, employed in a manner consistent with the best available science. That's our Section 26(h) portion of TSCA.

Next slide, please. This is what I was referencing previously. I want to make sure that we get some scientific terms properly understood here as we go through the evaluation of our work.

Specifically, the EPA will document the risk evaluation is consistent with the best available science and based on the weight of scientific evidence. So, in determining best

available science, EPA has to consider the extent to which scientific information, technical procedures, measures, methods, protocols, methodologies, or models employed to generate our information are reasonable for and consistent with the intended use of the information -- hence some of the charge questions that you see.

We also need to consider the extent to which the information is relevant for the Administrator's use in making decisions about the chemical substance or mixtures.

We also need to consider the degree of clarity and completeness with which data, assumptions, methods, quality assurance, and analyses employed to generate the information are documented; the extent to which the variability and uncertainty of the information -- or in the procedures, measures, methods, protocols, methodologies, or models -- are evaluated and characterized. That's why we have such focus on methodologies in our charge questions.

Then, finally, the extent of the independent verification or peer review of the information or of these procedures, measures, methods, protocols, methodologies, or models -- hence the reason why we're asking for this guidance.

Next question, please. Weight of Scientific Evidence -- what is this? In order to meet the law's requirement to base decisions in TSCA, risk evaluations must be made on the weight of scientific evidence. EPA relies on established Agency guidance documents, which provide consistency and formality to the process that looks to integrate multiple and often heterogenic lines of evidence.

The Weight of Scientific Evidence assessment is based on the strengths, limitations, and the interpretation of data available, the information across multiple lines of evidence and how these different lines of evidence may or may not fit together when drawing conclusions.

The Weight of Scientific Evidence assessment also examines multiple lines of evidence from scientifically relevant published or publicly available studies in peer reviewed scientific journals, studies conducted in accordance with OECD or EPA guidelines, gray literature, and/or any other studies, scientific information, or lines of evidence that are of sufficient quality, relevance, and reliability, are evaluated across studies and endpoints into an overall assessment.

So, EPA has provided a summary of the Weight of Scientific Evidence narrative or characterization to accompany a detailed analysis to transparently describe the conclusions, as well as explain the selection of studies or effects used in main lines of evidence and a relevant basis for those conclusions.

Next slide, please. TSCA Risk Assessment Considerations. We look at sources of potential exposure, the pathways by which those exposures may occur, the media in which those

exposures could take place, the receptors or the people and organisms that may be exposed, and then the routes by which people and environment ends. And animals and plants may also be exposed.

Next slide, please. The risk evaluation process is an incremental and iterative process. So, the methods that we're developing here may be used in the future as appropriate for different chemicals. And that's one of the reasons why we spend so much time asking questions about methodologies. It's so we can improve our strategies and assessments, but keeping in mind that we're time-bound and that the risk evaluations must be completed within three years of the publication of the scopes.

So, the risk evaluations ultimately land on a determination of risk, whether that be unreasonable, no unreasonable risk, or an unreasonable risk for a chemical. If the EPA determines that there is unreasonable risk for a chemical, even if one COU, we move to risk management. And the risk management phase is

where we impose restrictions in order to eliminate that unreasonable risk.

Next slide, please. So, in order to ensure the science quality and transparency, we go through several rounds of various internal and external reviews. Some of our internal review processes include peer review with our technical teams -- right here within the existing Chemical Risks Assessment Division -- and then continuing on to our senior scientists and management reviews.

And then we also work collaboratively with other offices within the EPA and sometimes even external to the EPA. This evaluation we've collaborated specifically with the Office of Research and Development, Office of Water, and Office of Air and Radiation, among others, seeking early guidance on methodologies and feedback.

And, of course, our external review process includes a public comment period -- which we've recently ended for these two -- and then, of

course, continuing on into various peer review possibilities, such as SACC, or in the case of other existing chemical risk evaluations, even consulting with the HSRB, NASEM, and others as well.

We also rely extensively on journal publications and then contract reviews and letter peer reviews, as you've seen in other evaluations, and then, of course, stakeholder engagement from various entities, whether it be the manufacturers that request the risk evaluations in this case, or our other stakeholders as well, from our NGOs groups.

Next slide, please. So what will we do with this feedback, and why are we seeking it? We're asking for the feedback to help us decide when and how the EPA uses different approaches to estimate potential exposures to the chemicals, define the conditions when specific approaches can be or should be applied to risk evaluations, and also assist the Agency in quickly identifying readily available data best suited for use in risk

evaluations, and also -- as you see with some of the future-oriented charge questions that we're asking here -- future steps in the method development and utilization in ongoing and future risk evaluations.

Next slide, please. With that I will turn it over to our very talented technical team in order to go through other portions of our presentations. Thank you.

DR. GEORGE COBB: Thank you for that. The next presenters will be -- I'm not sure which person is going to -- is Dr. Beachum going to be presenting? Or who's next?

DR. ANTHONY LUZ: Good morning, Dr. Cobb. This is Anthony Luz with EPA. I'll be presenting the next portion of this morning's presentation.

DR. GEORGE COBB: So this is the second part -- the Presentation 2?

DR. ANTHONY LUZ: No, this is still Part 1. We're now just switching gears to going

over some background information, specifically relevant to DIDP and DINP.

DR. GEORGE COBB: Apologies. I had a different name on my schedule. Please continue.

DR. ANTHONY LUZ: Thank you, Dr. Cobb. Good morning, everyone. Again, my name is Anthony Luz, and I'm a biologist in EPA's Existing Chemicals Risk Assessment Division. I'll be covering DIDP and DINP background information during the next part of the presentation.

Next slide, please. TSCA Section 6 allows manufacturers of chemical substances and/or categories of chemical substances to request an EPA-conducted risk evaluation on a chemical substance and/or category of chemical substances on the conditions of use of interest to the manufacturers requesting the evaluation.

On May 24, 2019, under the old TSCA risk evaluation rule, EPA received a request from ExxonMobil Chemical Company, Evonik Corporation, and Teknor Apex through ACC's High Phthalates Panel to conduct a risk evaluation for DINP, while

similar requests for risk evaluation for DIDP was also received from ExxonMobil Chemical Company, again, through ACC's High Phthalates Panel.

EPA reviewed the manufacturer request for DIDP and DINP and approved the request in December 2019 and then subsequently issued draft and final scope documents for the DIDP and DINP risk evaluations in 2020 and 2021. Following publication of final scopes, the next step in the risk evaluation process is to issue draft risk evaluations for peer review and public comments, which is why we're all here today.

Next slide, please. Both DIDP and DINP have a number of uses regulated under TSCA. One of the primary uses of both phthalates is their use as a plasticizer to make flexible polyvinyl chloride. However, both phthalates are also used to make building construction materials, automotive care and fuel products, and other commercial and consumer products, including adhesives and sealants, paints and coatings, electrical and electronic products -- all of which

are considered TSCA uses. The DIDP risk evaluation is focused on evaluation of exposure to these TSCA uses.

However, it is also important to note that there are a number of uses that are not subject to regulation under TSCA, including use in food packaging materials, medical devices, pharmaceuticals, and other personal care products, just to provide a few examples. These uses that can result in human exposure were not accounted for in the draft DIDP exposure assessments or draft DIDP risk evaluation.

Next slide, please. The DIDP and DINP risk evaluations are organized through a series of discipline-specific Technical Support Documents that summarize the technical analyses that in turn feed into the draft risk evaluations. This slide provides an overview of the draft DIDP risk evaluation package submitted to the docket for peer review.

First, you'll note the draft Technical Support Documents, summarizing the

physical, chemical, and fate property of DIDP. These support documents feed into EPA's environmental and human exposure assessments. There are three Technical Support Documents summarizing human exposure, including an Environmental Media and General Population Exposure Assessment, Environmental Release and Occupational Exposure Assessment, and a Consumer and Indoor Dust Exposure Assessment.

These three human exposure assessments, in conjunction with the DIDP Human Health Hazard Assessment, feed into the human health risk characterization for DIDP. Similarly, the DIDP Environmental Hazard Assessment, the Environmental Exposure Assessment, both feed into the environmental risk characterization in the DIDP Risk Evaluation.

Next slide, please. This slide summarizes the document map for the Draft DINP Risk Evaluation. Please note that the Draft DINP Risk Evaluation will be organized in a similar manor to the Draft DIDP Risk Evaluation. However,

for DINP, we have only released five draft Technical Support Documents on the docket as part of the current peer review.

These Technical Support Documents are highlighted with green boxes on the slide, including EPA's Draft Non-cancer Human Health Hazard Assessment, Cancer Human Health Hazard Assessment, Physical Chemistry and Fate Assessments, and Environmental Hazard Assessment.

Next slide, please. So, why have we only released several of the DINP Technical Support Documents as part of the current peer review when we need the same exposure methodologies, tools, and models used in the Draft DIDP Risk Evaluation? They're also being used in the DINP exposure assessments on Draft Risk Evaluation. Feedback received from the SACC as part of the current DIDP charge will be applicable to the DINP exposure assessments and risk evaluation, which EPA is actively working on.

Also, as you'll hear more about shortly, there are several key differences in

human health hazard assessments between DIDP and DINP, particularly on the cancer side. And feedback from SACC on EPA's proposed human health hazard approaches for DINP will inform the exposure assessment and risk evaluation for DINP.

Next slide, please. In addition to the manufacturer-requested risk evaluations for DIDP and DINP, we are also actively working on risk evaluations for five additional phthalates that are prioritized under TSCA by EPA for risk evaluation. This includes DEHP, DBP, BBP, DIBP, and DCHP. We anticipate that feedback received from SACC as part of the current charge will inform the ongoing risk evaluations for these five additional phthalates.

We are also actively working on a cumulative risk assessment of six phthalates, including DINP, DEHP, DBP, BBP, DIBP, and DCHP. And that assessment's being conducted in line with the Proposed Approach for Cumulative Risk Assessment of Phthalates. It was peer reviewed by the SACC during the May meeting of the SACC in

2023. Again, feedback from the SACC, in particular on the exposure methodologies and approaches being employed for DIDP, will be informative of EPA's cumulative phthalate assessment.

Next slide, please. We've reached the end of the Part 1 presentation, which covered background information on TSCA as well as on DIDP and DINP. We'll now be transitioning to the second part of this morning's presentation.

EPA TECHNICAL PRESENTATION 2

Next slide, please. For the second part of today's presentation, we will be providing an overview of the DIDP Human Health Hazard Assessment and Exposure Assessment.

Next slide, please. For this portion of the presentation, we are going to start with an overview of DIDP non-cancer and cancer human health hazards, followed by an overview of the DIDP Environmental Release Assessment, the

DIDP Environmental Media Concentration and General Population Exposure Assessment, and finally, the DIDP Consumer and Indoor Dust Exposure Assessment. This presentation will be focusing on the background information relevant to the DIDP charge.

Next slide, please. Let's just jump right in to the DIDP Human Health Hazard Assessment overview.

Next slide, please. This slide presents a copy of the DIDP Risk Evaluation Document Map. For this portion of the presentation, again, we will be going over the non-cancer and cancer human health hazards of DIDP pertaining to DIDP Charge Questions 3a and 3b. And the Draft DIDP Human Health Hazard Assessment's Technical Support Documents, or TSD, is the primary document that provides additional information pertaining to this portion of the charge.

Also, throughout today's series of presentations from EPA, I'd like to note that

charge question numbers will be indicated in the top right corners of each slide that provides relevant background information to each specific question.

Next slide, please. DIDP is a well-studied phthalate with a robust database of oral exposure studies, including studies conducted in multiple species and includes multiple short-term oral exposure studies, subchronic dietary studies and chronic dietary studies.

Additionally, DIDP has been evaluated in two prenatal developmental toxicity studies, one each of Sprague Dawley and Wistar rats and two two-generation studies of reproduction, both conducted with Sprague Dawley rats. On that, here are two relevant EPA guidelines.

However, there are no dermal or inhalation studies of DIDP relevant for dose response or driving non-cancer toxicity values. Therefore, we are proposing to use the oral non-cancer points of departure to assess risk for the

dermal and inhalation routes with route-to-route extrapolation.

Next slide, please. Across available oral studies of DIDP, liver and developmental toxicity were identified as the most sensitive non-cancer hazards, which is consistent with the conclusions of other regulatory and authoritative agencies, including U.S. CPSC, NTP, Health Canada, ECHA, as well as some others. And these hazard outcomes are the focus of EPA's dose response assessment.

Observed developmental effects include increases in the incidence of skeletal and visceral variations in two prenatal studies of rats at doses below those that caused maternal toxicity. Additionally, in the evaluable two-generation studies of reproduction, effects from life births, offspring survival, and offspring body weight were observed, again, at dose that's not cause overt parental toxicity.

I'll be talking a bit more about the observed developmental effects in a couple of slides.

What's also important to note here that unlike other phthalate diesters such as DEHP and -- as I'll talk about a bit more this afternoon -- DINP, gestational exposure to DIDP does not induce effects on the developing male reproductive system consistent with the disruption of the androgen action. This conclusion was endorsed by SACC during its May 2023 peer review meeting.

Next slide, please. Overall, no sensitive and robust non-cancer point of departure, or POD, that EPA identified was a NOAEL of 38.0 mg/kg-day. This NOAEL is based on reduced F2 offspring survival on postnatal days one and four, which is an effect that is observed consistently across both two-generation studies of reproduction, both of which adhered to relevant EPA guidelines.

Next, we converted the non-cancer NOAEL of 38.0 mg/kg-day to a human-equivalent dose, or HED, of 9.0 mg/kg-day, using allometric body weight scaling to the 3/4 power. As I'll talk about further in a couple of slides, we're proposing to use this non-cancer POD of 9.0 mg/kg-day to characterize risk from acute, intermediate, and chronic durations of exposure to DIDP.

Also, for the benchmark margin of exposure, or benchmark MOE, a total uncertainty factor of 30 was selected based on use of an intraspecies uncertainty factor, or UF_{H}=10 and a interspecies uncertainty factor, or UF_{A}=3, which is consistent with EPA guidelines, was reduced from a value of 10 to 3 because 3/4 body weight scaling was used to derive the HED.

Next slide, please. Overall, we have robust competence in the selected POD, and several lines of scientific evidence support the selected POD. First, it's important to note that developmental toxicity is observed consistently in

two prenatal developmental toxicity studies and both two-generation studies of reproduction.

So, again, in the two prenatal studies observed developmental effects included increases in the incidence of skeletal and visceral variations at doses that did not cause maternal toxicity or affect fetal body weight. In the first two-generation study, DIDP exposure reduced F1 offspring survival on postnatal day 4, reduced F1 and F2 offspring body weight on postnatal day 0, and reduced F1 and F2 offspring body weight gain through postnatal day 21.

Although the effects on F1 offspring survival and offspring body weight and weight gain were not observed in the second two-generation study, the second study tested lower doses below those that caused an effect in the first study. So, this is actually not inconsistent, but notably in both two-generation studies, F2 offspring survival on postnatal days one and four was reduced dose dependently on the doses that did not cause overt parental toxicity to either parental

generation, supporting the selected NOAEL of 38.0 mg/kg-day.

Further supporting the selected non-cancer POD, it is outlined in Section 6.1.1 through 6.1.3 of the Non-Cancer DIDP Technical Support Document.

We also derived five additional candidate PODs, ranging from 9.3 to 13.0 mg/kg-day from other acute, intermediate, and chronic duration studies based on liver and other developmental effects observed in several species. These are, of course, very similar to our selected POD, and it further supports EPA's selected non-cancer POD of 9.0 mg/kg-day.

Notably, across evaluable studies considered for driving the non-cancer PODs, only one study provided a potentially more sensitive candidate POD, an HED of 5.2 mg/kg-day, based on LOAEL from a two-year dietary study of rats.

Effects observed at the LOAEL included a slight and statistically significant increase in incidence of spongiosis hepatis and

microgranuloma in the liver of male rats. However, several uncertainties reduced our confidence in the findings of the study for use in risk assessment.

For example, the LOAEL is based on a relatively slight increase in incidence of spongiosis hepatis and microgranuloma. The incidence in microgranuloma was flat across tested doses, while the incidence of spongiosis hepatis was also relatively flat, particularly at the low- and mid-dose groups.

Further reducing our confidence in the findings of the study, spongiosis hepatis and microgranuloma have only been observed in a single study of DIDP and only in male rats at that. There's uncertainty related to the mode of action.

Next slide, please. As I mentioned earlier, we are proposing to use the non-cancer POD, 9.0 mg/kg-day, to characterize risk for acute, intermediate, and chronic exposure durations. We considered the POD based on decreased F2 offspring survival relevant for all

durations because it's unclear as to whether decreased pup survival was due to a single acute exposure during gestation or from repeated exposures during gestation and/or the postnatal period.

Because both scenarios are plausible and because repeated dose studies were used to investigate the hazard, and the mode of action for DIDP is uncertain, and other studies did not provide a more sensitive or robust endpoint, we considered the non-cancer POD relevant for all exposure durations, including acute, intermediate, and chronic.

Next slide, please. Now, we will be transitioning to an overview of cancer human health hazards for DIDP. DIDP has been evaluated for carcinogenicity in two chronic studies, including a 2-year dietary study of F344 rats and a 26-week dietary study of wild-type and rasH2 mice, which is a transgenic strain of mice overexpressing the human ras oncogene, making it more susceptible to carcinogenesis.

In the two-year study of fissure rats, increased incidents of mononuclear cell leukemia, or MNCL, was observed in high-dose rats of both sexes. MNCL is a spontaneously occurring neoplasm of the hematopoietic system that reduces lifespan, and it's one of the most common tumor types occurring at high background rates on F344 rats.

So, given the high and variable background rate of MNCL in F344 rats, it's important to consider historical control data, concurrent control data in time of the onset of MNCL to assist in determining whether observed increases in MNCL are tumor related or not.

So, though survival was significantly reduced in high-dose male and female rats, study authors do not report the cause of unscheduled deaths, and it's unclear if MNCL was the cause or not. Further, no information on time to onset of MNCL or laboratory historical control data as provided by study on thirds on lack of this, make it challenging to determine if the

increase in MNCL was due to DIDP. It is a source of uncertainty. There is additional uncertainty also related to the human correlate to MNCL and F344 rats.

Some researchers have suggested that MNCL shares some characteristics in common with an aggressive natural killer cell leukemia in humans and that this may be a human correlate. However, in contrast to MNCL, aggressive natural killer cell leukemia in humans is extremely rare and has a viral theology.

Finally, in addition to MNCL, hepatocellular adenomas have also been observed in high-dose male rasH2 transgenic mice at 1500 mg/kg-day. So, the dose is well above the limit dose. However, no significant increase in liver tumors was observed in female rasH2 mice or wild-type mice of either sex.

Next slide, please. Under the Guidelines of Carcinogen Risk Assessment, we have preliminarily concluded that there is suggested evidence of carcinogenic potential of DIDP in

rodents. This preliminary classification is based on the increase incidence of MNCL in male and female F344 rats in hepatocellular adenomas and male transgenic razH2 mice.

Also consistent with the cancer guidelines, we did not conduct a cancer dose response or conduct a quantitative cancer risk assessment. Notably, this approach is consistent with other agencies, including U.S. CPSC, Health Canada, NICNAS, and ECHA, all of whom also refrain from conducting a cancer dose response assessment or quantitative cancer risk assessment on their assessments of DIDP.

Next slide, please. Just to recap quickly, we are proposing to use a non-cancer POD of 9.0 mg/kg-day based on reduced F2 offspring survival to characterize non-cancer risk for acute, intermediate, and chronic exposure durations. We've also preliminarily concluded that there is suggestive evidence of carcinogenic potential of DIDP in rodents, based on increased incidence of MNCL in male and female F344 rats and

hepatocellular adenomas in male transgenic razH2 mice. And we did not conduct a cancer dose response assessment or quantify DIDP for cancer risk.

Notably, again, many of our conclusions and approaches are consistent with other regulatory bodies that have also identified a non-cancer liver and developmental toxicity as sensitive hazards associated with exposure to DIDP and also did not evaluate DIDP quantitatively for cancer risk.

With that, I'd like to thank you all for your time and attention. I'm now going to turn things over to my colleague, Yashfin Mahid.

Next slide, please.

DR. YASHFIN MAHID: How are you doing? I'm Yashfin Mahid, a chemical engineer here in OPPT, ECRAD, and along with my colleague Aaron Murray (phonetic), we are responsible for conducting the Environmental Release and Occupational Exposure Assessment for DIDP.

Next slide, please. Here in this figure, we can see all the parts of the risk evaluation for DIDP. The contents related to Charge Question 1.e can be found in Section 3 of the Draft Environmental Release and Occupational Exposure Assessment for DIDP.

Next slide, please. We have used occupational exposure scenarios, or OES, to conduct both the exposure assessment and environmental release assessment, but the for the purposes of this charge question, I would only talk about the use of OES, or occupational exposure scenarios, used to conduct environmental release assessment.

Other condition of uses in the risk evaluation were mapped to applicable OES based on similar release scenarios expected for the condition of uses. Each OES was developed based on a set of conditions such that similar environmental releases are expected from the use or condition of use covered under the OES.

We evaluated environmental releases to the air, water, and land for 15 out of the 17 OESs assessed in the risk evaluation. We did not quantitatively assess environmental release for the other two OESs due to the lack of available process-specific and DIDP-specific data. All the OESs for DIDP are shown at the bottom of this slide.

We also did not identify any release data from available literature sources and used modeling approaches to assess release estimates. We used both fixed input parameters and ranges and the focus of the Charge Question 1.e, which is Production Volume, was one of the input parameters that we used for our modeling.

Next slide, please. So, here on this slide, we can see a pie chart, which shows the breakdown of releases among OES for DIDP, and we have used the central-tendency values from the output release distribution, which has a 50th percentile to develop this pie chart. And we can

see that manufacturing represents the highest release, followed by import and repackaging.

If we use the kind values from the output release distribution, which is the 95th percentile, we can see a similar trend with manufacturing and import and repackaging counted for majority of releases.

All the 15 OES for which we calculated releases are shown below the pie chart.

Next slide, please. To calculate production volumes for the different OESs, we used different methods. For example, for manufacturing and import/repackaging, we used information from the 2020 CDR directly. For sites which had CBI claims, production volume was estimated by subtracting the known production volumes from the overall national DIDP production volume range in the 2020 CDR and then dividing by the number of sites which claimed CBI.

For other OESs, the production volume ranges were estimated using data from both CDR and systematic review. For example, the

production volume use percentages from the 2003 EU Risk Assessment Report on DIDP was used to calculate production volume for most of the other OESs, and we assume that the end uses of DIDP in the U.S. is similar to that in Europe.

For example, in the EU Risk Assessment Report, it is estimated that about 95.75 percent of DIDP is used in PVC end uses. Therefore, the production volume for PVC plastics compounding and PVC plastics converting was estimated to be 95.75 percent of the total national production volume from CDR for DIDP.

Next slide, please. So, to conclude, EPA is using information from the CDR database in combination with sources from literature review -- for example, the EU Risk Assessment Report -- to estimate production volume for most conditions of use for DIDP. We know that the annual production volume from CDR is quite broad, and, therefore, it introduces uncertainty in the estimation of the true production volumes. Also, ideally, we would have favor to use industry

use percentages from the U.S. rather than using industry use percentages from Europe.

For more information, you can see the Draft Environmental Release and Occupational Exposure Assessment for DIDP.

Next, I will pass it to Maiko Arashiro, who is an exposure assessor in our branch. Thank you.

DR. MAIKO ARASHIRO: Thank you, Mahid. Hi. My name is Maiko Arashiro, U.S. EPA, and I will be presenting an overview of the DIDP Environmental Media and General Population Exposure Assessment.

Next slide, please. The slides I'll be covering pertain to Charge Question 1.b. The relevant Technical Support Document for this charge is the Environmental Media and General Population Exposure Assessment Technical Support Document.

Next slide, please. To begin, here is a recap of the TSCA Risk Assessment Considerations as it pertains particularly to

exposure, getting from source of exposure through route of exposure. Here, we're showing a general overview relevant for consumers, workers, and the general population. But for the general population exposure, we're focused on the industrial and commercial releases as the source, which our engineer Mahid just did a wonderful job covering.

In the following slides, I will detail how we considered those releases and its impact on environmental media concentration and subsequent exposure to the general population.

Next slide, please. When considering general population exposure, we not only look at the environmental releases but also the fate and physical chemical properties of DIDP to predict where it may end up in our environment. We detail our fate and physical chemical properties in our Fate Technical Support Document. But here, to the left, I highlight a key finding of our Fugacity Modeling Results, which show the

environmental compartments in which DIDP will likely partition to base on the type of release.

Given our known releases and this partitioning analysis, we know that DIDP is predominantly expected to be in water, soil, and sediment given equal releases to the environment, which is why Charge Question 1.b focuses on those compartments. When released to air, DIDP will show strong affinity for absorption to particulate matter and is not likely to exist in the gaseous phase.

Next slide, please. With the understanding of where DIDP is likely to be present in the environment, based on what I've presented so far, EPA assessed various exposure pathways. For the pathways shown on this slide, EPA quantified exposure to the general population for ambient air and fish ingestion. More specifically, for ambient air, we quantified ingestion and dermal exposure to DIDP in soil resulting from air to soil deposition in a location specifically near the emission site due

to DIDP's rapid degradation in the atmosphere and not expecting long-range transport.

We did not quantify inhalation to gaseous phase DIDP due to not expecting DIDP in gaseous state due to the partitioning analysis. Based on the potential for DIDP to be in fish tissue through uptake from water and sediment and finding monitoring studies measuring DIDP in fish tissue concentration, EPA assessed fish ingestion, specifically for tribal populations to have a higher consumption of fish. All methodologies to assess these exposures have been utilized in prior risk evaluations and reviewed by the SACC.

For biosolids and landfills, we did not quantify any exposure because of the limited persistence potential and mobility of DIDP in soils.

Next slide, please. A continuation of the previous slide, for surface water, EPS assessed dermal and incidental ingestion of DIDP during swimming in potentially contaminated waters. Additionally, we looked at ingestion of

drinking water. These assessments were based on the potential for DIDP to be in water from TSCA releases and monitoring studies, albeit limited, that have detected DIDP in water.

Next slide, please. With an assessment of general population exposure, we took a screening level approach. We took this approach because we had little location- or scenario-specific information for DIDP exposure to the general population. In a screening-level approach, we rely on conservative assumption to estimate exposures likely to be on the high end of exposure distribution.

We assessed high-end exposures by utilizing high-end inputs, which included using the highest media concentrations modeled from our industrial and commercial releases and considering the highest potentially exposed population, which is based on the highest intake by lifestage -- in other words, highest intake by body weight based off of exposure factors -- and also consideration of lifestyle, such as tribal populations, who

consume a greater amount of fish. In using our high-end exposure estimates, we did not see risk. We did not proceed to refine our assessments.

Next slide, please. To give a quick overview of what yielded a high-end exposure scenario, here is this table to show that for each exposure pathway, different occupational exposure scenarios -- shown in the first column -- yielded high-end environmental concentrations for different media types. So, here, PVC plastic compounding yielded the highest soil concentrations from air to soil deposition, whereas releases from use of lubricants and functional fluids led to the greatest surface water concentrations.

You can also see here that based on different exposure factors, the most exposed lifestage -- shown in that third column -- varied across pathways. Surface water, here, is a good example to show that in assuming scenario an adult has greater skin surface area for greater dermal exposure, but youth have a higher ingestion rate

per body weight for greater incidental ingestion exposure. Exposure factors used for analysis are presented in the Environmental Media and General Population Technical Support Document.

Next slide, please. As mentioned in our Charge Question 1.b, we really want to bring focus to our surface water assessment. In the screening approach, using our generic scenarios to assess surface water, we evaluated high-end releases from conditions of use with greatest release to surface water, pairing that with low flow assumptions. Again, to mention here that for the generic scenario, we did not have location-based information for our releases.

We modeled using Point Source Calculator to include partitioning to sediment. We applied standard receiving waterbody geometry and characteristics; derived flow from distributions of receiving waterbodies from facilities with relevant NAICS codes. I'll speak on the low flow we utilized in the following slide.

We presented multiple treatment scenarios, which included with and without wastewater treatment and with and without drinking water treatment. The resulting model concentrations from screening analysis were much higher than the expected concentrations from actual releases, and if no risk was identified at the screening level, once again, no refinements were conducted.

Next slide, please. Now, we'll look more closely into how we analyzed the flow rate utilized for our screening level analysis for our generic scenarios. Again, not having individual releasing facility data, we followed established methods from previous risk evaluations, utilizing generic distributions of flows we derived from NAICS codes.

So, here on the right, we show the distribution of our combined plant effluent and receiving waterbody modeled flow. We assumed mean facility effluent rate from NAICS codes to be included in the combined flow. So, you can see

here that it's very skewed, with greater numbers of facilities with lower combined flows to the left, but a few that have very large flows sort of on that right-hand tail.

So, for our conservative assumptions, we utilized the median flow, which we show here with the dotted line, which you can actually see ends up being our low-flow scenario. So, in short, we combined a high release with a low flow to yield a high surface water concentration used for our screening level analysis.

In the case that we needed to refine our assessment for our screening level analysis, we would have moved to a higher percentile flow as our next refinement step, essentially moving to a higher flow to be paired with our high releases to be more representative of realistic scenarios under the assumption that high releases would not be discharged to receiving waterbodies with such low flows -- again, with the reminder that we had no facility-specific data and also very limited

water-monitoring data. This is where we seek input on refinement as asked in Charge Question 1.b.

Next slide, please. In conclusion, EPA used a screening level approach to assess general population exposure by using high-end environmental media concentration and considering populations with higher intake. For estimating surface water concentrations, EPA relied on a low flow value derived from a generic distribution of flow values paired with a high-end release loading.

In line with EPA's findings, prior assessments have not identified exposure scenarios that were assessed to the general population as contributing highly to exposure. Finally, EPA did not refine its assessment if there was no risk but is still seeking input in Charge Question 1.b for refinement considerations, particularly in regards to flow assumptions.

For more information on how Environmental Media and the General Population

Exposure Assessment was conducted, please see the Technical Support Document that's linked here. Thank you.

Now, I'll move over and hand it over to my colleague Laura Krnavek.

DR. LAURA KRNAVEK: Good morning. My name is Laura Krnavek. I'm the exposure assessor leading the Consumer and Indoor Dust Exposure Assessment.

Next slide, please. In this slide, we have the charge question relating to the Consumer and Indoor Dust Assessment and the reference documents in the active link.

In the picture below, you have the Consumer and Indoor Dust Exposure Assessment and the documents for your review, specifically the Draft Risk Evaluation and the Technical Support Document, TSD.

Next slide, please. The consumer and indoor dust exposure analysis main considerations are in this slide, starting with the lifestages and the designated labels and the

age groups. You also can see their users and bystanders, where the bystanders are people that are not in direct use or application of the product but are exposed via inhalation by proximity to the use of the product.

We also can see our use intensity -- high, medium, and low exposure scenarios -- where this captures a range of use pattern options regarding durations of use, frequencies of use, mouthing behaviors, numbers of items, surface area, a number of other parameters that we used.

We also assessed three exposure durations, specifically acute, intermediate, and chronic, where acute covers the exposures in 1 day; intermediate covers exposures in a 30-day period, approximately a month; and chronic covers the exposures in 1 year.

Next slide, please. In this slide, we have the main steps in performing the consumer exposure assessment in the left side of the table. And on the right side of the table, we have the

approach that we used to accomplish each one of these steps.

We start with identifying and mapping the products and articles to each COU and identifying evidence that supports the inclusion of the chemical in these products. Once we have that information, we compile information on how the products are used using online searches and manufacturer product use instructions.

Once we have this information, then we can identify targeted populations, and we also can identify the exposure routes that are applicable to these uses. Once we have that information, we also identify data gaps -- for example, for dermal exposures or mouthing exposures -- and we can also make, then, approaches in how we are going to fill in these data gaps. This is the most pivotal part of the steps that is related to the charge questions that you're addressing today.

Once we do the selection, we can parameterize the model. In this case, we selected

the CEM model -- consumer exposure model. And then we run the model, and we obtain the results.

Next slide, please. The indoor dust assessment was done using consumer exposure modeling data results for articles that are commonly found in indoor environments with large surface areas to collect the dust. Specifically, in this assessment and future assessments, we'll use surface areas larger than one square meter.

In the documents, we have a comparison of the modeling and monitoring consumer indoor dust assessments for your review. The important part here is, too, that the articles, the data, the assumptions, how we use the data, are important for us to obtain comments and review from you. In the next few slides, we'll go into more details on these assumptions.

Next slide, please. The Assumptions for Suspended and Surface Dust Inhalation and Ingestion. The key parameters that control the emission rates for the articles in the CEM model are weight fractions, density, article surface

layer thickness, article surface area, and any increases in these parameters will result in increases in emissions and, therefore, greater exposure. So, it's important for us to understand these assumptions and the data that we're using.

For example, in weight fractions, we prefer using data from SDSs and completed assessments, and lastly, from the CDR. That is because the CDR, for consumers specifically, they don't report the concentrations on finished products. So, there is considerable uncertainties when using CDR information.

For density, we use the material density for PVC -- the standard value for PVC -- rather than making assumptions and estimates for each article.

The article surface layer thickness -- we use the CEM value, 0.01 centimeters, for scenarios with emissions from the same or similar solid material. This is in agreement with what we did with density.

The article surface area -- we make different assumptions for each article. And the next few slides will cover those.

Next slide, please. The Assumptions for Suspended and Surface Dust Surface Area. These are the assumptions done on the surface area. Specifically, we're going to start with flooring materials -- vinyl, specifically. We assumed that the material was used in 100, 50, and 25 percent of the total floor space. We used the CEM default value for the whole house volume and assumed ceiling heights of eight feet, which is also a CEM default value.

For surface areas of wallpapers, we found a medium value from the Exposure Factors Handbook, and then we scaled to 200 and 50 square meters for the high and low exposure scenarios, based on professional judgment.

The surface area for textiles and foam furniture components were assumed to be the same across these articles. For each scenario, we assumed the presence of a couch and a loveseat in

the indoor environment. And for the low, medium, high exposure scenarios, we obtained standard sizes available from an online search on furniture retail stores on the descriptions on the dimensions of these articles.

Next slide, please. For children toys and wire insulation, we model them as collectives, as one item would have been too small and not go over our threshold of one square meter, that was from before, and also because consumers tend to have multiple of these items in the indoor environment.

For wire insulation, we use the typical circumference of copper wire insulation cords and a typical length cord of two meters -- that part is a professional judgment. We estimated the number of items in an indoor environment for 1-, 2-, and 6-person household, and then we calculated the surface area from these various estimates and assumptions.

For children toys, we had a similar approach. For the low-, medium-, and high-

intensity views, we estimated the number of items and the dimensions of the items. For the low-intensity views, we estimated five small toys with the dimensions of 15 by 10 by 5 centimeters. For medium, we estimated 20 toys, measuring 20 by 15 by 8 centimeters. And for the high-intensity views, we estimated 30 large toys, measuring 30 by 25 by 15.

For shower curtains, it was a little more straightforward. There's less variability for these items. We performed an online search of various manufacturers and retails. We found the dimensions were fairly stable, so we calculated the surface area, and we calculated it for the two sides that are both available to collect dust.

Next slide, please. The next assumption goes specifically to the exposure route of ingestion via mouthing, in which specifically we searched seeking input with what we did to select the chemical migration rate. Quickly, to calculate exposure via mouthing, the key parameters in these calculations are chemical

migration rate, the surface area mouthed, and the duration of mouthing.

For the chemical migration, specifically, this parameter depends on several factors -- the physical chemical properties of the article polymer matrix, the phthalate concentration in the polymer, and the physical mechanisms during mouthing -- for example, sucking, chewing, biting, et cetera -- and the makeup of the saliva itself, as well. So, all of these factors had considerable variability to the chemical migration rate.

So, what we did is we identified a reference -- the Denmark Environmental Protection Agency (2016) review study. They gathered 87 values from 4 studies they put together, and they split the information in a range of minimum, average, and maximum for various styles of mouthing, which they assigned the terms of mild, medium, and harsh.

Because there was no clear correlation between the weight fraction of DIDP

and the chemical migration rates, we decided to use the mean -- the average -- published by these studies in the idea that it would be representative and capture a range of chemical migration rates. And the ones in the square in the table are the ones used in the risk evaluation.

Next slide, please. In conclusion, EPA is seeking input regarding Charge Question 1.a, dealing with data, the methods, and assumptions used in the consumer and indoor exposure assessments.

EPA identified CEM as an appropriate tool to perform the modeling for the multiple lifestages that we identified using fit-for-purpose input parameters or model defaults, which are covered, specifically, and as a summary: the use of weight fractions and the sources, preferably SDSs, and completed assessments and any other sources where they had actually performed product testing, and ultimately, the CDR; the use of the PVC density value rather than product

specific approximations; the use of the surface thickness default from CEM; the use of specific surface areas based on multiple assumptions, depending on the articles, and the sources of those assumptions came from manufacturer descriptions and Exposure Factors Handbook; and, ultimately, for the ingestion via mouthing, the use of the Denmark Environmental Protection Agency (2016) review study for the use of the chemical migration rate values.

All this information is well explained in the Technical Support Document, and the active link is in this slide.

Next slide, please. I thank you all for your attention. I think this opens the floor now for questions on this Part 2. I think Part 1, as well.

DR. GEORGE COBB: Thank you.

QUESTIONS FROM THE SACC ON EPA PRESENTATIONS

DR. GEORGE COBB: This is George Cobb speaking. We will turn this back over to the Committee members for questions. And I see Dr. Chaisson has a question.

DR. CHRISTINE CHAISSON: Thank you. And thank you to the EPA presenters. That was excellent.

I have basically two questions -- the first one for the first presentation. It was mentioned in the presentation and also in the documents, more than once, that the review by the Agency was requested by a stakeholder, which brings up sort of a question in my mind, at least.

I don't know anything about the procedure, by the way, so these may be elementary questions. But they brought up the idea of is there any difference between the government-initiated review versus a stakeholder-initiated review in terms of what are the expectations around the completeness of the information that you have to work with or the data that is provided, and is there any difference,

subsequently, on how data gaps are expected to be filled or important information that you unearth during the review is -- who gets to look for that information or provide it?

And on that, particularly, since we, as a Committee, were asked to take a look at the existing data and EPA's classification, if you will, on the quality completeness or confidence in that data, are there differences that the Agency or the SACC should consider depending upon whether or not the review was initiated by a stakeholder -- it doesn't have to be industry; it could be any stakeholder -- or EPA?

Basically, I'm asking whether the SACC should be more particular, if you will, about what level of certainty the Agency should be expecting to have when making the statement that the databases were complete enough to reach a decision. So, that's basically my first question.

I have a another completely different topic I want to ask a question about.

But, Dr. Cobb, should I just stop there and let the Agency answer that?

DR. GEORGE COBB: Yeah. I think letting the Agency respond is good.

DR. ANTHONY LUZ: Hi, Dr. Chaisson. Thanks for that question. I think the short answer to your question is the manufacturer-requested chemicals in those risk evaluations and the EPA-initiated risk evaluations -- the chemicals undergoing those evaluations, they have to be conducted in the same manner and be treated the same way. We have to use reasonably evaluable information. We have to make decisions in a transparent manner using the best available science and draw conclusions based on the weight of scientific evidence in both cases.

I did hear you mention data gaps, so maybe that is one slight difference. For the manufacturer-requested risk evaluations, we can't issue test orders, whereas for the EPA-initiated risk evaluations that is on the table, and it is something we can consider.

I'll stop there. I know we have a number of senior science advisors. I don't know if Dr. Eisenreich, (inaudible)--

DR. CHRISTINE CHAISSON: Wait. Can I make sure I understood you? So, if the Agency finds a data gap on an Agency-initiated review, you can request more data. Is that right? But if the industry requested the review, and you find that data gap, you can't issue a request for the data. Did I hear that correctly?

DR. ANTHONY LUZ: Sorry. Give us one second to respond.

Dr. Chaisson, this is Tony Luz, again, with EPA. You are right. So, issuing test orders is on the table for the EPA-initiated risk evaluations. It's not on the table for the manufacturer-requested. But before EPA accepts the request, we have to make a determination whether or not we think there's enough data to conduct the evaluation.

DR. CHRISTINE CHAISSON: Thank you for that. Dr. Hodge (phonetic) --

DR. KAREN EISENREICH: I would like to add to this. This is Karen Eisenreich of the EPA. So, one of the things that we have to consider when putting out test orders when we can for our higher-priority substances is the timing. We have the three to three-and-a-half years to conduct a risk evaluation. So, when we identify data gaps -- if we identify data gaps within that three to three-and-a-half years that we're conducting the risk evaluation, it becomes very difficult to issue test orders that we can get the data back within that timing.

So, we are moving to try and identify data gaps earlier in the process, so if we need to issue test orders, we can to fill those data gaps and get that data back in time to use in our risk evaluations.

For the manufacturer-requested risk evaluations, it is correct that we review the information that the request submits to us and make sure that we have the information that we need to conduct the risk evaluation. So, once we

start the risk evaluation, we don't go back and require test orders for additional information.

DR. GEORGE COBB: Thank you. Hank Mariette (phonetic), I see your hand up. But I have a follow-up here for either of the EPA answers.

So, there is the opportunity to suggest that more information is needed before the request is granted for expedited reviews. Is that correct?

DR. ANTHONY LUZ: This is Anthony Luz with EPA. Yes, that's correct.

DR. GEORGE COBB: Thank you very much. And I thought that that was what the answer was given. I wanted to make sure it was clear. Dr. Ottinger.

DR. MARY OTTINGER: I have a quick question, I think, following up more along the lines of what Dr. Eisenreich was talking about. And that is that I found myself going to the literature and seeing quite a bit of information on DEHP and wondered if that figured into some of

the models when you were talking about a polymer matrix and how that then effects, for example, the toys and the things that are mouthed and how that would be used. I'm more curious about mechanisms of action, which seems to be somewhat lacking for DIDP.

DR. LAURA KRNAVEK: Hi, this is Laura Krnavek, working on the customer exposure assessment. I think you referred to the commenter in my presentation on looking into the prior ability that could come from the prior ability of how the products are made.

DR. MARY OTTINGER: Right.

DR. LAURA KRNAVEK: Yeah, that's one of those relatively large sources of uncertainty in the modeling. That's why we do try to obtain weight fractions and then understanding how the products are used and made and how the chemical is incorporated into the products. To the best of our knowledge, we do try that in the beginnings of building the scenarios to kind of understand how do we make assumptions about our modeling

approaches to dermal and mouthing, as we presented.

So, all those considerations are there. Some of it is very well described in the Technical Support Document. Lack of time and space here, I can't go through the details, but they're pretty well explained there -- the sources of the uncertainty and the level of understanding for the specific mechanical DIDP.

As to using DEHP, sometimes you can use that as an understanding to kind of understand how other phthalates are used. But there are differences in how the phthalates are incorporated into products. So, we do have to try to stick with the phthalate that we're addressing in the modeling. Yes, (inaudible).

DR. MARY OTTINGER: Thank you.

DR. GEORGE COBB: Dr. Wolf.

DR. DOUGLAS WOLF: I have two questions that are actually unrelated to each other, if I may. The first one was the comment around no unreasonable risk. And I think we've

had this discussion. But can you provide us some context on the definition of "unreasonable" because, you know, sometimes that's in the eye of the beholder.

I think for us to really help the Agency, whether it's a mitigation strategy or the human relevance or whatever, how are you -- in the focus being on margin of exposure -- how are you trying to define the context of "unreasonable?" That's anybody.

DR. ANNA LOWIT: Anna Lowit, Senior Science Advisor, OPPT. A couple things, Dr. Wolf -- how we make determinations of the interpretation of whether it's margins of exposure or other metrics of risk and how those are brought into the risk determination is outside of the scope of the SACC. The risk determination is outside of the science realm and in the policy realm. So, I guess if there's a way to maybe restate your question that asks a similar scientific question, that would be helpful.

DR. DOUGLAS WOLF: I'll think about that. But that actually is sufficient because, if it's policy, then we can just provide the scientific input, and then you can do the policy. That's fine with me.

The other question I have is around the exposure. So, as I remember from -- and maybe I'm misremembering the formaldehyde discussions we had at the previous SACC meeting, some of the source contributions for exposure assessment, it seems like for this discussion, it's a bit more expansive and a more holistic approach. And so, is the Agency moving to that more holistic approach because some of the things like toys and some other sources were off the table it seemed, unless I'm misremembering that, George, from formaldehyde, unless --

DR. GEORGE COBB: I think you're right.

DR. DOUGLAS WOLF: Is this approach a case-by-case, which is fine? Or are you -- because these were done at different times and on

different time scales -- are you moving toward this more holistic approach of expansive exposure determination?

DR. LAURA KRNAVEK: This is Laura -- I'm sorry.

DR. ANNA LOWIT: Go ahead, Laura.

DR. LAURA KRNAVEK: Thank you. Laura Krnavek -- just addressing that we are doing -- we have the COUs, and we identify products and articles that are appropriate for each COU. And for each one of those, we have various scenarios that can represent the various use patterns that is applicable to phthalates and across the phthalates. So, the methods, then, we're selecting for these are the ones that we're addressing and concentrating on. Anna, do you have anything else to add to that?

DR. ANNA LOWIT: I was going to say the exact same thing. Thanks, Laura. But I think the formaldehyde exposure assessment is really complicated because there are different parts of EPA who regulate different parts of formaldehyde.

So, the TSCA assessment evaluated by the SACC focused on those things that are within the bounds of TSCA, and some of the things that the SACC had talked about were outside of the TSCA in the TSCA realm.

So, I can see how maybe in certain circumstances, there might be that lack of -- confusion, and it's certainly within your bounds to point out those places where you think we're being inconsistent, so we can look at those internally. But Laura's 100 percent right. For each risk evaluation, as part of the process, we evaluate those COUs and get public comment on those COUs as they apply to that particular chemical, or in this case, broader to the phthalates. That's the only thing I would add.

DR. DOUGLAS WOLF: Thanks.

DR. GEORGE COBB: Thank you, Anna. I'll also point out it seems that the Agency -- this is George Cobb speaking -- it seems that the EPA is taking into consideration some of the things that the SACC recommended when we looked at

aggregate exposures with phthalates. And I think, Doug, that's probably why you're seeing some of the more holistic evaluation. It's in response to what was suggested in that risk evaluation.

Next, we have Dr. Fenner-Crisp.

DR. PENELOPE FENNER-CRISP: I have a question specifically to the DIDP cancer assessment. Summarized on the slide in the document is the transgenic mouse study, and it noted properly that the limit those had been exceeded in that.

But I'm curious to know -- and I didn't see anything either in the risk evaluation or summary or any place -- two things. What was the rationale for the selection of that single dose to be used? And were there any indications in the paper's results that would indicate that that dose exceeded the MT -- maximum tolerated dose?

DR. ANTHONY LUZ: Dr. Fenner-Crisp, Anthony Luz with EPA here. If it's all right with

you, I need to go back and take a look at that study before I can respond to that.

DR. PENELOPE FENNER-CRISP: Well, we won't be taking up that charge question until, I guess, Thursday, is it?

DR. ANTHONY LUZ: (Inaudible). I think so.

DR. PENELOPE FENNER-CRISP: So, it would be useful to have that information when we do start that discussion. Thank you.

DR. GEORGE COBB: Dr. Fanning.

DR. ELINOR FANNING: Hi. Thank you. And thanks to the EPA staff for those presentations. They're very helpful. I do have a couple of questions on the consumer product exposures, just for clarification.

The first question is just to make sure I understand that only residential exposure in use scenarios were computed. And I just wanted to ask whether other use scenarios were considered or would be considered. So, that's the first question.

I think my second question is fairly related, so I'll just go ahead with that. Some of the conditions' views for the phthalates are quite broad. For example, plastic products -- so we have just a large number of potential articles and products that could be chosen to kind of represent those conditions of use in the consumer modeling.

So, I would like to understand just a little better how EPA evaluated that body of products to really choose the representative ones to ensure that we have captured the whole range of the exposure distribution to people. Thanks.

DR. LAURA KRNAVEK: Hi, this is Laura Krnavek. Let me address first the first one with the residential. So, it does seem like it's mainly residential. A lot of these products are in larger amounts in residences, or the amount of time that people spend in these indoor environments are larger than other places. And we may get approached as making it more of a screening approach if the larger exposure scenario

would result in any risk then we would further investigate any other potential locations.

So, that's one of the reasons why residential seems to be the target, but it's not unique. We do have potentially places where certain products are used, like gyms, where they're more public spaces. Those were -- I think I'm getting off the DIDP; it's possible because I have all the phthalates mixed. DIDP may not have had that scenario, but it would be considered just for your peace of mind. In terms of selecting the pro- -- does that answer your first question, or is there further questions there?

DR. ELINOR FANNING: Yeah. I think that's very helpful. There are a couple of other location-specific scenarios that came to my mind during reading, but we can hold on those. So, thank you for the general answer.

DR. LAURA KRNAVEK: There's also inside certain products that can be found inside cars. We also looked into -- I think it was CarMax. I wouldn't have picked them specifically.

I think in the, potentially, ability to find monitoring data in non-residential places, we would have identified it and put it out there for people to see it. Other phthalates will have that information, but DIDP did not. So that's another data gap there for the monitoring part when we do that comparison, which is why we did the comparison mainly for residential. That's the available data, that we have it.

DR. ELINOR FANNING: That's very helpful because we were asked to look at these exposure methods with an eye toward how would they apply to DINP, to the other priority phthalates. And so, we don't see your work in the background on other locations and these kind of specific scenarios in this document, which makes it very hard to review the appropriateness of the methodology for all the phthalates. I just want to point that out. So, thank you.

DR. LAURA KRNAVEK: I don't think DIDP had -- outside or inside cars and vehicles -- had other possible potentials for that scenario.

So, yes, we are including it in other phthalates. Yes.

For the second question, in terms of how we are sure that we have all the possible plastics represented. It's a daunting job. I won't say it's not. So, there's various steps there.

I think, in summarizing, that first step is identifying the products and the articles that are representative of the COU. We looked at SESs, and they have to actively identify the chemical -- DIDP in this case. We start with the CDR as a way of guidance in terms of where they are reporting that they have used this chemical. But the CDR doesn't commonly report on the final products and the concentration of DIDP in the final products. So, that's a starting point.

Then, from there on, we do in-depth searches in databases, included are assessments and publications where they have actually made product testing, and they have identified the chemical and have measured it and provided a

concentration. So, we do that, and that means we identify them. So, when you see plastics in the COU, and we have identified the products within them, we have identified the presence of the chemical in those products.

DR. ELINOR FANNING: Thank you.

DR. LAURA KRNAVEK: That's specified in the Technical Support Document, Section 2 -- somewhere in it.

DR. ELINOR FANNING: Thank you very much.

DR. GEORGE COBB: I see Dr. Chaisson has her hand up.

DR. CHRISTINE CHAISSON: Thank you, Dr. Cobb. My second question that I was referring to earlier was really along the lines that we just heard. I was wondering if it's possible for EPA -- in the next day or so -- to give us a very brief outline on two things that have to do with the other phthalates that we're considering. This was an issue, I know, for me. And when I started trying to do my own tally of what should be

considered for the exposure assessment that relies really on two key points -- the first being, what are the different COUs that are going to be -- at least the obvious ones to EPA -- that need to be considered? And the second is what are the key differences in the hazard metrics that will likely drive the risk paradigm for the other phthalates, just as we have the non-cancer POD or the cancer or other endocrine effects or whatever.

If we can just get a really brief hand of what we might be looking at -- might be is underscored -- so that we can offer the advice that is in Question 1.a.v and 1.b.iv with a little more focus. I don't know if that's possible, but it was sort of really a challenge to be able to just quickly look that kind of stuff up. Also -- well, I'll leave it at that. But thank you very much for the opportunity to the question.

DR. GEORGE COBB: I see Dr. Lowit has appeared on our screen.

DR. ANNA LOWIT: Yes. Thanks, Dr. Cobb. Anna Lowit, Science Advisor. Thanks for

the question, Dr. Chaisson. Let me get with the team either this afternoon or at lunch on your question on the COUs and the extent to which they exist in public information from what we call the scope documents will help.

But on the hazard information, I will respectfully say no because mostly we're still working on those, and we haven't made our determinations. And they're certainly not publicly accessible at this point because we're still actively doing that work -- even this week, we're doing that work offline. So, I have to say no on the hazard. But we'll get back to you later in the afternoon on what we can do on the COUs.

DR. CHRISTINE CHAISSON: Thank you, Dr. Lowit. I really appreciate anything you could do there.

DR. GEORGE COBB: Let me offer a little bit of a, perhaps, breather for the EPA. We're scheduled to take that question tomorrow afternoon, and so if you need until just before or just after noon tomorrow to pull together whatever

response to Dr. Chaisson's question, that'll fit right into our schedule.

DR. ANNA LOWIT: That works. The COUs are very similar across, and the scopes should be publicly accessible, but it's also unfair to ask people to fiddle through probably what's a thousand pages in a short period of time. Let me huddle with my team and see what we can do to help. It may not be much more than the scopes, but we'll try.

DR. GEORGE COBB: That would be helpful. Thank you very much. So, are there other questions from the Committee about the presentations we saw today?

I do have a couple. Going back to the last presentation, were pet toys considered in the ingestion or inhalation contributions, and if not, does EPA think that they would have been important contributors or change the outcome?

DR. LAURA KRNAVEK: Thanks for that question. I'm Laura Krnavek, consumer and indoor exposure assessment lead. The question is -- so I

rephrase it again -- for the toys, if we had considered in addition to inhalation other exposure routes?

DR. GEORGE COBB: Were pet toys -- and accessories, actually -- for dogs and cats.

DR. LAURA KRNAVEK: Oh, all right. Pet toys -- I think we have not specifically pet toys. We have children toys. They have, compared to pet toys, probably larger times of exposure. Kids are playing with them for longer amount of time and longer durations. You wanted to know if there's exposures to animals or to people?

DR. GEORGE COBB: People.

DR. LAURA KRNAVEK: So, pet toys were not identified in DIDP -- one of the example products.

DR. GEORGE COBB: The reason I ask is the concentrations of phthalates in those kinds of materials may be actually fair amount higher than for children's toys. And a toddler does not care what they put in their mouth. If it's

squishy, and the puppy's playing with it, they might want to play with it too.

The other thing is some unpublished data that some of our students collected in the past was chemicals with similar properties to these phthalates that are pesticides turned out to be some of the highest concentration chemicals in carpet dusts. It was the chemicals that were flea and tick collars and that kind of thing were some of the highest concentration compounds in carpet dust. So, chemicals of this kind of volatility could very easily be coming from these types of sources. That's just the genesis of that question.

I see Dr. Fanning had -- thank you for the answer. I think that answered my question. Dr. Fanning has a question.

DR. ELINOR FANNING: Thank you. Dr. Cobb's question just reminded me of another of the exposure questions I had, which is does the consumer exposure model allow for carpeting as a sink and reservoir for dust in homes, or does the

model assume hard flooring? I know we had hard flooring as a product. But I'm wondering about the role of carpeting.

DR. LAURA KRNAVEK: This is Laura Krnavek. For carpeting, we can do that, and we will be doing that. Some of the phthalates will be having that COU. And then the model does allow for it. There are different approaches in doing that. It's very similar to flooring, other than the amount of dust it does collect in it -- the surface areas and the coverage in an indoor environment. However, I think we will use the same surface area of coverage to compare them. Also, the concentrations found in each one of these products are different.

DR. ELINOR FANNING: I wasn't specifically referring to carpet as an article for COU. I meant as a component of the household -- of the model that can entrap dust and change the way that dust moves through the compartments in the modeling system. That was kind of what I was getting at.

DR. LAURA KRNAVEK: I see. For that kind of modeling, the way we did it is the presence of the dust on the surface of the article. So, it wasn't done as in the whole entire house, in terms of the house is covered with all of these furnitures -- only the presence on the furniture -- the dust. So, then you would have the dust that covers that surface in that location.

We're just looking at how much is collected on that surface and how much of that surface becomes available for inhalation, rather than looking at the surface of the whole house, unless we're looking at the carpet or the actual flooring. Does that make sense?

We try to separate the surface areas, so we can make assessments specific to that article and that surface area. The couch, for example, is a surface area that is different from the whole flooring. So, you're asking how the whole flooring effects the indoor assessment, but we're looking at each one of them separately as a

source of dust, rather than doing it as in a collective of all of these things together.

We do a comparison of the aggregate of all of them, and that's available in the documents as well. But when we go by COU, we go by article and by scenario. So, that would be individual article and the contribution of that individual article to exposures.

DR. ELINOR FANNING: Thank you. I'll give it a think.

DR. GEORGE COBB: I'll follow up. That does mean the aggregate exposure is really important. That's a great question. Anna, thank you for that answer as well.

I see Dr. Li has a question.

DR. LI LI: Good morning. This is Li Li speaking. I just have a follow-up question about dust contamination, just to double-check if I understand this correctly. You just focus on the dust on the product or article surfaces because you assume that part of dust is more contaminated than the dust found on the flooring

of the carpet? So, that's why you focus on the dust of the surface only. Is that correct?

DR. LAURA KRNAVEK: Thank you for the question. This is Laura Krnavek. I think this is related to the last conversation. So, for the dust, we do have an aggregate where we collect all the articles that are potentially found in indoor environments. Then we calculate an aggregate, and we compare that to the monitoring, which is also an aggregate of all the contributions of dust and the chemical into dust for the indoor environment. But for the calculations further on, for risk calculations and the ultimate goal of determining risk, we do it for COU. Then we calculate the dust on that surface on its own. So, each article has their own dust contribution. So, it will be just the dust that can collect on that surface.

DR. LI LI: That means you do the modeling separately for the dust on the surface and the aggregate exposure, right?

DR. LAURA KRNAVEK: Yes. We do first the unique articles, and then we do the aggregate.

DR. LI LI: I got it. Thank you.

DR. ELINOR FANNING: I actually have another follow-up because now I'm wondering -- so, if the dust from our couch, if it's shedding particles, it's abrading; pieces of its DIDP coating are coming off and contributing to house dust generally, then isn't my exposure as I walk through the living room to any suspended dust that is in the space? Again, maybe we're taking too much of the group air time on a very exposure-specific question, but if there's a short answer to that, I appreciate it. If not, we can pursue in another way.

DR. LAURA KRNAVEK: I think I can do this shortly. For the purpose of it, we do have to do this by COU. So, for COU, we identify the articles and then we do this for COU per article, just so we can address the specific COU contributions to risk. Then, the aggregate is

performed to kind of provide an idea of what you just asked. The contribution of all these sources need to be indoor environment.

In addition, we compare it to monitoring data that also provides all the contributions, all the sources that are available in the indoor environment, and compare it. So, we can talk about the difference between the modeling and the monitoring and then talk about the differences because there are quite a few large differences between monitoring and modeling when we do the aggregate. We try to put it together as this in whole. I hope that was the fast way to show us.

DR. ELINOR FANNING: That's very helpful. I really do appreciate your time on these. Thank you.

DR. GEORGE COBB: Are there other questions from the Committee? If not, I think it's about time for a lunch break.

One thing I'd like to say before lunch is, as we discussed in the charge question

clarifications, there are some topics about the risk assessment for DIDP that we will probably cover in our charge question responses for the questions that have been asked. But we may need to revisit that at the end of the DIDP charge questions before we move into DINP. I did not want that to catch the Agency presenters off guard or anything like that. So, that's probably a slight change in the agenda that's not written there. With that, I think I'll turn it back over to our designated federal official, Alaa Kamel. Alaa, are you there?

DR. ALAA KAMEL: I'm here. As George was saying, we can go on a lunch break now, and we meet after one hour. So, it will be about 1:15, 1:20 -- one hour from now. Thank you very much, and see you later.

DR. GEORGE COBB: That's good. Let's reconvene at 1:20.

DR. ALAA KAMEL: 1:20 -- okay. Great.

[LUNCH BREAK]

EPA TECHNICAL PRESENTATION 3

DR. GEORGE COBB: Let's proceed and before we start with the EPA's next presentation, which would be presentation three, I want to circle back and see if any questions came up from the committee related to the presentations that were provided earlier today. Okay, if there are none, then we're going to look at the DINP Human Health Assessment and Dr. Luz is going to provide that for us.

DR. LUZ: Thanks Dr. Cobb. All right, welcome back everyone. I hope everyone enjoyed their lunch break. Again, my name is Anthony Luz with EPA and I'll now be giving an overview of DINP human health hazards. Next slide please.

Okay, so for this portion of the presentation, I'm going to start with an overview of DINP non-cancer human health hazards, which provide information relevant primarily to DINP

charge 2A and 2B, and then I'll give an overview of DINP cancer human health hazards, which provide information relevant primarily to DINP charge questions 2C through 2E. Next slide please.

All right, let's jump right into the DINP non-cancer human health hazard overview. Next slide please.

Okay, so this slide shows the DINP risk evaluation document map. For this portion of the presentation, I'll be providing an overview of non-cancer human health hazards. Again, this primarily will contain information pertaining to charge questions 2A and 2B, and to a lesser extent 2E. Also, I'd like to note here that the DINP non-cancer human health hazard assessment technical support document is the primary document that provides information pertaining to this portion of the charge. Next slide please.

Okay, similar to DIDP, DINP is a well-studied phthalate with numerous short-term sub-chronic and chronic oral exposure studies conducted in multiple species, including mice,

rats, beagle dogs, and monkeys. Further, the developmental and reproductive effects of DINP have been investigated in one- and two-generation studies of reproduction, indicator-relevant EPA guidelines, as well as numerous gestational and perinatal oral exposure studies of rats and mice, many of which focused on examination of effects on the developing male reproductive system. Also similar to DIDP, there are no dermal or inhalation studies of DINP relevant for dose response or for deriving non-cancer toxicity values. Therefore, we are proposing to use the oral non-cancer points of departure to assess risk for the dermal and inhalation rats. Next slide please.

Okay, across available studies, the two most sensitive non-cancer hazards identified by EPA were liver and developmental toxicity, which again is consistent with the conclusions of other regulatory and authoritative agencies such as USCPSC, NTP, Health Canada, ECA, and others. In the liver, across available studies, a spectrum of effects have been observed many of which are

consistent with activation of nuclear receptors, such as peroxisome proliferator-activated receptor alpha or PPR-alpha. Observed effects include increases in relative liver weights and hepatocellular hypertrophy, and with longer duration exposures, evidence of adversity can be observed, including increases in serum chemistry markers of liver toxicity such as serum ALT and AST, as well as histopathology, such as necrosis, spondyrosal pathos, and formation of hepatocellular tumors.

In contrast to DIDP, which did not show evidence of anti-androgenic effects on the developing male reproductive system, exposure to DINP does induce effects on the developing male reproductive system consistent with the disruption of antigen action and development of triolite syndrome. Notably, EPA has previously concluded that DEHP, BDP, DDP, DIBP, DCHP, and DINP are toxicologically similar and induce effects on developing male reproductive system consistent with thiolite syndrome. Importantly, SAC

previously reviewed and supported this conclusion during the May 2023 peer review of EPA's draft proposed approach for cumulative risk assessment of phthalates. Next slide, please.

Okay, so this slide summarizes the non-cancer POD selected for DINP that we propose to be used to characterize risk from acute and intermediate duration exposures. For this POD, we have preliminary selected a BMDL-5 of 49 milligrams per kilogram per day based on reduced fetal testicular testosterone. So this BMDL-5 was derived by the National Academies of Sciences, Engineering, and Medicine based on meta-analysis and BMD modeling of rat fetal testicular testosterone data in two medium-quality studies.

Next, the non-cancer BMDL-5 of 49 milligrams per kilogram per day was converted to a human equivalent dose or HED of 12 milligrams per kilogram per day using elementary body weight scaling to the three-quarters power. And finally, for the benchmark margin of exposure, total uncertainty factor of 30 was selected based on use

of an intra-species uncertainty factor or UFH of 10 and the inter-species uncertainty factor or UFA of 3, which was reduced from a value of 10 to 3 because three-quarters body weight scaling was used to derive the HED. Next slide, please.

Okay. Overall, we have robust confidence in the selected acute and intermediate POD, and several lines of scientific evidence support our decision in the selected POD. First, it's important to note, again, that we previously concluded that DINP is toxicologically similar with ballot diesters such as DEHP and can induce effects on the developing reproductive system consistent with the disruption of androgen action and development of thyroid syndrome. Again, this conclusion was supported by SAC during the previous peer review meeting, and our conclusion is consistent with how other regulatory bodies have characterized DINP, including agencies such as USCPSC and Health Canada and others.

So our conclusion is based on evidence that oral exposure to DINP during the

critical window of development in rats can consistently and dose-dependently reduce mRNA expression of genes involved in cholesterol transport and stearated genesis and the fetal testis, as well as reduce fetal testis testosterone content in their ex-fetal testosterone production in rats.

Additionally, exposure to DINP can cause increases in latex cell aggregation, increased incidence in non-nucleated gonocytes, and decreased sperm motility in adult rats, reduced malostrine in general distance, and increased malostrine nipple retention. Also, as discussed throughout our proposed approach for human risk assessment of ballots under TAXA, and in the current DINP non-cancer technical support documents, we acknowledge that DINP is a less potent antiandrogen compared to other dialect diesters being evaluated under TAXA, and certain apical outcomes associated with dialect syndrome, such as reduced malpup in general distance or increased malpup nipple retention, are observed

less consistently across available studies. Regardless, this observation is consistent with the DINP being a less potent antiandrogen compared to other ballots. Next slide, please.

Okay, so as I mentioned earlier, we are proposing to use the non-cancer POV of 12 milligrams per kilogram per day based on reduced fetal testis testosterone to characterize risk for acute and intermediate durations of exposure. Although no studies are available for DINP that have evaluated effects on the developing mal-reproductive system following a single acute exposure during the critical window of development, studies are available for toxicologically similar phthalates, dibutyl phthalate, or DBP, and available studies indicate that a single exposure during the critical window can reduce mRNA expression genes involved in cholesterol transport and steroid genesis, and reduce fetal testis testosterone content. Further studies of DBP have also demonstrated that as few as two exposures to DBP during the critical window

of development are sufficient to cause severe later life male reproductive tract malformations.

Therefore, we considered the effects of reduced fetal testicular testosterone relevant for assessing risk from acute duration exposures to DINP. The POV was also selected for assessing intermediate duration exposures to DINP because the POV has one of the most sensitive and robust candidates identified across available studies.

Okay, so this slide summarizes the non-cancer POV selected for DINP that has been proposed to be used to characterize risk from chronic duration exposures. For this POV, we have preliminarily selected a NOAEL of 15 milligrams per kilogram per day from a high quality two-year chronic dietary study of F344 rats reported by LinkedIn et al. So the NOAEL is based on a spectrum of liver effects, including increases in relative liver weight, increases in serum alanine and aspartate transaminases at various time points throughout the study, and histopathologic lesions such as spongiosis of paddus and cursus at higher

doses. Again, using allometric body weight scaling to three-quarters power, we derived an HED of 3.5 milligrams per kilogram per day, and a total uncertainty factor of 30 was selected for use as the benchmark MOA based on use of an interest species uncertainty factor or UFH of 10 and an interspecies uncertainty factor or UFA of 3. Again, the interspecies uncertainty factor is reduced from a value of 10 to 3 because three-quarters body weight scaling was used to derive the HED. Next slide, please.

Okay, so overall, we have robust confidence in the selected chronic POV. Several lines of scientific evidence support our selected POV. First, the selected POV came from a study that received a high overall study quality determination and represents the most sensitive POV identified by EPA across all studies considered, including four three-year chronic dietary studies, six 13-week sub-chronic dietary studies, as well as one and two generation studies of reproduction. At the loyal, a spectrum of dose-

related effects consisting of liver toxicity were observed, including treatment-related increases in relative liver weights, increases in serum ALT, AST and ALP, and histopathologic findings such as spondylus and sopatus.

Further, a similar spectrum of liver effects, including increases in liver weights, changes in the serum chemistry markers, indicative of liver toxicity, and other histopathologic lesions in the liver have been observed in other sub-chronic and chronic studies of DINP in several species. Finally, it's also notable that other regulatory bodies such as Health Canada, USCPSC, EFSA, and ECA have also set the same noel for use in risk characterization. Next slide, please.

So just to recap quickly, we are proposing to use a non-cancer POV of 12 milligrams per kilogram per day based on reduced fetal testicular testosterone to characterize non-cancer risk for acute and intermediate duration exposures. Importantly, we've previously concluded that exposure to DINP can induce effects on the

developing of our reproductive system and the disruption of androgen action. This conclusion was previously supported by the SAC. For chronic durations, we are proposing to use a non-cancer POV of 3.5 milligrams per kilogram per day based on liver toxicity, notably other regulatory agencies have also set the same noel for use in characterizing risk.

Okay, so now we're going to be transitioning to an overview of the DINP cancer human health hazards.

Right, here again, you can see the DINP risk evaluation map. And for this portion of the presentation, I'll be providing an overview of the cancer human health hazards, finding background information that primarily pertains to charge questions 2C, 2D, and 2E. Also, the DINP cancer human health hazard assessment technical support document is the primary document that provides information providing this portion of the charge.

Okay, so DINP has been evaluated for personogenicity in four two-year dietary studies, including two of F344 rats from the Sprang Valley rats and one of B6C3F4 mice across the four reliable studies. Three tumor types have been consistently observed, including liver and kidney tumors, as well as MNCL and F344 rats. As we're talking a bit more about each tumor type a bit more over the next couple of slides. But I would like to note here that we are focusing our cancer emotive action analysis and dose response assessment to the liver tumors, and reasons for this will become more apparent over the next couple of slides.

Again, at this stage, I'd also like to note that while the DINP has been classified as a carcinogen by California OCEA, and is listed as a carcinogen under Proposition 65, other regulatory agencies, including USCPSC, Health Canada, Australian ICNAS, and that got not classified DINP as a carcinogen or evaluated DINP for quantitative cancer risk.

So this slide provides a summary of available genotoxicity and mutagenicity data for DINP. The mutagenic and genotoxic potential of DINP has been evaluated in 20 studies. Across studies, no evidence of mutagenic activity was observed in five bacterial reverse mutation assays or two in vitro mast lymphoma assays, further without metabolic activation. Further, DINP did not induce chromosomal aberrations in Chinese hamster ovary cells in vitro, cause unscheduled DNA synthesis in primary hepatocytes, or induce clastogenic effects on the pro-nuclei formation in vivo in studies of mice or rats.

Of the nine available in vitro transformation assays, only one study reported a positive result for transformation on the absence of metabolic activation. So overall, based on the weight of scientific evidence, we've preliminarily concluded that DINP is not likely to be genotoxic or mutagenic, which is consistent with conclusions of other regulatory agencies.

Okay, so this slide covers kidney tumors. So two different types of kidney tumors have been observed in male F344 rats. Here, it's important to note that no kidney tumors have been observed in female F344 rats, male or female sprague dolly rats, or male and female mice. The two tumor types observed include transition cell carcinomas and tubular cell carcinomas. As you can see from the data table on the side, incidence of transition cell carcinomas in both studies was low, was not statistically significant, did not occur in a dose-related manner.

For these reasons, the transition cell carcinomas observed in male F344 rats were considered to be of uncertain toxicologic significance. For the tubular cell carcinomas observed in two studies of male F344 rats, there is evidence to support a mal-rat specific alpha-2 globulin mode of action, which is not considered human relevant. Lines of evidence supporting this mode of action include the facts that kidney

tumors were only observed in mal-rats and DINP is not genotoxic or mutagenic.

Further, in a retrospective re-analysis of archived kidney tissue taken from a 12-month interim sacrifice and study by Olmton et al., a dose-dependent increase in accumulation of alpha-2 globulin, an increased droplet size on the kidneys of high dose males, but not female rats, was observed. Further, photomicrographs for proliferating cell nuclear antigen in alpha-2 mutaglobulin staining showed foci of proliferating cells in alpha-2 mutaglobulin accumulating in proximal tubule cells in the kidney. Notably, other agencies run similar conclusions regarding in alpha-2 mutaglobulin mode of action and human relevancy.

So, this slide provides an overview of the data for mutagenic cell leukemia or MNCL. As you can see from the tables of instance data off to the right of this slide, MNCL has consistently been observed in two two-year dietary studies of male and female f344 rats conducted by

Cobant's labs and LinkedIn et al. However, in two other chronic dietary studies of sprague valley rat's mice, MNCL was not observed. However, this isn't necessarily surprising given the high rate of spontaneous background occurrence of MNCL on f344 rats. As I previously discussed for DIDP, there are several important uncertainties related to MNCL and f344 rats.

This is uncertainty of MNCL. It's important to consider historical control data and time-to-onset data in addition to concurrent control data when determining if MNCL is treatment-related or not. For DINP, again, we do not have historical control data from the laboratories conducting the studies.

DR. GEORGE COBB: So, Dr. Lois, your audio and video are freezing. Do we have any solution to that problem, Ella, Charlene? We'll try to reach the EPA team. They're presenting from North Carolina. Or has unclear human relevance? Tony, excuse me. So, we lost you for like a minute or so. You were frozen and we didn't hear

anything. So, if you can go back like a minute worth of talking.

DR. ANTHONY LUZ: Which slide was I on when I froze? I'm sorry for that.

DR. GEORGE COBB: You were still on 80 and you had gotten through the MNCL and the different regulatory agencies. I think that's where you had regulatory bodies. I think that's where you ended or where we stopped hearing you.

DR. ANTHONY LUZ: Okay. So, you heard all the uncertainties related to MNCL, that part of the discussion. I think the main conclusion from this slide is, you know, overall, just as for DINP, there's scientific, you know, uncertainty remaining related to MNCL and F344 rats. And therefore, we did not consider MNCL for cancer dose response assessments. And again, this is consistent with how several other regulatory bodies have characterized MNCL. So, agencies such as USCPSC, Health Canada, AstraZeneca, NICNAS, and ECA have concluded that MNCL is not human relevant

or has unclear human relevance. Next slide, please.

Okay. So, moving on to liver tumors. So, this slide provides a summary of studies in which hadicellular adenomas and or carcinomas have been observed. This can be seen from the table off to the right of the slide. Across the four available two-year dietary studies, liver tumors have been observed in male and female B6C3F1 mice and male and female F344 rats in the two studies conducted by Cobant's labs. Hepatocellular carcinomas were also observed in high-dose female sprague dolly rats in the biodynamics study. No significant increases in liver tumors were observed in male female F344 rats in the study conducted by LinkedIn et al.

However, the highest doses achieved in that dietary study, which were 307 to 375 milligrams per kilogram per day, were less than the doses required to cause liver tumor genesis in the other two-year studies of rats. So, it's actually not that surprising that liver tumors

weren't observed in the study by LinkedIn et al. So, given that treatment related tumors were observed consistently across species and both sexes, that liver tumor genesis appears to represent a progression from non-cancer liver effects. We focused our mode of action and cancer dose response analysis to liver tumors. Next slide, please.

Okay, for liver tumors observed in rodents, so mice and rats, we postulated that DINP causes liver tumors to repeat our alpha mode of action. We evaluated the postulated mode of action consistent with EPA cancer guidelines and the IPCS mode of action framework. Here, I'd also like to note that consistent with EPA, some other regulatory agencies have also hypothesized a rule for PFR alpha in DINP liver tumor genesis. All I see you coming off mute. Do we have any connectivity issues still?

DR. GEORGE COBB: I'm good. I don't know if I can speak for anybody else. I can hear you fine.

All: Yeah, we can hear you.

DR. ANTHONY LUZ: Great. Thanks, Dr. Cobb. Okay, so the PPARα mode of action is described in several publications reported by Courtney All is depicted on the bottoms of the slide. So, in this mode of action, the first key event is activation of PPARα in hepatocytes. So, PPARα activation can be assessed directly using trans activation assays or indirectly by measuring specific events associated with PPARα activation, such as increased activity of palmitoyl co-oxidase, increased peroxisomal weight oxidation, or changes in expression of genes regulated by PPARα.

Key event two involves alterations in cell growth pathways. It can involve activation of cryptocells in the liver leading to increases in secretion of cytokines, such as tumor necrosis factor alpha or interleukin 1 alpha or interleukin 1 beta, which in turn can affect hepatocyte traits. However, I would like to note here that there is some uncertainty in how PPARα and other

nuclear receptors for that matter can actually alter cell fates.

For key event three involves perturbation of cell growth and survival, which is characterized by increased replicative hepatocyte DNA synthesis and cell proliferation in both normal and premium plastic hepatocytes as well as suppression of apoptosis. This can lead to a fixation of DNA damage and genes controlling cell growth, which in turn can lead to silencing of tumor suppressor genes or activation of oncogenes contributing to clonal expansion of initiated cells.

Finally, for key event four, it involves the selective clonal expansion of premium plastic liver cells, which in turn leads to the outcome of paticellular adenomas and or carcinomas. Next slide, please.

Okay, so this slide provides a high-level summary of available data to support the PPARα motive action. As you can see, there's considerable data for key event one or PPARα

activation. So activation of PPARα in hepatic cells by DINP has consistently been demonstrated in five in vivo studies of mice and four in vivo studies of rats. While no evidence of PPARα activation in hepatic cells is observed in two in vivo studies of monkeys. Additionally, four in feature studies are available that consistently demonstrate that rat mouse hepatocytes are more sensitive to PPARα activation following exposure to DINP compared to human and monkey hepatocytes.

For key event two limited data is available. EPA identified a single study of mice that reported increased TNF alpha and interleukin one and liver homogeneous following 14 days of exposure to DINP, providing some evidence for key event two. However, this study is limited due to the fact that study authors did not identify the specific KE one subtypes being measured for key event, three, evidence of increased hepatocyte DNA replication and cell proliferation comes from multiple studies, crossing vivo studies of mice and rats, an acute cell proliferative response in

the liver is consistently observed. In contrast, cell proliferation in the liver is not sustained chronically in either species.

However, it's discussed in the literature and publications by corneal cited on some of the earlier slides. Weak PPARα activators tend to produce transient increases in replicative DNA synthesis during the first few days or weeks of exposure followed by a return to baseline levels, and therefore lack of a sustained proliferative response is not inconsistent for the proposed mode of action.

Finally, for suppression of apoptosis. There's limited in vivo data to provide support for suppression of Apoptosis in the liver following exposure to DINP. However, two studies of primary wraps hepatocytes have demonstrated that exposure to DINP can suppress apoptosis. Finally, for key event four, you identified no data. This is a data gap. Next slide, please.

Okay. So across available studies, we observed some evidence of dose response

concordance in mice and rats. For example, key events one and three occurred at lower doses than liver tumors hover concordance if cross key events was less evidence, which was in part due to the fact that available studies were a varying design. Were somewhat limited by dose selection and dose spacing.

There's also some evidence of temporality. For example, there's evidence that key events one and three procedure liver tumor formation in rats, and that key events one, two and three proceeded liver tumor formation in mice. As part of our analysis, we also considered other modes of action in addition to PPAR alpha, all of which are also non genotoxic threshold modes of action.

For other modes of action, there's some evidence that di NP can inhibit gap junction, intercellular communication, cause cytotoxicity that might contribute to regenerative proliferation of hepatocytes, as well as modulate other nuclear receptors in addition to PPAR alpha,

for example, in vitro studies are available that have shown that damp can activate constitutive androgen receptor or pregnant X receptor or PXR and arrow hydrocarbon receptor AHR. However, evidence for these other modes of action is generally limited to a few studies. Regardless, there is some potential that these other modes of action could potentially contribute to carcinogenesis and not the liver.

There are also some uncertainties and limitations in the current mode of action analysis, but it is important to note here that there are, of course, uncertainties in every mode of action analysis. For example, there's limited data for key event two and no data for key event four. There's also limited data for in vivo suppression of apoptosis, which is part of key event three. However, lack of this in vivo apoptosis data is somewhat addressed by the in vitro data that shows DINP can suppress apoptosis in primary hepatocytes.

There are also some unexplained inconsistencies. For example, liver tumors were observed at lower doses in female mice than in male mice, while increases in Pyro activation and proliferative DNA responses were observed at lower doses in male mice compared to females. However, despite some of the remaining uncertainties and limitations, we believe there'd be strong evidence to support a non-genotoxic threshold, PPARα, motive action for liver tumors. Next slide please.

Okay, so under the guidelines for carcinogen risk assessments, we have preliminarily concluded that DINP is not likely to be carcinogenic to humans docipital levels that do not result in PPARα activation, so that's again, key event one in the proposed mode of action, this classification was based on the following way to scientific evidence considerations. First, there's no evidence for mutagenicity or genotoxicity of DNIP. Further, much of the available data supports a PPARαmotive action, with PPARα activation being observed in mice and rats at lower doses than the

dose of our liver tumors in mice and rats were observed. So given the weight of evidence supporting the non-genotoxic threshold, PPARα mode of action. We have further concluded that the non-cancer chronic pod based on NOAEL of 15 milligrams per kilogram per gram based on non-cancer liver effects, will adequately account for all chronic toxicity, including carcinogenicity, which could potentially result from exposure to the DINP, because the lowest low Al and the lowest no al for puber health activation are 117 75 milligrams per kilogram per day respectively. Next slide please.

Okay, so just to recap, here quickly, we've preliminarily concluded that kidney tumors and male rats occur through a male rat specific of the 2u globulin motor action, while there is too much uncertainty associated with mncl and fissure rats to use for quantitative dose response assessment or cancer risk assessment, therefore we focused our cancer assessment on liver tumors overall. We've preliminarily concluded that there is strong evidence to support

a non-genotoxic threshold, PPARα mode of action for liver tumors and rodents, concluded that DINP is not likely to be carcinogenic to humans at their simple levels that do not result in PPARα activation. Next slide, please.

With that, I'd like to thank everyone for their attention now we have some time in the agenda some questions from the panel.

QUESTIONS FROM THE SACC ON EPA PRESENTATION

GEORGE P. COBB: All right, thank you, Dr. Luz. Are there questions from the committee? Dr. David.

DR. RAYMOND DAVID: Hi, I have a question about the conclusion that DINP is not likely to be carcinogenic below dose levels that activate PPARα, but there are certainly data to suggest that even if humanized PPARαis activated, that there's not likely to be any downstream events that would lead to the development of cancer. So I'm just curious have the agency

considered those data and in their assessment. And what are your thoughts?

DR. ANTHONY LUZ: Hey, Dr. David, thanks for your question. Yeah, you know, I think the agency fully acknowledges that there are species differences in sensitivity. You know, we acknowledge that, you know, several other panels and workshops have been convened, you know, to try to, you know, answer that question. Just, just pose that, you know, these effects might occur in rodents, but maybe not in humans. You know, I think it's a, it's a really tough, tough question. I think there's still some scientific uncertainty. And those panels, you know, I think, you know, despite their efforts, you know, there's still not necessarily 100%scientific consensus related to this, this tumor type. It's kind of with that being the case, you know, I think looking across the available data and rodents, most of the data indicates a threshold mode of action, which, allows us to look at risk, you know, using a margin exposure approach. But I'll pause there. I

see our senior science advisor, Dr. Lowitz, come on, Karen, and see if she wants to add anything.

DR. ANNA LOWITZ: Yeah, thanks for the question. And Tony is right. We certainly acknowledge that there has been a lot of conversation about this in the public domain for a long time, and I would fully anticipate this panel adding to that conversation, just from a logistics and process point of view, to the extent that the panel is aware of DINP specific data that would make that link to the human P part that would be the most helpful to us. So the from a proximal proliferation PPARα, point of view, to take the step to calling that mode of action not relevant to humans, if I use the jargon and the cancer the cancer guidelines is a larger conversation beyond DINP. It's a conversation that's relevant to our colleagues in the pesticide program, and our colleagues and the Office of Research and Development in the iris program, and from a practical standpoint, based on what you heard from Tony. Irrespective of whether or not the proximal

proliferation mode of action is human relevant or not human relevant, it actually doesn't change our assessment.

If the panel is an agreement that we have a nonlinear mode of action for the liver tumors and are in concurrence on Tony's conclusions on the on the other tumor types. The proposal that we have to use the liver end point would be maintained, irrespective of the PPARα. That we would still be have a chronic point of departure that's protective of both cancer and non-cancer, irrespective of the human relevance of the proximal proliferation. So if you go back to what we heard from you hall this morning, and the resource constraints so we have on the program, but also the statutory deadlines that we have in the program. It's an analysis that's not entirely value added to the assessment.

If it were going to fundamentally change the assessment, it would be an analysis that would be value added. But in this case, given the points that you heard from Tony, if the panel

concurs with those. It doesn't have a meaningful impact on the assessment.

DR. RAYMOND DAVID:

I understand and I appreciate the fact that the for the agency to say not relevant for humans is a quantum step and requires a lot of information. I get that. So thank you for getting to the conclusion you did.

DR. GEORGE COBB: All right. Thank you. I see Dr. Ottinger has her hand next.

DR. MARY OTTINGER: I wanted to say I really appreciated what Dr. Luz just said about the nonlinear responses. And thank you very much for that one question I have. Well, I have two quick questions, hopefully. One is, Is there information about what the timing sensitivity is for the testicular effects to be exerted? Is it early, developmental or perinatal or what? And then the second question is, were thyroid or adrenal axes considered in any of the two Gen studies.

DR. ANTHONY LUZ: This is Tony laws with EPA for your first question pertaining to the critical window development for those now reproductive effects. So the critical window is actually pretty well understood in rats and mice and to a lesser extent, humans. We've covered quite a bit in our previous cumulative proposal on phthalates. But for rats, it's, around gestational days 14 to 18.

DR. MARY OTTINGER: Okay, post HPG axis formation. Okay, all right. And then, yeah, the thyroid, and I was just curious about other endocrine systems.

DR. LUZ: Yeah, I'll have to double check I believe in that, that study, I mean, it was a guideline, so I believe that looked at, you know, the organ weights, and it should have looked at histopathology, but to confirm.

DR. OTTINGER: Okay,

DR. GEORGE COBB: Dr. Fenner-Crisp.

DR. FENNER-CRISP: May we assume that Dr. Corten will be available for a conversation on

the day we take out the charge question on DINP, 2d.

DR. CHRIS CORTEN: I can make myself available. Just let me know when.

DR. FENNER-CRISP: Hi, Chris, you

DR. GEORGE COBB: I have too many screens open. Thank you. I was saying, if there are no more questions, we can move to our next presentation by EPA, and it's going to be Dr. Brennan.

DR. ANN LOWIT: Dr. Cobb. Before you move on, I have a clarification about the question that Dr. Fenner-Crisp just asked to Chris Corten. I just want to make sure that we're within the FACA rules, that when you charge, start those charge questions, Will Dr. Corten be in a position to be answering her questions? Or I just want to make sure that we're in the bounds of the proper rules.

DR. GEORGE COBB: That's a good point. And let me see what Dr. Fenner-Crisp was intending there. And yeah, I should have, I should

have picked up on that actually, Dr. Fenner-Crisp, do you?

DR. FENNER-CRISP: Well during the course of our discussions, they're often I have observed interactions between the panel and the agency staff to get some clarification. And I just thought that in this particular case, it would be helpful if he were available in that kind of dialog, not outside the bonds of the ground rules, though.

DR. GEORGE COBB: Yeah, I think that at times we have made comments that this would be improved, or it would be helpful to know which data are used that are not necessarily part of these presentation.

DR. FENNER-CRISP: right? That's all I had in in mind.

DR. GEORGE COBB: So I think we can move to the EPA presentation now.

EPA TECHNICAL PRESENTATION 4

DR. JENNIFER BRENNAN: Great, welcome to the last portion of this presentation for today. This is part four. Will be overviewing information on the DI DP environmental hazard and exposure, as well as the DI NP environmental hazard and the information pertaining to the charge questions for those portions of the assessment. Next slide please.

So the DIDP environmental hazard and DIDP environmental exposure assessments have several charge questions related to them. For the environmental hazard portion, it's 2a and 2b the charge questions for the DIDP environmental exposure assessment are charge questions, 1c and 1d and for the DINP environmental hazard, we have a single charge question. Charge question one. Next slide, please.

I'll be starting off with the DIDP environmental hazard overview and the information related to those charge questions. This is JENNIFER BRENNAN with US EPA. So an overview of the map of the draft DIDP risk evaluation and the

portions that evaluation that are relevant to charge questions 2a and 2b. We have the environmental hazard assessment in the green box, and the information also relevant to the charge questions can also be found in the environmental risk characterization as well. Next slide please.

So overviewing the DIDP environmental hazard summary. EPA identified hazard data on fish, frogs and aquatic invertebrates and sediment invertebrates in that data set, no hazard was observed, and so no hazard thresholds are established for those taxa exposed to DIDP EPA was not able to identify reasonably available soil invertebrate data for hazard when exposed to DIDP. So EPA conducted a Read Across from DINP earthworm hazard data. Read lines of evidence form the basis for the read across so that was structural similarity between DIDP and DINP physical, chemical, environmental, fate and transport similarity between DIDP and DINP, as well as toxicological similarity between DIDP and DINP.

No hazard data were reasonably available for avian species and terrestrial plants exposed to DIDP. EPA did establish a hazard threshold in terrestrial mammals, and this hazard threshold was based on ecologically relevant endpoints from laboratory rat data, in lieu of not having hazard data available for wildlife species. Next slide please.

Just to overview DIDP, environmental hazard in other assessments. So both the European Union risk assessment for DI ISO delight, as well as the Environment Canada, Health Canada, State of the Science Report, phthalates, substance grouping, long chain phthalate esters, DIDP and DINP. Both determined that DIDP had low hazard potential to aquatic taxa with no adverse effects on survival, growth, development or reproduction at concentrations at or beyond solubility and water. So this was very similar to what EPA concluded in the draft DIDP environmental hazard characterization for aquatic taxa. Next slide please.

So now we're moving into information pertaining to charge question 2a. So this is the DIDP hazard threshold in terrestrial mammals, and the methodology used to establish that hazard threshold for terrestrial mammals. So as mentioned earlier, the DIDP hazard threshold in terrestrial mammals was based on ecologically relevant endpoints from animal toxicity data for DIDP, these were rat laboratory studies containing ecologically relevant endpoints. The hazard threshold is called the toxicity reference value, or TRV. This TRV represents hazard in mammalian species, although it's derived from laboratory rat data, the TRV is meant to be representative across semi aquatic mammals such as the mink, or representative insectivorous mammals such as the shrew, so not just the rat, data from which it was derived.

The TRB derivation uses the ecological soil screening level guidance by EPA. This is known as eco SSL, guidance and the endpoints considered for the DIDP TRV, included

reproduction, growth and survival endpoints. And briefly, and I'll go over in the next couple slides, more in depth on the methodology for TRV derivation. But briefly, the TRV derivation is conducted by comparing the low ALS in the data set to a geometric mean of the NOALS and for DIDP, the TRV was established as 128 mg per kg body weight per day DIDP. And again, that value would be representative across terrestrial mammals. Next slide please.

So this is a figure s6.1 from the DIDP draft environmental hazard technical support document. It's the terrestrial mammal TRV flow chart. I'll step through briefly how the DIDP TRV was established. You start with step one in your data set. So are there at least three toxicity values for two species for reproduction, growth or mortality? It's important to note, in the case of both the DIDP and the DINP TRV, which will be discussed later, strains of animals were counted as separate species for the purposes of the TRV derivation here. So for DIDP, yes, we had what

consisted of two or more species with those values. So going to step two, are there three or more NOALS in reproduction and growth for the DIDP data set, yes there were.

That brings us to step four, where you then calculate the geometric mean of NOALS across the reproductive and growth endpoints. You then compare the geometric mean of the no Al and find if it's lower than the lowest found at low al in the reproductive growth or mortality end points, and for DIDP data set, that was not the case. We actually had a lowest found at low al that was below the geometric mean of the NOALS. So in that case, the TRV then follows the no arrow to the yellow box, and the TRV is then set as the highest found at NOALS, below the lowest, found at low al for reproduction growth or mortality. Next slide please.

So this is looking at the laboratory rat data for DIDT that consisted of ecologically relevant endpoints across the reproduction, growth and survival categories, shown in the red, blue

and pink circles respectively. The open circles in the data set are low ALS for an endpoint, and they're connected by a line to their respective NOALS for a particular endpoint, the black line spanning the reproduction and growth endpoints with the arrows connected at each end of the black line that represents the geometric mean of the reproductive and growth endpoints of those no ALS.

So, as I was showing and explaining in the earlier Slide, if you look across the rat data set, here, you actually find that you have a bounded low al that's lower than the geometric mean of the no ALS. So in the in this case, the toxicity reference value then defaults to the highest bounded no al that's below that lowest found at low Al and the data set, and so that highest found at NOAlS shown as that black circle with the blue circle inside. That value is 128 make per KE body weight per day. This is done to refine the hazard threshold that's representative of the effects that you're looking at. It's also important to note that we EPA had enough data in

the animal toxicity data to work with that the data set is limited to bounded, NOAL, low AL pairs, and that decision was also made to refine the hazard threshold. Next slide, please.

So conclusions and key points for the information for pertaining to charge. Question 2a no hazard threshold was established for most of the taxa, specifically fish, frogs, aquatic and sediment dwelling and vertebrates, and that was due to a picture of no effects in the reasonably available hazard data. A single hazard threshold was established for di DP environmental hazard, and that was consisting of terrestrial animal toxicity references that had growth, reproductive and mortality endpoints identified from laboratory. Rat data, and the hazard threshold is described as the toxicity reference value known as the TRV. This TRV is representative of hazard across terrestrial mammals, although it's derived from laboratory animal data. And to recap, no hazard data were reasonably available for avian

species and terrestrial plants exposed to DIDP. Next slide please.

So now moving into the information pertaining to charge question 2b for DIDP. This is pertaining to the methodology used for the DIDP environmental hazard read across so, as mentioned earlier, no reasonably available data were obtained for soil invertebrates exposed to DIDP. EPA conducted a read across using soil invertebrate hazard data from the DINP data set, and this was a no effect hazard that was read across to DIDP and three lines of evidence fed into the basis for the read across and that is structural similarity between DIDP and DINP, physical, chemical, environmental, fate and transport similarity between DIDP and DINP, as well as eco toxicological similarity between DIDP and DINP. Next slide.

So for the first line of evidence, which is the structural similarity, EPA conducted a structural similarity analysis between DIDP and analog DINP, and this was done using several

programs. So analog identification methodology, OECD, qsart toolbox, where PubChem fingerprints were generated using the similar analysis, and then Chem informatics search module, where the tanamoto index was used to make that comparison. If we look at the first row in the table where DIDP is being compared to itself in a structural similarity analysis, you can see an aim.

It's an exact match to itself, and it receives a score of one, which is the maximum score possible for both the PubChem fingerprints as well as the tanamoto index in the kind of informatics search module. So both of those scores for the PubChem fingerprints and tanamoto index are on a scale of zero to one. In the second row, where di NP is compared to di DP in these programs, it's a first pass analog and aim which is the highest pass, indicating high structural similarity between the two chemicals. And it received a score of one for the PubChem fingerprints, which again is a maximum score, as well as a score of one for the tanamoto index

using the Chem informatics search module. So high degree of structural similarity is indicated across several different programs, between DIDP and DINP. Next slide, please.

The second line of evidence that was used in the Read Across for the analog selection was comparing the physical and chemical fate properties between D and analog DINP, and because this is a soil and vertebrate hazard read across the physical, chemical and environmental fate properties were pertinent to the chemicals behavior and soil as in addition, the hazard study also took place over 28 to 56 days. So the properties also addressed behavior in soil over time as well. So if you look at the first column with some of the physical, chemical and environmental fate properties, and then you look across that DIDP.

For water solubility and the log optimal water partition coefficient, we see a picture of highly insoluble chemicals that have a high preference to partitioning to the optimal

phase for log, organic carbon water partition coefficient also is very high for both DIDP and NP, so both are going to soar very strongly to soils and sediments. Biodegradation in the aerobic portion of the soil happens over a matter of weeks to months for both DIDP and DINP in the anaerobic portion of the soil, we expect minimal to no biodegradation for both DIBP and DIP.

Bioaccumulation factor and earthworm is identical between the two chemicals, with very low bioaccumulation potential for both DIBP and DINP and earthworm very low vapor pressure, we do not expect either of these to volatilize out of the soil. Molecular weight is very similar between the two, which speaks to ability to cross cell membranes and both exist as clear liquids at room temperature. So for both DIDP and DINP, we would expect these to behave very similarly in a soil environment. Next slide, please.

The third line of evidence that fed into the Read Across for selecting DINP as an analog is the Eco toxicological similarity,

because we don't have soil invertebrate hazard to directly compare DIDP and DINP. If we did, we likely wouldn't be proposing a read across what we do have to compare their eco toxicological similarity is hazard in related taxa. So the focus of this slide is showing hazard of both DIDP and DINP in sediment dwelling invertebrates as well as invertebrates in the water column. So each row has a species exposed to both DIDP and DINP within the same study. And if you look down the rows, what you largely see is a picture of no hazardous effects from exposure to both DIDP as well as exposure to DINP in either the sediment dwelling or the water column invertebrates.

The one exception is the daphnia Magna 21 day exposure, where entrapment values were noted in the form of a chronic value for both DIDP and DINP, but the authors noted in this study that this was due to a physical film at the top of the water in the daphnia Magna being trapped in that film, rather than the chemical being solubilized in the water and causing chemical

toxicity. So very similar hazard profile for both DIVP and DINP in taxa that could be relevant for earthworm toxicity. And so EPA felt very confident. Then in the last row, conducting a read across based on a no hazardous effect from di MP to DIDP with support from the other two lines of evidence as well and analog selection. Next slide, please.

So conclusion and key points, di NP, soil invertebrate hazard data was used in a read across to di DP. And DIDP and DINP exhibit the following similarities, supporting that selection of di MP as an analog for di DP, again, structural similarity between DIDP and DIP, physical, chemical, environmental fate and transport similarity between DIDP and DINP, as well as eco toxicological similarity between DIDP and DINP. And very interested in the sax input on both charge questions to a and to be for the DI DP environmental hazard. Next slide, please.

With this, I'm going to hand this over to my colleague, Dr. Christopher Green.

DR. CHRISTOPHER GREEN: Hello, I'm Dr. Christopher Green with OPPT's existing chemical.

DR. GEORGE COBB: Can you give us a second? It looks like Dr. David had a question.

DR. RAYMOND DAVID: Yeah, I was, I was hoping to get in a question before we move on to the next phase of the questions, and it has to do with slide number 96.

DR. CHRISTOPHER GREEN: So thank you. Dr. David just like we did with the other presentations earlier today. Would you Would it be acceptable for us to continue with the next few components and then tally that? Is that acceptable to people?

DR. RAYMOND DAVID: That's fine, if you'd rather do it that way. I just yep, that's fine.

DR. CHRISTOPHER GREEN: Yeah? Okay. Thank you very much. I apologize. Yeah. So thank you for asking, but we'll keep going, and then, obviously utilizing the slide numbers that are on

the lower portion of the screen will be very helpful to get back to that. So thank you very much. Dr. David and others for letting us go on and then we'll hear this really good input. My name is Dr. Christopher Green. I'm with the OPPT's existing chemical risk assessment division as a biologist here in EPA. I'm going to be addressing the environmental exposure technical support document for DIDP. Next slide, please.

So this technical support document and the reference documents are listed on the screen here. We have two targeted charge questions to address certain things associated with this presentation. Charge question 1c centering towards the environmental exposure analysis, and question 1d which integrates the weight of scientific evidence and conclusions associated with this section and the components related to it. Diagram, which you guys have been seeing throughout the day demonstrates that we are in the middle green square the lower portion of the screen for

environmental exposure analysis. Next slide, please.

So when we look at the landscape of evidence that's presented within the physical, chemical and fate technical support document, as well as reviewed and referenced within the environmental exposure technical support document, we're presented with a large body of evidence indicating that DIDB does not bio magnify. It can be found in tissues, but it does not bio magnifying, bio accumulate in terms of bioaccumulative substances. However, as we heard earlier today and throughout reading of this document, we understand that dietary exposure can still occur, and we want to represent that dietary exposure to the fullest in terms of a screening level trophic transfer analysis for the protection of a variety of our different animals in our ecosystems.

To do this, we looked at a couple of different scenarios where we looked at the pathways of surface water releases into sediment,

as well as air deposition into soil. For a representative mammal for this aquatic oriented screening level analysis, we're looking at the American mink as a piscivorous aquatic mammal and in the soil component. To really take, you know, the best picture of animals taking in soil in their diet and then eating other animals that have soil in their diet. We're looking at the connections between soil, earthworm and shrew as a insectivorous mammal. The way we did this is we calculated dietary exposure estimates.

And there were two pathways represented within the environmental exposure technical support document. The first one was we utilized the highest releasing cou that you know, led us to the highest model concentrations of DIDP within the sediment and soil. We also within the landscape of our literature for environmental monitoring. We're representing the highest reported DIDP concentrations in soil and sediment within the literature, and these are characterized as industrialized sites, sites that have been

studied for, other chemicals, as well as the DIDP specifically.

In our screening level analysis, we looked at those dietary exposure estimates, and due to our hazard values that Dr. Brennan just demonstrated, we looked at the toxicity reference value with those mammals in comparison to those dietary exposure estimates for either a representative aquatic individual or our terrestrial mammal, comparing that 128 milligrams per kilogram body weight per day. Next slide please.

So this is figure five, one from our DIDP draft environmental exposure technical support document. And I really want to emphasize that the goal of these representative species is to look at the maximal potential uptake of the compound, and specifically. We're looking at the role of this compound in soil and the role of this compound in in sediment, predominantly because of our information and our modeling, as well as the environmental exposure analysis. On the left hand

side of the screen, you'll see the earthworms represented as a soil invertebrate. Think of those as kind of a running a sock through soil, and so we looked at their concentration in their body as being the concentration that was projected or modeled within soil that earthworms then consumed by a shrew in the aquatic environment. Wanted to represent the animals that would have a lot of sediment from their natural history. And my background as a fish biologist, in addition to a few other things, led me to utilizing a castom species. This is a black tail Red Horse. Suckers and catfish take in a lot of sediment as a component of their diet when they're rooting around the benthopes and eating and so I wanted to really represent that as a screening level and highly conservative approach to show who is getting the most sediment in that could get that in their body and then potentially be eaten by something else. These conservative exposure factors are really integral to the screening level approach, and I wanted to represent that as

closely and cautiously as possible. Next slide, please.

These equations are from the EPA ecoSSL, which Dr. Brennan talked about a few slides ago. They're adapted from that, and they're representing a variety of exposure factors, and they're representative of the screening level approaches that EPA took for this assessment. The terms represented within these equations are intended to be very conservative. So for example, this is not assuming any in vivo metabolism or excretion the absorbed fraction of the contaminate from the soil or sediment into the organism. Say, for example, af si, af, wi, and af ij, for sediment, water and prey were all set to one. We also utilized one as an area use factor, indicating that all the biota that are included in the different connections from soil to animal to animal are all residing within an area that has DIBP present. So the exposure factors for things like feed intake rate, water intake rate were derived from the EPA's Wildlife Exposures Factors

Handbook, while factors associated for the representative fish or the Catastomid species were derived from published literature. Next slide, please.

So in this slide, this is Table 5-4. It's an example of the calculations and the work to represent DIDP concentration from a variety of different sources for the screening level of tropic transfer analysis. The top column represents the CO use, the highest amount of sediment from point source calculator with PVC plastic compounding as the occupational exposure scenario. The next columns then represent the concentration ingested from sediment, concentration taken in from the mink from water intake, and finally the total, the fish concentration from consuming fishes that have that amount in their body from incidental or other sources. And then finally, the DIDP exposure for that mink in milligrams per kilogram by weight per day.

Now, in the lower portions of Figure 5-4, it represents the highest concentrations in industrialized ecosystems and aquatic areas that we know of around the world to represent high concentrations of DIDP in the sediment. I think this is very ecologically relevant. It is demonstrating what we know, what we have environmental monitoring for. And when we go across those formulas that I showed and demonstrate, you can see that both from the environmental monitoring on the lower portion of the slide as well as our COU, those modeled sediment concentrations, we do not approach the DIDP toxicity reference value of hundred twenty eight milligrams per kilogram per day. So it's just a representation. There are several components to this, but I think for the aquatic mammal as well as the other slides in here, we'll be able to see what we have observed with respect to projecting the modeled concentrations as well as environmentally relevant concentrations within sediment and soil. Next slide.

So for conclusions and key points with this, the results for the calculated dietary exposures of DIDP to mammals from those modeled concentrations within the relevant pathways, within the aquatic environment, within the terrestrial environment, indicate exposure concentrations below the toxicity reference value. The maximum concentrations of DIDP reported within the reasonably available literature were also used as a comparator and describe no intersection of exposure of DIDP with the calculated toxicity reference value from the screening level transfer analysis. In a similar way, the level transfer analysis for the terrestrial components, those earthworm to shrew from soil concentrations also demonstrate dietary exposure concentrations below that toxicity reference value.

It's really important to emphasize that these conservative approaches within both the environmental media modeling and the screening level trophic transfer analysis are likely over-representing DIDP's ability to transfer among the

trophic levels and this confidence that the risks will not be, or would not be, would not be underestimated. Next slide.

DR. GEORGE COBB: Right, I think that ends this portion of the, does that end this portion of the presentation or are we going back to Dr. Brennan?

DR. JENNIFER BRENNAN: Hi, this is Jennifer. No, we have probably seven more slides here and then that concludes the presentation.

DR. GEORGE COBB: All good.

DR. JENNIFER BRENNAN: So I'll go ahead and get going with this portion, which is our last slide. So this is the DINP environmental hazard overview, a summary of the environmental hazard characterization and then the information pertaining to the charge question for this portion. Next slide, please.

So there's a single charge question for the DINP environmental hazard. If you look at the diagram, the portion of the assessment that's relevant is highlighted in green, so that we're

talking about the environmental hazard assessment for DINP. Next slide.

So an overview of the DINP environmental hazard. Again, EPA was able to identify hazard data for algae, for earthworm, for aquatic invertebrates, and sediment invertebrates, and those data indicated no hazardous effects. Therefore, no hazard was observed for those taxa exposed to DINP. No hazard data were available for avian species or terrestrial plants exposed to DINP. Hazard data were available for fish. Several papers did indicate hazardous effects, but these effects were either not consistent between replicates or did not behave in a logical dose response dependent manner, or there were experimental design concerns with the study.

Therefore, no hazard threshold was identified in fish in exposures to DINP. So no hazard thresholds were established for the above taxa. EPA did establish a hazard threshold for terrestrial mammals based on ecologically relevant endpoints from animal toxicity data, both rat and

mouse laboratory data. And again, that was in lieu of not having reasonably available wildlife hazard data for DINP. Next slide, please.

Just an overview of DINP environmental hazard and other assessments. Both the European Union Risk Assessment for Dye Isonomal Phthalate and Environmental Canada Health Canada's State of the Science Report, Phthalate Substance Grouping, Wrong Chain Phthalate Esters, DIDP, and DINP both determined that DINP has low hazard potential to aquatic taxa with no adverse effects on survival, growth, development, or reproduction at concentrations at and beyond solubility of water. So again, very similar to the hazard characterization conclusions in the draft DINP environmental hazard technical support document for aquatic taxa. Next slide, please.

So now the information pertaining to charge question one. This charge question I want to note is identical to charge question 2A for DIDP. The difference is that we're asking it for DINP as well. So this is the methodology used to

establish the hazard threshold for terrestrial mammals. So DINP hazard threshold and terrestrial mammals was based on ecologically relevant endpoints from the animal toxicity data. These were rat and mouse laboratory studies, again in lieu of having wildlife hazard data for DINP. The hazard threshold is called the toxicity reference value TRV. Again, the TRV represents hazard across mammalian species such as mink and shrew, not just the rat and mouse data from which it were derived. And this derivation process for the TRV uses the ecological soil screening level guidance by EPA. This is known as ECOSSL guidance.

And the endpoints considered for the DINP TRV consisted of reproduction, growth, and mortality endpoints. The methodology used to derive the DINP TRV is the same as was explained for the DIDP TRV. Briefly, it's a comparison of low ALs in the data set to a geometric mean of the no ALs. In the case of the DINP TRV, the value was established as hundred thirty-nine make per king body weight per day of DINP. Next slide, please.

This is Figure 6-2 from the DINP draft environmental hazard technical support document. We saw this earlier for DIDP. This is the TRV flowchart. I'll step through very briefly the steps for deriving the DINP TRV. This followed the identical steps that the DIDP TRV followed.

So starting with step one, are there at least three toxicity values for two species for reproduction, growth, or mortality? In the case of the DINP data set, yes, there were. Step two, are there three or more no ALs in reproduction and growth? Yes. And so this leads us to step four, calculate the geometric mean of the no ALs for reproduction and growth, and then compare that geometric mean of the no ALs to the lowest bounded low AL for reproduction, growth, or mortality. In the case of DINP, there was a lower bounded low AL that was lower than the geometric mean of the no ALs. So the no arrow is followed to the yellow box, and the TRV is set as the highest bounded no AL below the lowest bounded low AL for

reproduction, growth, or mortality with each step refining the hazard threshold. Next slide, please.

We're looking at the data set for the DINP animal toxicity studies that contain ecologically relevant endpoints that were used in the TRV derivation. Again, we have our reproduction endpoints, growth endpoints, and survival endpoints, represented by the red, blue, and pink circles respectively. Open circles are indicating low ALs for an endpoint, and they're connected by lines to their respective no ALs.

Again, DINP had enough animal toxicity data with ecologically relevant endpoints that EPA limited the data set to bound no AL low AL pairs to further refine the hazard threshold. The black line with spanning reproduction and growth that have arrows at each end of the line represents the geometric mean of the no ALs across the reproduction and growth endpoints.

And if you look across the data set, there are low ALs, bounded low ALs that are falling below the geometric mean of the no ALs. So

then the TRV defaults to the highest bounded no AL, excuse me, highest bounded no AL below the lowest bounded low AL. And that highest bounded low AL is shown by the black circle with the red circle in the middle to refine the hazard threshold. And that TRV value again is 139 make per king body weight per day, DINP. Next slide, please.

Conclusion and key points. No hazard threshold were established for most taxa that we had data for due to no effects from DINP exposure. Again, EPA wants to note that there were inconsistencies in the fish hazard data from chronic exposures to DINP. And these inconsistencies resulted in no hazard threshold being established for fish. A single hazard threshold was established for DINP environmental hazard.

This was based on terrestrial animal toxicity references that had growth, reproductive, and mortality endpoints in rat and mice studies. The hazard threshold is described as the toxicity

reference value or TRV and is meant to be representative across terrestrial mammals, not just rats and mouse from which the data were derived. The no hazard data were reasonably available for avian species and terrestrial plants exposed to DINP. And just to note again, the DINP draft environmental exposure and draft environmental risk characterization documents will be released later this year for public comment. And that concludes the information pertaining to charge question one for the DINP environmental hazard technical support document. Next slide, please.

And this concludes the part four of the technical presentation. So thank you for your attention and review.

QUESTIONS FROM THE SACC ON EPA PRESENTATION

DR. GEORGE COBB: All right. Thank you, Dr. Brennan and Dr. Green for that presentation. We can go to questions now. And I

believe Dr. David had asked one earlier. So let's circle back to that. We can't.

DR. RAYMOND DAVID: Yes, thank you. Actually, the question pertains not only to slide number 96, but also to 116. And I was just struck by the number of studies. I mean, effect levels, no effect levels are always dependent on the dose levels that are selected. My experience is that when you have a number of these studies with different spread of dose levels, I thought it was common practice to use benchmark dose calculations. But you didn't seem to do that. Is there a reason you didn't do that?

DR. JENNIFER BRENNAN: Thank you for the question, Dr. David. So the TRV derivation process does not use benchmark dose process, but it uses a similar process in that it is refining the hazard threshold to be representative of the entire data set. So the first step is when you do calculate that geometric mean of the NOAEL s across reproduction and growth endpoints, which are typically considered to be more sensitive than

mortality endpoints, although you see in this data set that's not necessarily the case, that's typically where the TRV defaults to. But if you are showing hazardous effects or more sensitivity in certain endpoints that's below that geometric mean, the threshold then refines even further between that low AL that's below the geometric mean of the NOAEL and the NOAEL that's closest in value to that low AL.

DR. RAYMOND DAVID: Well, that's OK, but I mean, as I look at these studies on the left here, the RAT studies, and these are developmental studies, is that correct?

UNKNOWN MALE: Yes, they're repro studies.

DR. RAYMOND DAVID: So you've got four studies that have a nice spread and no effect levels that are above your line, and then one that falls below. And so, you know, stuff happens. And yet you've based your TRV apparently on that lowest value. Is that correct?

DR. JENNIFER BRENNAN: The TRV actually is not based on the lowest NOAEL. It's based on the NOAEL that is closest in value below the lowest low AL in the data set. So if you're looking at data point eight, that is where the TRV is established. We do have NOAEL s that are lower than that, but the goal for this method is to refine the hazard threshold instead of increasing the spread of where the hazard should be occurring.

Yeah, and Dr. David, part of the reason for that is that you're dealing with protecting multiple species and not simply a human, that human species were one species. So this is trying to protect across all taxa, if that's correct, Dr. Brennan. And so you have to account for that.

DR. RAYMOND DAVID: Well, don't you do that in the uncertainty factors? So, and again, this is the practice that had been developed to empirically determine to protect species that are

trying to be managed through these kinds of assessments.

UNKNOWN MALE: Okay. Thank you.

DR. RAYMOND DAVID: I should probably let an EPA answer these questions. I apologize, Dr. Brennan.

DR. JENNIFER BRENNAN: No, Dr. Cobb, that was fantastic. Thank you.

DR. GEORGE COBB: I see Dr. Chaisson has a question.

DR. CHRISTINA CHAISSON: Thank you. Yes, I actually have a couple and I'm really out of my wheelhouse here, so I hope you can put these together. I'd like to quickly read a couple of questions slash notes that I took and maybe EPA could address these all together. First of all, looking at the KOW and the KOC, and you concluded from that that the phthalates would go into the sediment, but given the KOW and KOC, wouldn't it be just as likely?

The phthalates would sort into things like aquatic eggs or the biota, not just

the soil, but just go into them directly. Related to that, it appears that the phthalates are clearly, apparently not particularly toxic. Is that because it's going through the animals or you made a comment I didn't understand.

It does not bioaccumulate, but somehow it's in there. I don't understand what that means. And also, does any of this relate to bivalves? So you've got things like the Jeesapeake oysters sucking an awful lot of stuff through them. I mean, what happens to animals like that that are taking in what could be, as I understand it, huge amounts of the water? And particularly if you have animals that are in. I mean, your example showed this really nice swimming pool kind of thing over top of sediment.

What about waters that are murky or swamps? How does that kind of thing fit into this? Now, I have to admit, what I'm going for here is try to take this lovely information that you have here and in my mind, try to determine if you are looking at human exposure. All of these lovely

things that people, particularly who are on subsistence diets, are going to be eating or people who live along the coastal regions. And I'm struggling to try to even get an indication as to whether this stuff just passes through these animals or whether it could be found in their tissues.

UNKNOWN MALE: Thank you. Yes, I think you raised. Thank you very much for that input. I think you raised some really good things. I want to point towards... There is a body of literature on the presence of DIDP and a number of phthalates within biota, within gooey ducks, within mussels, within spiny dogfish, etc. Those are McKinsey 2004. They're in Section 3.1 of the Environmental Exposure Technical Support Document. That's really important. There are lipid normalized and then wet weight reported values across the literature. There's also a thesis from the same research group that worked on this within British Columbia in an industrialized ecosystem up

there. So we do see this within tissues. I do report it. We note it.

One of the things that's important is that the McKinsey group has gone to great lengths with some of our leading scientists in bioaccumulation and trophic transfer, like on a global kind of folks, on trophic magnification factors. And those are also reported within Section 3.1. There's bioavailability. There's the intersection of physical chemical properties and the role of DIDP within suspended sediments. That's discussed in Section 3.2 in the same technical support document. And they really have looked at how a lot of those compounds are bound very tightly to those. And even within the animal, the transference of those are extremely limited compared to a lot of other compounds.

So again, 3.1 and 3.2 will answer a lot of those questions, hopefully. And I think that those are really revealing for me. They're really revealing for the team and all of us at EPA to help us with that. And that landscape and

literature is really important to this. So hopefully I helped with that answer. If there's a follow-up, let me know. But yeah, check out those sections and obviously I can contribute and help as much as possible with any other things.

DR. CHRISTINA CHAISSON: Can you spoil the ending of the movie for me and just tell me what the answer is? Does it go right through them or do you get significant any kind of accumulation or at least occurrence of it getting into the tissue?

EPA PRESENTER: No, it shows up in tissues, but it does not bioaccumulate. A lot of the comparisons with things that are bioaccumulating and magnifying, we're not seeing that. We see it in the body. It will be there, but it's not building. It's not growing and for example, trophic magnification factor for DIDP from a very well regarded study is 0.44, which, you know, when we think of one as building under one is not building, that makes me feel pretty good about it, not bioaccumulating. And then

obviously the things you saw in the screening level approaches really trying to ramp up all those conservative assumptions.

DR. CHRISTINA CHAISSON: And then what about bivalves and things like that?

EPA PRESENTER: Those were included in that trophic analysis by McKinsey. It's in section 3.1. They looked at phytoplankton, gooey ducks, mussels. They had a bird in there. They had a scooter. I didn't even know that was a name of a bird, but it is. They had a variety. They actually had herbivorous fishes and piscivorous fishes in there as well. They had pyphosids in there, I believe. So that's important.

DR. CHRISTINA CHAISSON: And they don't get very high levels in their tissues either?

EPA PRESENTER: They were seeing DIDP concentrations, but it was not building as you go from trophic level to trophic level.

DR. CHRISTINA CHAISSON: Okay. Thanks very much for that. Appreciate it.

EPA PRESENTER: Well, thank you. That was really good. Thanks.

DR. GEORGE COBB: So just to follow up. So I agree with what you're saying, Dr. Green, about the trophic transport and about not biomagnifying. I do want to make a point of clarification, and perhaps it's my perspective on this, but the McKinsey and Gobus studies in Vancouver are not in industrialized areas. They're in urban areas, but they're not in industrialized areas. And that is an important distinction. And if there's information to say otherwise, I'd be happy to hear it, but I looked at the maps, the satellite photos, and that's not an industrialized area.

EPA PRESENTER: I apologize for that. There is a Taiwan study that I got that sediment values were, which was industrialized. And you're absolutely correct. They refer to it as urbanized ecosystem. Is that correct?

DR. GEORGE COBB: Correct.

EPA PRESENTER: I apologize for that. I apologize for that.

DR. GEORGE COBB: We're all dealing with a lot of information here. Mary Ann, I'm sorry. Since you mentioned the study in Taiwan, I want to kind of follow up. Was that study included in the aquatic hazard assessment for invertebrates that was done?

EPA PRESENTER: So can you put the Taiwan, sorry, I got distracted for a second. The Taiwan study provided concentrations across the harbor for DIDP and sediment. They did not, if I recall correctly, have biota monitoring values in that study.

DR. GEORGE COBB: Correct. But you could use those in assessing hazards or risk to aquatic organisms based on toxicities from laboratory studies. I guess that's what I'm trying to get to.

EPA PRESENTER: Yes, and I ran those concentrations from that study in our screening level terrific transfer analysis.

DR. GEORGE COBB: Okay.

EPA PRESENTER: Thank you.

DR. GEORGE COBB: Dr. Ottinger.

Dr. MARY ANN OTTINGER: Cool conversation. Thank you. By the way, scoters are not at the top of the food chain. So they're not going to be that representative of biomagnification, just FYI. But that does bring me to the point that is there any potential for using egg embryo studies where they're administering many of these chemicals or even some of the plastics works that's coming out in birds showing uptake of lots of microplastics?

EPA PRESENTER: I thank you for that question. I don't think I can completely address that. I do know, however, when you look into the thesis work from the McKinsey Group McConnell, they did specifically look at dogfish embryos. And one of their components was DIDP across not only the dogfish, but the embryos. And as you know, the egg yolk associated with that really increased that value. Your question about microplastics is

noted. And I'd like to hear more. But yeah, thank you very much.

Dr. MARY ANN OTTINGER: A question about the mink. I think that's a fine choice. And I guess one of my questions would be from Steve Bercyan and Bob Ringer's work, they showed them to be exquisitely sensitive. So was that part of the rationale with choosing them?

EPA PRESENTER: The rationale for choosing the mink is predominantly that piscivorous diet. And maximizing the intake of the screening level intake of the fish into that. And then keep in mind that the TRV was representing the hazard value in the mink, not an actual mink hazard value study.

Dr. MARY ANN OTTINGER: Yeah, but part of that hazard or the risk, I guess, would be production of the lesions and other outcomes that Ringer and Bercyan and others saw with PCBs. So does that become incorporated into the model?

EPA PRESENTER: I'll transfer over to Dr. Brennan. Do you want to answer that?

DR. JENNIFER BRENNAN: Okay. Give me just a second.

DR. GEORGE COBB: Do we have Dr. Brennan?

DR. JENNIFER BRENNAN: There we are. Thank you. I think, Dr. Ringer, are you referring to the TRV derivation again? And whether that's representative of the hazard? So again, for DINP, it was laboratory rat and mouse data. They were ecologically relevant endpoints, such as for DINP, I think we had progeny weight, a lot of body weight, mortality, general reproductive. This is certainly an uncertainty in whether it picks up species-specific sensitivities, such as if mink are going to be more sensitive to a particular chemical than a mouse. This is what we're asking the SAC to weigh in on as well.

Dr. MARY ANN OTTINGER: One last question, hopefully it's very quick, which is for the DINP, the source, I assume, for eco exposure would be primarily through air release and then settling on water and land?

DR. JENNIFER BRENNAN: I could answer this too, but I'll let Dr. Green answer this portion because this is his portion of the presentation. Okay. Thank you.

DR. CHRISTOPHER GREEN: Hello. Hi again. So with DINP, much like DIDP in terms of physical chemical and fate parameters and some of that analysis that you saw presented earlier, really the surface water releases and then deposition of sediment is a big thing for that. That's a big one. The modeling for air releases to soil was conducted for DIDP and you can see it within the screen level terrific transfer. However, it pales in comparison to water release to sediment deposition. Okay. So similar. Thank you very much.

Dr. MARY ANN OTTINGER: Thank you very much.

DR. GEORGE COBB: So are there other questions from the committee?

DR. GEORGE COBB: Okay. So I have several questions. I'm going to try to consolidate

most of them. First thing I want to say is I really like slide 98, and it's a similar slide to the one that Dr. David asked about. And I think that could be very helpful in the overall hazard assessment document. I found it in the underlying data, but I didn't necessarily remember it in the main hazard document. So I think that's the TRV slide. I'm sorry. I must have mislabeled that. Perhaps. I may have mistyped that. Yeah. This family of slides, those images are really good and should be early in the documents where people can see them. They make this very... So this is a... Thank you for showing this and try to highlight this as best you can in the reports. I think it's helpful.

DR. CHRISTOPHER GREEN: It is included in our hazard TSDs, Dr. Cobb. Correct. But it's not in the body of the text that talks about the hazards as I understand it.

DR. GEORGE COBB: Yeah. That's the best point. I don't know how many people are going to dig that deep into the documents. A couple of

questions, and this goes directly to some of the toxicity data, and I think Dr. Brennan would be the person to answer this. There were toxic effects observed in the... I think it was Daphnia, and they were not used in the assessment, and neither the chronic nor the acute values were used. I understand what you're saying about the film, but that was only in one study, and regardless of how it happens, it's still toxicity. It's a toxic effect of the chemical. So I guess, first of all, why did you discard those values?

DR. JENNIFER BRENNAN: So maybe if we go to slide 100 or 101, that might help have something to look at for the hazard values you're talking about. For entrapment, EPA would not consider physical entrapment the same as chemically induced toxicity. And these values that the authors tested... and these values that the authors tested... I apologize. Next slide.

Perfect. So I think you're referring to the 21-day chronic value here with the entrapment values in Daphnia magna for DIDP DINP.

Yes, Daphnia magna did have immobilization or lethality in that study, but it was due to actually being physically trapped in a film of the chemical at the top because the authors had exceeded water solubility for both of those chemicals by a large degree. So for the purposes of chemically induced toxicity, EPA did not consider those hazard values for setting hazard thresholds.

DR. GEORGE COBB: But it does not matter how the toxicity occurs if the chemical is causing it. It does not matter if I drowned in the water or if it causes a toxic effect, it has still killed me. And this is the same thing with this. It does not matter how the toxicity occurs. It's a matter that it did occur. Now, are there environmental concentrations above this that have been measured in water for DIDP?

DR. JENNIFER BRENNAN: I'm going to turn the screen over here to... Well, we have two folks that could answer. One is Dr. Arashiro with the environmental media as far as the

concentrations, and then our senior science advisor, Dr. Eisenreich, could also weigh in here.

DR. KAREN EISENREICH: Yeah. Hi, this is Karen Eisenreich. I'm just wondering here if we're not getting actually into the charge questions, discussion on the charge questions a little bit. Maybe this should be discussed when we discuss the charge questions. That's more of a question here.

DR. GEORGE COBB: That's fine. Especially in the interest of time.

DR. KAREN EISENREICH: Yeah, I think that's where I'm going. I mean, this is definitely an interesting conversation, and I think there's things here that we can discuss. One thing that I would say just quickly is that one of the issues is when you're doing a laboratory study with these variable soluble compounds and you get that film on top, that usually doesn't mimic the environmental physical environment that you would potentially see those concentrations on, because they're often done in static conditions. And not

speaking directly on this particular study, but you often have static conditions that allow that film and your overwater solubility that allows that film to form.

And we generally don't see releases in the environment in that type of system where you're going to have a static system for our releases. But I do think that our exposure assessors, Michael, can potentially address this with the actual data and information that we have for our releases as well to specifically address this particular issue for this chemical. But in general, working with low soluble compounds in the laboratory just is very challenging, and it creates different physical conditions within that particular experiment that we just don't likely see in the environment.

DR. GEORGE COBB: Okay, well we can revisit this in the actual charge questions and not necessarily belabor this one any further. I do have one more question that I wanted to ask, and that's related to the concept of read across.

Was there any attempt made to do a read across analysis for toxicity of DIDP or DINP using other phthalates as was done with the, and I know you used DINP for DIDP and that was a near perfect match, but was there attempt to do anything like that for toxicities of fish or other things where the data were of limited availability or not available?

DR. KAREN EISENREICH: Yeah, thank you for the question, Dr. Cobb. So for comparing DIDP to other phthalates or even DINP for other phthalates, of the phthalates we're currently assessing right now, DIDP and DINP have fairly unique properties for being the most insoluble of the phthalates we're currently looking at for risk evaluations. And so in the read across screening methodology, which we are asking a charge question on for the SAC to apply on the methodology, when it reaches the physical, chemical, and environmental fate transport similarity, we have a fairly simple screening step by log KOW and log KOC and both DIDP and DINP met that screening

criteria for each other, but the other phthalates did not agree with either of those.

DR. GEORGE COBB: Okay, that explains it. Thank you.

DR. KAREN EISENREICH: You're welcome.

DR. GEORGE COBB: So are there other questions from the committee? Okay, seeing none, I want to ask our DFO, Alaa, do you think we should take a break now or should we continue? Do I have Alaa there? Yeah, but it's taking me a long time to unmute.

DR. ALAA KAMEL: Okay. Yeah, we could take a quick break like 10 minutes or so.

DR. GEORGE COBB: Yeah, let's take a 10 minute break and then we'll start back with the oral public comments and that'll give the media folks and the public commenters time to get things aligned. All right. So yeah, we'll see everybody back in at what time? 26 after the hour.

DR. ALAA KAMEL: All right.

DR. GEORGE COBB: All right. See everybody then.

PUBLIC ORAL COMMENTS

DR. GEORGE COBB: You, All right, welcome back and I see a lot do you have anything that you'd like to say before we start with the public comments?

DR. ALAA KAMEL: No, we can start the public comments.

DR. GEORGE COBB: All right, and I have a list of the commenters here. I hope I have the right order. If for some reason I do not I may turn it back over to Alaa to introduce our speakers. And these will be five minute presentations and then the committee can ask questions of the presenters after they're finished. So let's proceed to the first presenter and it's Amanda Berger from Talks Strategies.

MS. AMANDA BUERGER: Hi, thank you for the introduction. My name is Amanda and I'm a senior scientist at ToxStrategies. Today I will

present on the substantial body of evidence demonstrating DINP induced liver tumors and rodents are mediated by the paroxysome proliferator activated receptor alpha mode of action including lines of evidence and data that were not included in EPA's evaluation of the PPARα mode of action. Before I begin I want to note that this presentation was funded by Exxon mobile biomedical sciences. The comments and these expressed are my own next slide, please.

In the draft cancer human health hazard assessment for DINP, EPA evaluated the evidence for the posh related PPARα mode of action for liver tumors and rats and mice following DINP exposure. EPA concluded that there is strong evidence to support that the rodent liver tumors are mediated by the PPARα MLA. There are additional lines of evidence and data that further support that the DINP induced liver tumors are mediated by the PPARα MLA. That were not included by EPA and their evaluation of the rodent data for DINP next slide, please

The well-established PPARα MLA for formation of liver tumors includes four key events as shown in this figure. Which is adapted from the 2018 court net all publication. The lines of evidence supporting each key event are shown in the colored boxes. Lines of evidence presented in standard black text represent those that were considered by the EPA in the PPARα mode of action evaluation. The three lines of evidence shown in bold and green indicate lines of evidence that were inadvertently not assessed by EPA. But for which there are data to support the PPARα mode of action and rodents exposed to DINP.

Specifically regarding key event one EPA did not consider two associative events. Decreased circulating triglycerides and hepatocellular hypertrophy or cytoplasmic alterations. And regarding key event three EPA did not consider increased liver weight. These additional lines of evidence further support EPA's conclusion regarding the PPARα mode of action for DINP induced liver tumors and rodents. Next slide

This slide shows the number of additional study data sets for lines of evidence that EPA inadvertently did not assess. Which are highlighted in green as well as the number of additional study data sets for lines of evidence that were included in the PPARα mode of action evaluation by EPA which are shown in white. A total of 23 additional peer-reviewed and laboratory report rodent studies were identified for key about one and 17 studies were identified with data regarding increased liver weight and rodents for key event three.

Additionally there is an unpublished gene study that further supports the PPARα activation in rodents by DINP Which was submitted to the docket. The inclusion of these data further increases the strength of the evidence for key events one and three and therefore contributes to an increase in the strength of the evidence that DINP induced liver tumors are mediated by the PPARα mode of action in rodents. We've provided a reference list as a part of the submitted

materials which identifies all of the additional studies that were inadvertently not assessed by EPA. Next slide, please

This slide identifies the studies that contain the additional data pertinent to the lines of evidence for key events one and three. These additional rodent data sets come from both peer-reviewed studies and publicly available laboratory reports that were either not previously cited by the EPA in the mode of action evaluation for which there were ten studies. Or studies that were cited by the EPA within the mode of action evaluation for some lines of evidence. But were inadvertently not included for other lines of evidence for which they were not in studies. Next slide

In summary there are additional lines of evidence and study data not cited by the EPA in the PPARα mode of action evaluation that further support that the PPARα mode of action mediates DINP induced liver tumors and rodents. These lines of evidence include associative events

of decreased circulating triglycerides and hepatocellular hypertrophy for key event one and increased liver weight for key event three.

Further there are additional study data supporting key events one and three including 23 data sets from 17 studies that are pertinent to the associative events of key event one and 17 studies with rodent liver weight data pertinent to key event three. This larger evidence base further increases the confidence and EPA's conclusion that the DINP induced liver tumors and rodents are mediated by the PPARα mode of action.

I appreciate the opportunity to present these comments. Thank you

DR. GEORGE COBB: Thank you. Are there questions for the speaker I see a hand raised from the meeting contact, but I don't think that's real or for the speaker. Is the clock. So are there any other comments from this from the committee questions? Dr. Fenner Chris

Dr. Fenner Chris: Yes, and my question is did you find and any data that

describes better the differences in the receptor itself the species driven

MS. AMANDA BUERGER: There are data for mouse and human PPARα receptor activation, which I believe someone else has submitted comments on. But there are also comments we submitted on the docket that explain the differences in the sensitivity. Yeah,

DR. GEORGE COBB: Right if there are no other questions, thank you for your comment and we'll move to our next speaker which is Paul DeLeo from the American Chemical Chemistry Council

MR. PAUL DELEO: Yes, thanks. Good day. I'm Paul DeLeo the senior director of chemical management at the American Chemistry Council. Yeah, I'm just speaking. This is my I don't have slides per se. Appreciate the opportunity to provide our comments in the draft risk evaluation for the IDP in particular. I'll be speaking to the occupational exposure assessment and charge question 1d regarding the screening level approach and potential refinements.

ACC sponsored development of a framework for evaluating EPA's exposure assessment under TOSCO risk evaluations, which was submitted to the SAC during the peer review of the formaldehyde draft risk evaluation. Purpose of the framework is to provide a step ways stepwise procedure for the critical evaluation of exposure scenarios. Exposure assessment methods and individual exposure, exposure assessments performed by EPA and the TOSCO risk evaluations.

We applied the same framework to evaluate the exposure assessment portion of the DIDP risk evaluation. One of our consistent comments on the EPA risk evaluation process is that the agency needs to follow a tiered assessment approach consistent with agency guidance or other standard occupational exposure practices. In the case of DIDP, the draft risk evaluation we find that EPA used an approach similar to other risk evaluations where it used worst-case to assumptions to derive a bounding

estimate of occupational exposure for a condition of use.

Those include assumptions of no engineering controls, no personal protective equipment daily exposures for the entire day and use of data for surrogate conditions of use or surrogate chemical DINP that result in higher exposure estimates. There are a number of these bounding estimate assumptions that the SAC should consider. We bring to your attention the approach to potential exposure to chemical sorb to dust EPA used particles not otherwise regulated PNOR that is general dust data to estimate the range and respiratory fraction size distribution of dust considerations for a worker who may be exposed during operations involving DIDP.

EPA refined the respirable PNOR range using OSHA chemical exposure health database data sets. Which has unknown worker activity or sampling locations. The OSHA exposure monitoring data is intended to characterize exposure profiles for workers with the highest exposures and yields.

Statistically biased high estimates of mean and upper bound percentiles for the entire worker population.

According to EPA's 2019 guideline for exposure assessment a bounding estimate is an estimate of exposure that is higher than the highest anticipated exposure to an individual life stage group or population. Bounding estimates show that true exposures are not greater than the estimated exposure. Assessors often use bounding estimates during screening level assessments to eliminate exposure pathways of minor importance from further consideration. So that's on page 63 of the guideline exposure assessment.

So the use of bounding estimates is an appropriate part of a tiered assessment. However, those bounding assessments are not appropriate for conclusive assessment of unreasonable risk. Using a tiered approach refinement would occur when exposure-bounding estimates exceed the exposure benchmark. However in this risk evaluation unreasonable risk was

identified for only one of 47 conditions of use. As such the screening approach is appropriate for those COUs and only in the case where unreasonable risk is suspected. Additional for refinement is needed prior to making such a determination.

Regarding occupational exposure scenarios, we found them found them well organized and clearly mapped to the conditions of use in this risk evaluation. In addition, EPA followed its published hierarchy of data for occupational and consumer exposure information by prioritizing the use of monitoring data then model approaches and then other exposure and then other approaches if needed. However, we note that this approach is contrary to most tiered assessment approaches where the collection of monitoring data would be considered a higher tier approach.

Then we believe EPA should clarify the discrepancy between their data hierarchy and the guidance on exposure assessment. We commend EPA on the use of a flux based approach for estimating dermal exposure. We believe this is a

preferred approach rather than the dermal loading based approach found in many of the previous risk evaluations particularly given the highly conservative dermal loading assumptions that accompany EPA's use of that approach.

We encourage EPA to continue the use of the flux based approach for dermal exposure estimate. But reassured by the improvements in occupational exposure assessment approaches in this risk evaluation and urge the SAC to continue fostering further progress. Thank you. That's all I have

DR. GEORGE COBB: Thank you for that comment. Are there questions from the committee? Seeing none, we can move on. Next presenter, and that is Jennifer Foreman from the ACC high phthalates Panel.

MS. JENNIFER FOREMAN: Great. Thank you. my name is Jennifer Foreman I am a regulatory affairs advisor with ExxonMobil and we'll be presenting on behalf of the ACC high phthalate panel today. EPA has preliminarily selected the HD

of 12 mix per day based on decreased fetal testicular testosterone production. For assessing risk from acute and intermediate duration exposures to DINP. I would like to briefly highlight two areas that contribute to a possible overestimation of risk when relying on this HD. Next slide, please.

First is regarding the pod utilized this HD is based on the default BMD 5 response rate calculated by the national academies of science in the report published in 2017. While EPA does not have clear and fan guidance to assist in making judgments on the selection of response levels. EPA's BMD guidance reflects the principle of considering both statistical and biological significance of the response level selected.

In particular the BMD guidance states the ideal is to have a biological basis for the benchmark response for continuous data. There's little evidence to support a 5% change in testosterone production represents a biologically relevant response. Rather evidence supports a

reduction of at least 40% during the male programming window is required to induce effects associated with phthalate syndrome. A BMD 40% response rate was calculated by the national academies and is available for use by the EPA.

The biological basis of the 40% testosterone BMD in the national academy report is based on data and analysis published by how to shell and gray the gray study concluded a 57 to 72 percent Reduction in testosterone is needed to induce a 5 percent increase in any phthalate syndrome malformation.

The data for DINP are consistent with this high level of testosterone reduction needed to induce adverse outcomes. The few studies that have evaluated both testosterone and adverse outcomes report the low frequency low severity outcomes reported in the studies coincide with testosterone Reductions of greater than 60% of note chance and bias cannot be ruled out for the few spurious effects identified in these studies at those reduction levels.

Additionally one study detected a greater than 65% reduction in testosterone at doses of 750 mix per cake and no associated apical outcomes. Use of the five percent BMD 5 over the BMD 40 represents an order of magnitude difference in the HED used for assessing risk at these life stages. As such, we request the SAC advise the EPA to characterize these data and remaining uncertainty associated with relying on a biologically relevant testosterone response rate. Next slide, please

The second consideration of where risk may be overestimated is regarding life stage relevance. It is well established that effects associated with rat phthalate syndrome require exposure during a very limited window of gestational development referred to as the male programming window marked by the red star in the figure on the right side of the slide. Only exposure during the male programming window causes the spectrum of disorders associated with rat phthalate syndrome to manifest at birth and or

into adulthood. Whereas reduction of androgen outside of this window do not elicit rat phthalate syndrome. As such the HD and related mode of action for effects associated with rat phthalate syndrome indicates the relevant exposures for human health risk assessment are during a human male programming window equivalent, which is approximately eight to 14 weeks gestation.

Therefore the reduction in testosterone that serves as the basis of the acute and intermediate POD Is considered of relevance for assessing risk to fetal males thus relevant only for exposure to women of reproductive age. For DINP specifically, there is no evidence that exposure after the male programming window elicits any androgen dependent outcomes. Such as cryptorchidism or perturbed postnatal growth of reproductive organs to their pre-programmed size.

Finally, the use of the BMD5 response for acute exposures is also likely to be an overestimation of risk as applicability to acute exposures was supported by limited evidence.

That high doses of DBP can induce effects after a single or successive doses during the male programming window. The doses for these studies were almost two orders of magnitude higher than the BMD5 l calculated for DBP by the national academies. So 500 makes per gig per day in those studies versus the five percent response rate of at eight makes per gig per day.

In closing we propose that the evidence suggests uncertainty associated with the selected pod and life stages points to an overestimation of risk. And ask the SAC to comment on the scientific strengths and uncertainty for the presented refinements which could be applied to the EPA screening assessment, particularly where MOAs are close to the selected benchmark of 30. Thank you, appreciate letting me comment

DR. GEORGE COBB: Thank you for the comment. Are there questions from the, I see Dr. Ottinger has her hand

DR. MARY ANN OTTINGER: Thank you for a very interesting presentation. Were other

androgen dependent, prenatal and perinatal effects considered in terms of recommending any kind of lowering of the required you know of the requirement? Because the critical window you're talking about only refers to really anatomical and other HPG axis as well as thyroid and other axes are also dependent on androgen effects

MS. JENNIFER FOREMAN: So this is specific to looking at studies and results, which have occurred during that specific window. When you look at studies that occur outside in that window the doses are much higher and it's pretty much limited to some histopathological effects going to testes and that's generally with DVP or DEHP. You don't see those effects with DINP, so if you look at juvenile exposures or adult exposures it occurs at much higher doses than what's selected from the prenatal exposures and it also is not the full slate of effects which have been associated as rat phthalate syndrome, which are particular to that window of um exposure.

DR. GEORGE COBB: Thank you for the question and the answer, seeing no further questions. Thank you for that presentation and we can move on to our next presenter and that's will be Suzanne Hartigan from the American Chemistry Council. I think you're muted if you are talking

DR. SUZANNE HARTIGAN: Apologize unmuting. I'm Suzanne Hartigan with the American Chemistry Council and I will be presenting to you today on the uncertainties of the selected human equivalent doses for DINP and consider heart and

DR. GEORGE COBB: Dr. Hartigan can you speak up a little you're a little bit Low volume there.

DR. SUZANNE HARTIGAN: Apologies hold this closer. Can you hear me now?

DR. GEORGE COBB: Better

DR. SUZANNE HARTIGAN: Okay, great. Thanks, you can go to the next slide

So in the draft non-cancer human health hazard assessment for DINP EPA developed human equivalent doses based on alimetric body

weight scaling to the three-quarter power. The guidance EPA followed for HED derivation and selection of default UFAS for the benchmark MOA states that when a default HED approach is used in the absence of additional data informing consideration of interspecies differences a residual default interspecies uncertainty factor of three remains. Additional guidance from EPA was published in 2014, which outlines considerations for deviating from default values titled guidance for applying quantitative data to develop data derived extrapolation factors for interspecies and interspecies extrapolation.

Specifically this guidance highlights consideration of human relevance for informing the interspecies uncertainty factor such that the residual uncertainty of three may be modified based on available data. The guidance states the default uncertainty factor value is applied unless it can be concluded that the test species is equally or more susceptible than humans. We believe there are sufficient data to

conclude that the test species is more susceptible than humans for the endpoints used as the basis for the derived DINP HEDS. Next slide, please

EPA's proposal is to use a point of departure for decreased fetal testicular testosterone Production to characterize risk from exposure to DINP for acute and intermediate exposure scenarios. As summarized in the report in 2017 from the national academies the linkage between phthalate exposure decreased testosterone and phenotypic changes across species is uncertain.

There are differences in the reported responses of rat, mouse, non-human primate, and human fetal testes. Especially with regard to testosterone suppression in particular the data qualitatively indicate that human testes are less sensitive to the effects of phthalates than the rat testes. Multiple studies using human fetal testes implanted into an animal host to demonstrate human fetal testes are insensitive to the anti-steroid eugenic effects of DBP. The human

xenograft model was tested to determine if it was sensitive enough to detect compounds known to decrease testosterone in humans. And was able to identify impacts with a positive control compound while seeing no impacts due to exposure to DBP.

DBP is a phthalate consistently shown to decrease testosterone in rats the test species for the HED. EPA can use this data to conclude the test species is more sensitive than humans for the endpoint used for the selected Point of departure and justify the use of a one for the remaining UFA when calculating the benchmark MOA. Next slide

EPA's proposal is to use a point of departure based on liver toxicity to estimate non-cancer risks from oral exposure to DINP for chronic durations of exposure. Liver toxicity in the key study was characterized by increased liver weight increased serum enzymes

And histopathological findings for example focal necrosis and spongiosis hepatis. All of these endpoints except for spongiosis hepatis

occur as a result of PPARα activation and are either key events are associated events of mode of action. There is no human correlate for spongiosis hepatis. Data from ability et al looking at species differences in PPARα receptor activation have demonstrated. There's approximately a five-fold difference in sensitivity of the human receptor to activation by DINP.

EPA can use this data to conclude the test species is more sensitive than humans for the endpoint used for the selected point of departure and justify the use of one for the remaining UFA when calculating the benchmark MOA. Additionally, there is secondary high quality study that provides a no effect level of 88 that is between the no effect level of 15 and the effect level of 152 per day in the key study. This is a greater than three-fold difference in viable points of departure that could have been selected by EPA which provides EPA with additional confidence or reduction in the benchmark MOA would not be underestimating risk. The last slide has

the references associated with this talk for your information and I thank you for the opportunity to provide feedback.

DR. GEORGE COBB: Thank you for your presentation, are there questions from the committee? If there are none, thank you again and we can move on to our next presentation. My list has Eileen Conneely again from the American Chemistry Council

DR. RAYMOND DAVID: I think she was going to be a backup for Suzanne. So we can move on

DR. GEORGE COBB: I understand now what that meant so the next presenter then will be Thomas Hmiel, apologies.

THOMAS HMIEL: That's okay. And based on that I'm assuming that my audio is adequate that you can hear me. Thank you for the opportunity to present today. My name is Thomas Hmiel. I am director regulatory affairs for Teknor Apex company. Teknor Apex is one of the companies that was party, requesting the manufacturer's

review of DINP and also our primary businesses as a custom compound or plastics including PVC. My comments today are on behalf of the ACC higher phthalates panel and reflect information that the panel gathered in discussing, the conditions of use for PVC compounding with downstream users and they also reflect information that was submitted to the docket as part of the higher phthalates panel of comments. Could I have the next slide, please?

This slide, to orient you it provides an overview of the , a generic overview of the PVC compounding of the process. The comments that I'm making it are really directed more towards the central tendency. And some of the assumptions that were made with regards to the PVC compounding condition of use.

The hexagons represent a line with the numbered bullets below for the first part when you're manufacturing PVC compounds you initially mix all of the dry ingredients including the PVC resin before adding the plasticizer to the blender

as such when you have dust monitoring issues in an occupational exposure setting the dust that typically is involved contains no plasticizer. When the plasticizer is added, EPA is assumed that the material will be handled in drums. However, DINP and DIDP are both commodity plasticizers and almost all situations they're going to be handled in bulk and pumped into the blender once the lid has been closed. So any exposures to dust that would occur from the initial ads would not contain DIDP or DINP. And once that addition to the blender has been initiated the operator will typically move to another job and there really would be no exposures at that time.

Once the blending is completed, we move on to hexagon number three. The blending vessel or the contents of the vessel will be transferred into a feed hopper. So you may there would not be any exposures at that point to the worker because there's no contact that is that is necessary at that stage. Moving on to the extrusion process and um item number four. The

extruders are equipped with vapor removal and vapor capture devices because there may be volatiles that are emitted during the extrusion process. The hoods or vents are generally vented outside and are subject to clean air act permitting requirements. Those requirements would be dependent upon the size of the facility and they could be subject to title five requirements.

But from a worker exposure standpoint, you are not going to see the potential for dust exposures from that point on through the process including during packaging because any aerosols or any emissions would be drawn away from the worker and they wouldn't necessarily come back into the occupational environment. Finally for on this slide when we're looking at producing compounds what you will do is schedule them in campaigns so that there is not cleaning between batches, this is a batch operation and so what you will try to do is minimize the number of cleaning events that you will have by just rerunning the

next material over it and again reducing dermal exposures. Can I have the last slide, please?

So this slide summarizes the conclusions that we are the concerns that we've raised from this from the condition of use. The facilities in the compounding industry generally operate on five day a week 24 hour a day schedule and not 365 days a year as indicated in the COU. The batches are the process is batch in nature. So you're not going to have exposure for more than eight hours per shift. And the exposure to dust does occur prior to plasticizer admission. Orthothalates are also only a portion of the plasticizers used in the flexible PVC compounding world.

We're looking at anywhere from a half a percent to 80 percent and it's dependent upon facility in the end use market. So that that we see a lot of variability in that and even where DIDP and DINP are used. It's typically less than 15 minutes per batch and there is a typo on that it should say 15 minutes per batch. Where the

material is transferred from the tank into the blender and then finally if we go downstream of the blending process the exposures are assumed to be minimal. There is some limited occupational monitoring data on it, but not a whole lot. But generally it's about in order of magnitude lower than what we see in the blending area and I apologize for running over and appreciate the opportunity to submit these comments.

DR. GEORGE COBB: All right, thank you for your comment, are the questions from the committee? I actually have one and it's based on your extruders and the exhaust you mentioned the exhaust might be subject to different rules and I wonder if you can speak to what those rules might be for instance are they heavily filtered? Those types of things in that exhaust for the extruders.

THOMAS HMIEL: So the requirements would be dependent upon the size of the facility and the emissions under the clean air act if you admit a large enough quantity of pollutants you'd be subject to title five operating permits and

also pollution control devices. Generally what you would be looking at would be particulate matter. So you would generally have that screen through a dust collector. However, you have to be very careful in your material selection because PVC if you heat it up too much it involve HCl. So generally you'd have to have some type of acid gas. The fabric would have to be resistant to any acids that you would get through but that would be the standard. A smaller facility that would be the emissions would be low, might be some object to lesser requirements for control. On all of our events off of our processes where our facilities are located, but I can't speak to every facility that would be in that in the industry.

DR. GEORGE COBB: Certainly I see a question from Dr. David.

DR. RAYMOND DAVID: Hi, just a question about the layout of the process of compounding and that is as I understand for Teknor Apex our representative is that for other manufacturers, do you know?

THOMAS HMIEL: The information that we gathered the panel surveyed some other manufacturers and so the overall process where you would bring the resin and the plasticizer together in a blending vessel and then transfer that to the extruder is was consistent with the companies that we surveyed. I can't speak to say a plastisol process that could be more of a continuous process. But on the compounding side we're in the end. We're making pellets. It is a batch nature and it's fairly standard processing across the industry to my knowledge.

DR. RAYMOND DAVID: And that would include the engineering controls?

THOMAS HMIEL: Yes, yeah, because if with the particularly off the extruder because as I mentioned in the last question you have the possibility of evolving HCl from if the PVC starts to degrade so the recommended practice is to pull the vapors away from the breathing zone in the in the working environment and get that off out of the facility

DR. RAYMOND DAVID: Thank you

DR. GEORGE COBB: Thank you for that presentation. If there are no further questions we can move on to our next speaker and I have Rashmi Joglekar, is that right on the talk it next.

MR. RASHMI JOGLEKAR: Yes. Thank you so much. Good afternoon. I'm Rashmi Joglekar and the Associate Director of science policy and engagement at the UCSF Program on Reproductive Health and the Environment. The DIDP draft risk evaluation and the DINP draft hazard assessment failed to incorporate the best available science. And make a number of scientifically unsupported assumptions that if adopted will result in acceptance of serious risks to human health and set a dangerous precedent for future task risk evaluations. We submitted detailed comments in response to both documents and I encourage you to read those. Today I'll just be highlighting our main concerns that we urge this act to take into consideration.

First EPA has failed to identify and evaluate relevant health effect studies for DIDP and DINP in a manner that's consistent with the best available science. For example both assessments inappropriately excluded all human epidemiological studies from dose response assessment. And relied on systematic review methods that lack transparency and inappropriately excluded toxicity studies without scientific justification. For both DIDP and DINP epi studies published after 2019 were only considered if they were submitted to the EPA docket. Toxicological studies published after 2019 were not considered at all. These practices are inconsistent with the best available science. Both the NAS and the EPA SAC have recommended systematic review methods. That require a comprehensive and transparent review and EPA has still not implemented these recommendations

Second EPA's hazard assessments for both chemicals are inconsistent with the best available science and lead to a serious

underestimation of risk. EPA violated its own guidance and failed to apply benchmark dose modeling to derive non-cancer points of departure. Leaving uncertainty whether the most sensitive endpoints were selected. EPA also failed to rely on best available scientific methods to quantify non-cancer risks for both chemicals leading to serious underestimations of risk. We apply methods developed by the World Health Organization to quantify the non-cancer risk of developmental toxicity from chronic DIDP exposure and found that EPA's current MOA approach.

Consider exposures acceptable that result in an upper bound risk level of one in one hundred. A risk level ten thousand times higher than the one in one million target risk level that EPA typically applies for protection of personogenic risks. Similarly for non-cancer risk of liver toxicity from chronic DINP exposure. We found that the MOA approach. Consider exposures acceptable that result in an upper bound risk of

one in two hundred a risk level. Five thousand times higher than that target risk level.

Third there are serious inconsistencies between EPA's risk estimates and EPA's conclusions regarding unreasonable risk for DIDP. Not only did EPA rely on the flawed MOA risk characterization approach, but they also downplayed and discounted risks that were identified using this flawed approach. EPA used primarily central tendency exposure estimates for workers and consumers and its unreasonable risk determination. Disregarding unreasonable risks of non-cancer effects for 50% of the human population including potentially exposed or susceptible subpopulations. For example in the DIDP draft risk evaluation EPA found that only one occupational condition of use presented unreasonable risk to human health despite nine other COU's having MOA's less than the benchmark MOA.

Results that would have previously translated into a determination that all 10 occupational co use contributed to unreasonable

risk. Instead, EPA dismissed these risks without scientifically supported rationale. It's concerning that EPA disregarded high-end risk estimates at the final stages of risk determination. Only after finding that these risks are high an approach that has only been previously employed in a task of formaldehyde draft risk evaluation. In doing so EPA continues to set a dangerous precedent that even when EPA calculates risk it can disregard that risk without scientific justification.

Finally EPA does not consider real world exposures and risks for example EPA failed to consider exposures from non-taxa uses. For DIDP and DINP including exposures through food packaging and personal care products. Given that food is the primary route of exposure to both chemicals in children and adults EPA will understate the risks to the general population. From the taxa uses of these chemicals if it does not take these background exposures into account. Now EPA also failed to adequately identify

potentially exposed or susceptible. Sub-populations and consider factors that increase susceptibility to harm. The best available science shows that individuals are more susceptible to harm from chemical exposures due to both intrinsic factors like life stage or underlying disease and extrinsic factors like psychosocial stress from racial injustice.

EPA failed to adequately consider any of these susceptibility factors in the draft risk evaluation ignoring the best available science and leaving communities at continued risk of harm from DIDP exposure. Improvements to its assessments for both chemicals can be made today using existing scientific methods to better protect human health. And we encourage you to read our detailed comments to refer to these recommendations. Thank you for your time

DR. GEORGE COBB: Thank you for your comment, are there questions from the committee? So, I'll just say I found your comments

very interesting and we will certainly be considering them carefully. So thank you very much

MR. RASHMI JOGLEKAR: Great. Thanks so much

DR. GEORGE COBB: So then we can move on to our next speaker Kelly Lester from Earthjustice.

MS. KELLY LESTER: Hi, thank you for the opportunity to speak today. My name is Kelly Lester. I'm an attorney with Earthjustice. Earthjustice and other organizations including environmental defense fund who you'll hear from shortly. Submitted written comments on the draft DIDP risk evaluation and draft DINP hazard assessment. Today, I want to highlight two points we made in our comments both of which were just touched on by Dr. Joe Glicker regarding how EPA inappropriately derived and interpreted its risk estimates in the draft DIDP risk evaluation. Essentially EPA impermissibly concluded that risks that exceed its own risk benchmark do not contribute to unreasonable risk. And even the

risks that it calculated were understated because EPA failed to consider relevant exposures.

So first in deciding whether various conditions of use which I'll call CO use of DIDP contribute to unreasonable risk. EPA interpreted its risk estimates in a manner that is inconsistent with its past practice and is not justified. EPA calculated non-cancer risks to both workers and consumers that exceed EPA's long-standing unreasonable risk benchmark. That is it calculated MOA's for multiple exposure scenarios that are below the benchmark MOA. But nonetheless concluded that the relevant co use do not contribute to unreasonable risk. As one example EPA calculated risks to workers from high-end exposures associated with multiple co use that exceed EPA's risk benchmark. But instead of finding that those co use contribute to DIDP's unreasonable risks

EPA asserted that the co use at issue are best represented by central tendency exposures which did not generate risks exceeding

EPA's benchmark. That's not only contrary to EPA's past practice of making risk determinations based on high-end exposures. But it also violates taxa which requires EPA to consider the risks to those who face higher than average exposures to a chemical. And EPA failed to rationally explain why the co use at issue are better represented by central tendency exposures.

As another example EPA calculated risks to infants from exposure to DIDP. And wallpaper that exceed EPA's benchmarks, but it nevertheless determined that this exposure scenario does not contribute to unreasonable risk. It attempted to justify its decision by casting as overly conservative its exposure assumptions. Including the entirely realistic assumption that some infants stay home all day. Here too EPA's conclusion is not rationally supported and is contrary to taxa's mandate to address risk to individuals who experience above average exposures.

Second EPA underestimated DIDP's risks because EPA did not consider all relevant exposures. I'll highlight three areas where EPA failed to do so, but there are others identified in the comments that we submitted to the docket. So one, EPA failed to consider all relevant exposure routes for consumers. For example EPA only assessed exposures from ingestion of dust for DIDP containing articles that EPA characterized as contributing to DIDP dust concentrations significantly because those articles have a large surface area. This approach violates taxa, which requires EPA to consider all DIDP exposures

It also rationally assumes that an article surface area is the only factor that determines its contribution to DIDP dust concentrations rather than for example how an article is used and how much DIDP it contains. And EPA did not consider dermal exposures that are reasonably foreseen such as from adults handling children's toys or toddlers touching a shower curtain.

Second, two EPA failed to aggregate exposures to workers and to consumers across conditions of use that are reasonably foreseen to occur in combination as it must do under taxa. EPA said it did not consider total exposures associated with multiple co use because it supposedly did not find any evidence to support such an aggregate analysis. But it's foreseeable that individuals will be exposed to DIDP from for example both wallpaper and shower curtains in their homes and that workers exposed to DIDP on the job will also be exposed from products in their homes. And authorities such as the CPSC chap have developed scenario-based exposure assessments for DIDP that account for aggregate exposures for multiple conditions of use.

And three EPA did not account for background exposures from so-called non-taxa uses such as food contact materials and cosmetics. Instead proceeding as if those exposure sources do not exist and do not contribute to people's overall DIDP body burden. This is contrary to

taxa's mandates including its directive to conduct risk evaluations in accordance with the best available science. That compel consideration of these background exposures. In order to fully account for the risks presented by DIDP, EPA must consider how all sources of exposure to this chemical contribute to overall risk. And exposure faced by individuals including and especially potentially exposed in susceptible subpopulations. EPA must correct these errors in the final DIDP risk evaluation so that it accounts for all relevant DIDP exposures. And appropriately considers how those exposures contribute to risk. Thank you for your time

DR. GEORGE COBB: Thank you for your presentation, are there questions from the committee? All right, seeing none, thank you again for your presentation and we can move to our next speaker. I have Silvia Malberti on my list

MS. SILVIA MABERTI: Thank you, good afternoon, my name is Silvia Maberti and I am a senior exposure scientist at ExxonMobil Biomedical

Sciences. Today, I will be discussing comments submitted to the docket by the ACC high-end tireless panel

I thank you for the opportunity to provide the EPA with comments regarding the transfer escalation for the DIDP. In particular, I will be speaking to the consumer exposure assessment methodology and charge question 1a regarding the screening level approach and potential refinements. As stated in slide one or next one EPA used its own consumer exposure model. Developed to estimate human exposures from diverse consumer products through various pathways. The model uses many default parameters or calculates them using basic physical chemical properties such as vapor pressure. The combination of these conservative assumptions tends to represent worst-case scenarios, which can yield a bounding estimate. In other words more than a high-end estimate for a plausible distribution of exposures. This is a streamlined approach to screen out pathways that do not present

unreasonable risk. Even though the predicted exposures might not be well physically possible.

In general, EPA's exposure assessment guidelines require that tiered approach for refinement is required. To a certain exposures, especially when using a bounding estimate. However, since unreasonable risk was not determined for any of these conditions of use. This screening approach is sufficient and no additional refinement would be needed. Nevertheless if these estimates of exposures were to be used for other purposes like a cumulative risk assessment. Additional refinements would be needed. Slide two, next slide.

I present some recommendations for refinements with regards to inhalation exposures. EPA could consider some recent studies demonstrating the low concentration of DIDP and even DINP in the gas space. Such as by et al 2024 or et al in 2018. For DIDP and similar higher molecular weight plasticizers the concentration in the air does not seem to follow the linear

relationship of concentration and vapor pressure as utilized in the CEM model, which might explain the overestimation of the predicted inhalation exposures.

With regards to dust ingestion EPA estimated DIDP exposure by aggregating modeled mouthing suspended dust ingestion and subtle dust ingestion. They acknowledge that the relative contributions for it, interested source will differ among life stages. But this approach yields an unreasonably high dust ingestion rate. This is shown in table 4.8 where the modeled exposures are much higher than the monitored exposures. This indicates that the modeling approach views is conservative and fit for purpose for screening. But would likely need to be revisited for a refine if a refinement is pursued as EPA anticipates. But for the refinement EPA could consider comparing these modeling approaches with the dust ex modeling tool from RIBM. Although the DIDP physical chemical properties might fall outside of this domain. This is useful also for other values.

Additionally EPA could investigate the use of their risk assessment identification and ranking indoor and consumer exposure model or radar eyes described by Li et al in 2008. It provides a multimedia modeling approach based upon a function that predicts indoor dust concentrations of plasticizers and other chemicals. As a benchmark exercise, EPA also considered the enhanced biomonitoring data to aid in estimated exposure to solids from all pathways taxa and not taxa uses. Although the biomonitoring data may like contextual information, on what consumer products an individual might have to use contact with and national biomonitoring data would capture widespread uses with everyday contact. This data could also be used to validate model exposures from a single source in widespread views. So the references mentioning these comments are also provided in the recontained document and they're submitted to the docket. Thanks for your time.

DR. GEORGE COBB: Thank you for the presentation, are there questions?

DR. CHRISTINE CHAISSON: Yes, this is Dr. Chaisson. I have a question. I couldn't find my hand thing. So I'm sorry

DR. GEORGE COBB: Okay, don't worry go ahead.

DR. CHRISTINE CHAISSON: Do you have an estimate of how? If we use the rhythms dust modeling tool. And if we use NHANES biomonitoring, can you do you have some kind of estimates to how much of a change that would actually make in the exposure? Assessments of equivalent?

MS. SILVIA MABERTI: Well, I did run them. Actually I didn't present them here because it is submitted to the docket and it would take a long time. For air, we're talking an estimate that would be at least three orders of magnitude lower, and for dust, it's about two orders of magnitude lower. I'm happy to share my estimates. I use the EPA inputs and I use the dust sites model for that. However with the DIDP as I mentioned

earlier. Because of the KOA being outside of the of the model parameters. I had to use a lower KOA which would over predict them the exposure.

DR. CHRISTINE CHAISSON: It might be helpful if you provided that calculation or some descriptions of the calculations

MS. SILVIA MABERTI: Okay. Full disclosure, they have not been peer reviewed, but I'm more than happy to share them, and from the MAYA monitoring data, my colleague Wahyan will be presenting in a few minutes.

DR. CHRISTINE CHAISSON: So you'll see that. so were you using the. What were what were the factors that you did had the greatest impact on the differences in the answers because the DustEx modeling tool has some very different approaches than CEM. So in your opinion what were the driving factors that could get three orders or two orders of magnitude difference for the dust? Do you have a data any guess on that?

MS. SILVIA MABERTI: I'm not an expert in the calculations per se but definitely

the KOA the way the KOA is used and estimated but and that drives the estimation of the concentration of saturation in air will then drive super high concentrations in air and if you compare the predicted exposures the predicted concentrations in air. I use in the CEM I used I compared the EHP the DINP and DIDP. And oddly enough the concentrations the predicted concentrations in there were six times greater than the prediction concentrations predict the concentrations in from DEHP Which makes no sense because DEHP is more volatile. And if you see all of the literature the concentrations in of DEHP are much greater than DINP and DIDP. So it's definitely the way the concentration of saturation is as measured and it's because of that linear relationship between concentration and vapor pressure, I believe.

DR. CHRISTINA CHAISSON: Thank you very much very helpful.

DR. GEORGE COBB: Other questions. I actually have one about you were talking about

the vapor concentrations, how does the approach that you were using or include aerosols rather than actual vapors in that context.

MS. SILVIA MALBERTI: So I do not believe that the CEM or the DustEx model would use aerosols in the way I'm an industrial hygienist. So the way I define aerosols is very particular. And so I would think that a substance is not even it's beyond semi-volatile, right? So especially these higher molecular weight ballots. They're like very barely volatile so you wouldn't expect having an aerosol, but definitely maybe some migration and then adsorption into surfaces or into dust that has been all hypothesized and measured. Dr. Li who's in amongst you guys has done some of that and Dr. Li. Many others who have done those measurements for sure, so I wouldn't expect aerosols. By themselves I would expect if it's volatilizes it would immediately deposit.

DR. GEORGE COBB: Thank you for answering our questions and thank you for that

presentation and now we'll move to our next speaker who is Hua Qian.

DR. HUA QJAN: Yes, Hi everyone, this is Hua Qian. I'm exposure scientist with ExxonMobile Biomedical Science. I'm here to present exposure estimates and risk determinations based on enhanced by monitoring date for benchmarking EPA exposure modeling. EPA has preliminary concluded DIDP process on reasonable risk based on one condition of use. Following a screen level assessment that includes the multiple areas of conservativeness. While this is appropriate in a screen level assessment EPA should further refine their assumptions if they're going to determine unreasonable risk. So we recommend EPA use enhance by monitoring date as a bonding exposure estimates. For condition of use in the margin of exposure estimation because it represents exposure from both taxa and non-taxa exposure sources. Next slide, please

The CDC has been collecting the urine metabolized date for DINP and the DIDP since

2005 and 2006 cycle. And with the 2017 and 18 being the most recent data cycle available for phallids. Hence is designed to provide the results representative to the U.S. general population and subpopulation. And by considering all the potential exposure sources through all relevant exposure pathways. And from the graph there you can see the total exposure levels to DIDP and DINP have been decreasing since their peak in 2011 and 12, and we just showed the change of the DINP exposure level over time for the DINP just as example here and the 2017 and 18 this cycle can represent exposure levels today. And the 2011 and 12 can be used as the high end exposure bonding, and then there are 95 percentile. And can be a benchmark highly exposed individuals due to taxa and or non-taxa sources. Next slide, please.

On this slide we outline daily intake levels calculated for the general populations. At the different life stages based on two separate methodologies. The value depicted for the 50th percentile so you can look at the top two

lines in the table. And are calculated using linear interpolation following the standard methods, and the value depicted as the median and its 95th up bound value are from a publication by US EPA center for computational toxicology and exposure. Office research and the development so the paper characterized the chemical exposure trends from Anhang's urinary bimonthine data by Sinterfield in 2024. And if you're focusing on the blue line in the table, you can see exposure levels based on the linear extrapolation methods about order of magnitude more conservative than those generated by the Bayesian methodology from the EPA's paper. Next one, please

Here we combine the exposure database on the linear interpolation methods the one I just mentioned before. It's more conservative than the EPA's methodology for the most recent Anhang cycle 2017 as well as the 2011, 2012 as this cycle represent peak exposure to DMP and the DIDP which has been decreasing since then we propose the peak levels from 2011 and 12 can be

used as the upper bound estimation for individuals that include those exposure taxa condition of uses. Next one

This table shows the margin of exposure for both DINP and the DIDP for the two survey cycles and for US populations and there are different life stages. Risk estimates based on the high end exposure levels like 95th percentile are generally intend to cover individuals with sentinel exposure levels where risk estimates at the 50 percentile value exposure are generally presented for average or typical exposure level. In the table you can see the aggregate exposure to all sources both taxa and non-taxa yield the margin of exposure above the benchmark value of 30 established by EPA at both today's exposure level and the peak exposure levels.

When benchmark against EPA's exposed estimates. This value should give EPA confidence. That realistic exposure and high-end exposure to both DINP and the DIDP from all sources do not

present unreasonable risk. Thank you for the opportunity to provide comments today.

DR. GEORGE COBB: Thank you other questions for Dr. Qjan. If not, thank you very much we'll move to our next speaker

DR. RAYMOND DAVID: Dr. Cobb, sorry to interrupt.

DR. GEORGE COBB: I see you, that's okay.

DR. RAYMOND DAVID: Hey, it took me a minute to find the button. I do have a quick question and two short questions just to put that conversation about NHANES data in context. First my understanding is that production volume of DIDP has actually been increasing since that last NHANES data cycle so that exposure trends may be up again. So I'll pause there if you have any response to that.

DR. HUA QJAN: Yeah, I think the latest NHANES survey cycle available for families in 2017 and 18. So that's the latest information we can. So if you are thinking about the recent

years like you know since pandemic and that it may not be available yet for us to make any of the observational comments on that.

DR. RAYMOND DAVID: Right. Thank you and then second question has to do with the metabolites of DINP and DIDP that are represented in the NHANES analyte list and so just when we back calculate to get to do the reverse dosimetry to figure out what the dust or total exposures were sorry total exposures. If we're not looking at every metabolite then there has to be a correction for that. So just wondering with the method with the data that you presented how that was done.

DR. HUA QIAN: I think for the linear tribulation, we're basically considering the metabolites which coming from the parent compound and also considering the urinary excretion rate and the cleaning level and the molecular weight for both the parent and the metabolites to do the back calculation. Then the reason we're comparing with the EPA's Bayesian

approach just to benchmark see. Because they do the whole literature mining to see the creator. They call the parent chemical and metabolites map. So by mining all the public match literature, so it should be more comprehensive. Then so the level from our approach is higher than the what has been published by the EPA using the Bayesian approach.

DR. RAYMOND DAVID: Okay, that's helpful, thank. And also sorry just add to the previous question you have regarding the reason to you know production of volume and but like when we see the pattern at least for the last couple cycles, we see actually 2011 and 12 actually reach to the high level concentration and it goes down. So that's why kind of we using 2011 and 12 data to benchmark or even the 95th percentile for the cycle to represent a high exposure level.

DR. HUA QIAN: So, okay, and we don't know then how 2011 12 sort of production volumes of DIDP compared to say the last couple of years. Jack thanks for the question.

DR. GEORGE COBB: Dr. Chaisson.

DR. CHRISTINA CHAISSON: Yes they have two questions. What if the production volume goes up. I'm going to make an assumption here and please, I'm asking you to correct it or to elaborate on it. Even if a production volume goes up for this kind of chemical that's used in conjunction with different kinds of polymers. Would it automatically mean that the exposure or the amount that was available to pick up by humans, would necessarily also be higher or would the amount that was biologically available be highly influenced by the type of polymer or the type of use of the combination and related to that question I saw reference to phthalates being used in fracking. Can you speak to that? Thank you

DR. HUA QIAN: Let me try to answer the first question first. I think the second question is beyond my knowledge scope or my expertise to answer and so I think the first question is not necessary depending on the use of the phthalates. You're making right the increase of the production volume depending on how you use

that the phthalates whether you're using the working environment or you actually become certain, why do you spread use and which the general public has more available to them so the level of exposure will be different because in the working environment and they have the engineer control they have other type of the control to make sure the exposure level actually is below the safe level for work population. And then the enhance should be using more as additional line of the evidence to provide information for the general public which may contain the worker and the consumer.

And the various of the different populations. So I think that the short answer is not necessary link to the production volume on the exposure it depending on the use and depending on the you know as you mentioned like whether some of the product may be in a design and the phthalates may not be easily migrated. So there's different elements and it's not simple one-to-one relationship. Thank you

DR. CHRISTINA CHAISSON: What about uses in fracking? How prevalent is that with any of the phthalates? Do you know?

DR. HUA QIAN: I have no idea. Sorry, that's beyond my knowledge.

DR. GEORGE COBB: Sorry, I was meeting we'll move to our next speaker who is Nigel Sarginson. Did I get that close?

MR. NIGEL SARGINSON: That's very good. Dr. Cobb. Thank you. Yeah, good afternoon. My name is Nigel Sarginson. I'm a senior advisor with person in Brussels working as consultants for ExxonMobil. My presentation concerns the low hazard potential of DINP for the male rat reproductive system. EPA has initially selected the HED of 12 milligrams per kilogram body weight per day based on decreased fetal testicular testosterone production for assessing risks from acute and intermediate duration exposure to DINP. Setting an HED on a key event upstream from adverse outcomes is reasonable. When the assumption that the intrinsic ability of the

substance to cause the downstream toxic effect are consistent with existing evidence. However, the assumption that DINP reduces testosterone to an extent necessary and sufficient to induce malformations on the reproductive tract is counter to the existing evidence. And it is my contention that EPA has not clearly characterized this evidence. How it informs confidence in the HED and how it lends to an overestimation of risk for acute and intermediate exposures to DINP. Turning to slide one

Apical outcomes associated with phthalate syndrome have either been inconsistently reported or not reported at all following exposure to DINP. Given that the short time today not all data can be shown, but I will emphasize three end points. The first is AGD. AGD is a sensitive indicator of in utero androgen levels. Such that a shortened AGD serves as a useful biomarker for biologically meaningful reductions in fetal androgen levels in the male programming window. DINP's ability to reduce AGD is shown on the top

right of the slide. Each color represents an individual study that evaluated AGD at the doses tested. The colors with black outlines indicate when a statistically significant finding was reported. As can be seen only at one dose in one study was there a statistically significant finding. Hence, the figure shows that overwhelmingly the data do not support an ability of DINP to induce a statistically significant measurable change in AGD. The low frequency low magnitude changes and lack of reproducibility of findings lend low confidence to a conclusion that DINP is able to induce effects on AGD.

Similarly gross male reproductive tract malformations such as crypt orchidism or hyperspadias have not been reported in any studies of on DINP. The figure on the bottom right shows that for none of four studies have observed a significant increase in these outcomes. So by and large the weight of evidence reflects that DINP does not induce the adverse outcomes. Encompassed in rat thalin syndrome including hyperspadias

crypt orchidism underdeveloped wolfian duct. Decreased accessory sex organ weight or impaired fertility. Now, of course the data set is not entirely void of observations. There are physically significant increase in tissue abnormalities. These have been reported in some studies at high doses of DINP.

However, the low frequency low severity lack of reproducibility in the nature of observations across studies does not allow ruling out of chance confounding factors or bias as an explanation for these outcomes. As well the high dose which at which effects have been observed must be considered when concluding on hazard potential particularly because saturation of DINP metabolism has been shown to occur at 750 milligrams per kilogram body weight per day. If efficacy of DINP is maximized at 750 milligrams per kilogram body weight per day and DINP does not induce adverse outcomes in rat studies below this dose. This indicates that the concentration of DINP necessary and sufficient. To induce the

maximal cellular response necessary to manifest out adverse outcomes is not achievable. This calls into question the appropriateness of testosterone or rat phthalate syndrome in general as a pod in the risk evaluation for DINP.

In its weight of the evidence conclusion, EPA implies DINP can induce adverse outcomes downstream of androgen disruption. We request the SAC to advise EPA to clearly represent the weight of the evidence in relation to adversity and that the uncertainty in DINP's efficacy to induce toxic effects. Be better characterized in the pod justification. The next slide shows the key references relevant to the presentation. Thank you very much for your attention and thank you for the opportunity to present

DR. GEORGE COBB: Thank you for your presentation, and are there questions from the committee? Thank you. Seeing none, thank you again and we can move to our next speaker who is Chad Thompson from Talks Strategies.

DR. CHAD THOMPSON: Mike can you hear me. Okay, so I'm, Dr. Chad Thompson I'm a senior managing scientist at Talk Strategies. I am speaking at the request today of ExxonMobil. The views expressed will be my own and I'm going to be presenting evidence that the DINP. PPARα motive action and rodents is not relevant to humans. So you could skip to slide three, please.

So once a mode of action has been established in rodents the human relevance of that mode of action can be assessed by answering two questions described in the IPCS human relevance framework. The first question is whether there are sufficient qualitative differences in rodents and humans that would preclude that mode of action from occurring in humans.

The second question is whether there is evidence for quantitative differences that render the mode of action in rodents unlikely to occur in humans. In the case of the PPARα mode of action for liver tumors an expert panel in Corten et al 2014. Concluded that there were some

lingering uncertainties that would prevent the panel from broadly concluding that the PPR mode of action cannot occur in humans based on potential qualitative difference.

However, if we go to slide four. There was a broad consensus that there were quantitative differences that supported that the PPARα mode of action quote was not relevant to humans. And among those panelists that were hesitant to make absolute conclusions. They considered the mode of action as unlikely to be relevant to humans.

Slide five. This conclusion was further refined for weak PPARα alpha activators as quote highly unlikely to be relevant to humans with one of the Examples provided being ethylate DEHP. Slide six. These conclusions in Corten et al 2014 were subsequently reaffirmed by another expert panel in a publication by Felter et al 2018. And the authors of an AOP wiki PPARα induced liver tumors in rodents provide the strongest conclusion stating that the PPARα mode of action

slash AOP has quote no potential application for human health risk assessment.

Slide seven. So the draft non-cancer human health hazard assessment for DINP concluded that the weight of evidence supports a PPARα mode of action for DINP induced liver effects and rodents. EPA concluded that the DINP was not likely to be carcinogenic to humans at doses below levels that do not result in PPARα activation. This conclusion is generally consistent with those previously mentioned regarding the overall lack of human relevance of this mode of action. However, there are DINP specific data that support making a chemical specific determination that the mode of action for this weak PPARα activator lacks human relevance.

Slide eight. So qualitative differences exist between rodent and primate responses to DINP including associative events related to key event one, which is receptor activation. And key event three altered cell growth and survival as shown in this table.

Multiple studies demonstrate a lack of paroxysmal beta-oxidation in human and monkey hepatocytes. Which would be indicative of PPARα activation nor has paroxysmal beta-oxidation in the paticellular hypertrophy been observed in vivo in monkeys exposed to DINP. Likewise downstream events such as altered cell proliferation and suppression of apoptosis have not been observed in human hepatocytes. And nor has increased the paticellular proliferation or increased liver weight been observed in exposed monkeys

Slide nine. So in addition to these qualitative differences quantitative differences exist between rodent and human PPARα receptor activation by MINP, which is the primary metabolite of DINP. Here you can see species differences in the potency of MINP With regard to the PPARα receptor activation in vitro. Where the activation of the human PPARα occurs at a much higher concentration than in the mouse.

Slide 10. So in conclusion using the IPCS framework, There is qualitative and

quantitative evidence that the PPARα mode of action for DINP lacks human relevance, And while it may be the case that EPA cannot conclude that the mode of action for all PPARα activators lacks human relevance. The EPA could make a chemical specific determination that the PPARα mode of action for DINP is not relevant for human health risk assessment. And the final slide are some references. For some of the slides and thank you for your time.

DR. GEORGE COBB: Thank you for that presentation, and other questions? Seeing none, I think we have one more presenter, and that is Paige Varner from the Environmental Defense.

PAIGE VARNER: Yep, thank you and thank you for making it with me to the end of these comments. My name is Paige Varner and I'm a scientist with Environmental Defense Fund. Thank you for the opportunity to comment.

While EPA claims have taken a pragmatic and conservative approach in the draft risk evaluation for DIDP. We believe that EPA has

instead underestimated exposures to and risk of DIDP particularly in vulnerable and highly exposed populations. This is first exhibited in EPA's failure to consider background DIDP exposures and cumulative exposures to other phthalates and developmental toxicants in the risk evaluation.

As mentioned previously EPA must account for background exposures to DIDP. These exposures include significant non-taxa sources of DIDP such as through personal care products and food and food packaging. For example studies such as the 2024 study by Shildrith et al have found that elevated concentrations of DIDP. Metabolites and black women that correlate with use of products such as perfume lotion makeup nail polish and vaginal powders and deodorants. FDA studies have also found DIDP and other phthalates in food packaging with other studies finding ultra-processed food is associated with urinary concentrations of DIDP metabolites

Additionally EPA's failure to account for cumulative exposures from other

phthalates and other developmental toxicants has also underestimated DIDP's potential for harm. It shares the common endpoint of developmental toxicity with numerous other phthalates as the national toxicology program concluded 25 years ago. EPA has already heard from the SAC that the best available science for chemical assessment includes consideration of cumulative risks and that such assessment is a necessary step under taxa. To comply with taxa's mandate to use the best available science and to complete a comprehensive obsess assessment. EPA must at minimum consider the cumulative risk posed by co-exposure to DIDP and other phthalates. Either in the final DIDP risk evaluation or an EPA's pending phthalates cumulative risk assessment.

These background and cumulative exposures are especially important to consider for potentially exposed or susceptible populations who are at greater risk than the general population of adverse health effects. EPA failed to consider relevant populations that face greater exposure or

susceptibility. For example evidence shows that black and Latina pregnant people experience disproportionately higher exposures to phthalates including DIDP. Which is associated with shortened gestation lower birth weight and lower birth length of offspring compared to White people

Further studies show that individuals with lower incomes are more highly exposed to phthalates including DIDP. Prevalent non-chemical stressors commonly experienced by these groups such as food insecurity and psychological stress from racial injustice also likely contribute to this disparity in health outcomes. EPA must use available data to characterize the increased risk to these groups in its final risk evaluation rather than relying on the interspecies uncertainty factor to account for these adverse exposures and risks. The interspecies uncertainty factor does not address increased risk faced by specific subpopulations due to greater exposure. Instead it is designed to

account for inherent variations in susceptibility within the general population of healthy adults.

Lastly for EPA's risk evaluation of DIDP EPA failed to consider information that it could possess or reasonably generate obtain and synthesize partly by not considering any studies after 2019 as part of its systematic review. In doing so EPA failed to consider important studies on DIDP. Such as the 2021 toxicokinetics study by Jiang et al that measured DIDP and its metabolites in urine suggesting urine as a major biomarker of DIDP. Another study by Zia et al in 2024 reports depression like behavioral changes in mice offspring falling prenatal exposure to both DIDP and ozone. Which supports the identification of an additional susceptible subpopulation as those who are also exposed to high levels of ozone. As it relates to the draft hazard assessment for DINP. EPA unreasonably dismissed benchmark dose modeling results based on liver endpoint variability and model uncertainty. Variability in liver endpoints is expected giving the broad range of liver

effects assessed along the toxicological continuum.

Further a BMD/BMDl ratio above three does suggest model uncertainty. But this is not an established criterion for dismissing BMD modeling results. In fact, the use of a noel is itself a source of uncertainty. EPA should instead use the lowest BMDl from its benchmark dose modeling rather than noel as a point of departure for chronic oral exposures to DINP. We have submitted these comments and more in written comments along with our justice to EPA in the SAC and thank you for your time.

DR. GEORGE COBB: All right, thank you for your comment, are there questions? Seeing none I think we can close the public comment section. Is that everyone? Alaa?

DR. ALAA KAMEL: Yes, this is everyone

DR. GEORGE COBB: Okay, well we are about 10 minutes before the planned adjourning time is that correct. Right, but

DR. ALAA KAMEL: The agenda is flexible. Well, I'm not sure we want to. I think we're right on time for the agenda. So I do not think we should move into the charge questions today. I think we can begin that tomorrow. I do want to ask the committee quickly if there's interest in using some of the breakout groups rooms that we had talked about for zoom.

DR. CHRISTINA CHAISSON: Dr. Cobb, this is Dr. Chaisson. I would appreciate it if people who are involved with one in particular would be able to use a breakout room to get some of our responses, I mean a little better organized for presentation tomorrow.

DR. GEORGE COBB: Understood. I think that's feasible Dr. Otter you had your hand up.

DR. MARY ANN OTTINGER: Yeah, same for me and I guess we have to sort out who is in which one and organize them.

DR. GEORGE COBB: So which question for you, Dr. Otter?

DR. OTTINGER: I believe it's 2a. Let me double check. It would be 2a

DR. GEORGE COBB: So we have 1a and we have 2a Dr. David

DR. RAYMOND DAVID: And same for me 2b and 2c

DR. GEORGE COBB: That's right. 1a, 1b and 1c. Okay, Dr. David

DR. RAYMOND DAVID: I was just going to suggest that the lead discussions as we go through these. If they feel that there's need for some further discussion and maybe we can they can recommend that rather than necessarily all groups.

DR. GEORGE COBB: I agree. I agree. And so that's what I think that's what we're doing now. Did you have a need for your group?

DR. RAYMOND DAVID: I don't believe so. Okay. I think we're good. I think the ones and twos are the ones coming up sooner

DR. GEORGE COBB: So I have right now 1.a, 1.b, 1.c and 2. What was it? Marianne.

DR. MARY OTTINGER: 2.a could I mean maybe I don't know when you want to do what I was going to suggest

DR. GEORGE COBB: Let's think that through for just a second. Dr. Fenner Crisp

DR. FENNER-CRISP: My question to Dr. Otter that is 2a for DIDP not 2a for DINP, right?

DR. MARY OTTINGER: Correct. Yes I know it's confusing

DR. FENNER-CRISP: And I did have another question about availability of the commenters presentation sooner rather than later.

DR. MARY OTTINGER: Yeah, it would be very helpful if we had them. Yeah I think. So we'd have at hand while we have our discussion.

DR. GEORGE COBB: I will try as best to get those to us as quickly as possible Dr. Li.

Dr. LI LI: Actually, I just have a quick question. So tomorrow would for example the lead discussion need to read off all the comments from the whole group or they just read for example

some very brief summary and then invite every single one to present their own ideas

DR. GEORGE COBB: So we have found that it is most efficient for the lead to present the entire.

Dr. LI LI: The entire response. But you don't have to put all the detail, right? We can talk about this maybe offline either on the phone call or email, it doesn't have to have every bit of detail just so that the spirit of it is captured, right? But we can talk about this afterwards so that everybody in the public meeting isn't addressing this. Okay. Yeah. Okay. All right. Thanks.

DR. GEORGE COBB: Dr. Chaisson

DR. CHRISTINA CHAISSON: Yes, if Dr. Li is going to be in his own breakout then he won't be participating in the one we're having so Dr. Li to simplify this, why do we keep, there was a long list of things that you noted that were worthy of comment for 1.a.i. Okay, this gets complicated and what I'll do in the presentation

tomorrow is let you, I've summarized a lot of the pieces that are coming in but I will specifically ask you to take a look at that list and add that at the end for anything that wasn't addressed in the presentations today. Okay, or however you want to handle then thank you, and Dr. Li I'll join you in your breakout group

DR. LI LI: Yeah, actually that's also my question. I also got very long comments from some reviewers and I was wondering whether I need to.

DR. GEORGE COBB: Let's talk about this when we get into our session. Okay? That way we can get that arranged and then we can talk that through real quick as we get started. All right. Thanks. If the discussions for today are over and we can talk about the breakout sessions after the meeting has been adjourned. Thank you

I think we can adjourn for the day. Alaa are there things you would like to say as we close. That's all. If we're done then I would

say that this meeting is adjourned everybody can leave except this act.

DR. ALAA KAMEL: Please remain in the meeting. Thank you to everyone

[MEETING ADJOURNED FOR THE DAY]

OPENING OF MEETING DAY 2

DR. ALAA KAMEL: Good morning. My name is Alaa Kamel, and I will be serving as the designated federal official to the U.S. EPA Science Advisory Committee on Chemicals -- SACC -- for this meeting. And in my role, I will be opening the second day of the public meeting on EPA's Draft Risk Evaluation for Di-isodecyl phthalate -- DIDP -- and the Draft Hazard Assessment for Di-isononyl phthalate -- DINP.

I'd like to repeat that the SACC meetings are subject to all FACA requirements, and this includes open meetings, timely public notice of meetings, and document availability to the public. All documents are available to the public

in the dockets at regulations.gov, and please see the docket number in the meeting agenda.

Also note that this meeting is being webcasted, transcribed, and recorded. Also, a livestream of today's meeting is available on YouTube -- and see the link on the meeting website listed in the agenda, which also has a link to yesterday's meeting.

Yesterday, we had a successful opening day, and I would like to thank the SACC, the ad hoc reviewers, the EPA team, and the public for their presentations and discussions. And now I hand it over to the chair, Dr. George Cobb. Thank you.

DR. GEORGE COBB: Thank you, Dr. Kamel. I would like to thank everyone, as well, for attending. And give EPA a little bit of a heads up, we have a couple of questions that we may want to clear first thing this morning. But we're going to take the roll first, and then we'll get to those questions. So starting off, I see Dr. Apte knows he's first up.

DR. UDAYAN APTE: Hi, I'm Udayan Apte. Am I introducing or just say yes, I'm here?

DR. GEORGE COBB: No, we're just taking a roll.

DR. UDAYAN APTE: Okay.

DR. GEORGE COBB: Uh, Dr. Baker.

DR. MARISSA BAKER: Here.

DR. GEORGE COBB: Dr. Chaisson.

DR. CHRISTINE CHAISSON: Present.

DR. GEORGE COBB: Dr. Eick.

DR. STEPHANIE EICK: Here. Good morning.

DR. GEORGE COBB: Dr. Fong. I'm not sure he's going to join. Dr. Gentry.

DR. ROBINAN GENTRY: Here.

DR. GEORGE COBB: Dr. Graham.

DR. CYNTHIA GRAHAM: Here.

DR. GEORGE COBB: Dr. Heiger-Bernays.

DR. HEIGER-BERNAYS: Here.

DR. GEORGE COBB: Dr. Jenkins.

MS. ALLISON JENKINS: Here.

DR. GEORGE COBB: Okay. Dr. Li. I think you were muted. Dr. Merced-Nieves.

DR. FRANCHESKA MERCED-NIEVES: Good morning. Here.

DR. GEORGE COBB: Dr. Ottinger.

DR. MARY OTTINGER: Here.

DR. GEORGE COBB: Dr. Przybyla. She said she had an appointment. Dr. Reif.

DR. DAVID REIF: Here.

DR. GEORGE COBB: Dr. Jennifer Sahmel-Elliott.

DR. ALAA KAMEL: No, she's not attending.

DR. GEORGE COBB: Not attending -- I forgot to note that yesterday. Dr. David.

DR. RAYMOND DAVID: Here.

DR. GEORGE COBB: Dr. Fanning.

DR. ELINOR FANNING: Here.

DR. GEORGE COBB: Dr. Fenner-Crisp.

DR. PENELOPE FENNER-CRISP: Here.

DR. GEORGE COBB: Dr. Howdeshell.

DR. KEMBRA HOWDESHELL: Here.

DR. GEORGE COBB: All right. Dr. Martinez.

DR. JEANELLE MARTINEZ: Good morning. I'm present.

DR. GEORGE COBB: Dr. Schuman Goodier.

DR. MOLLY SCHUMAN-GOODIER: Good morning. Here.

DR. GEORGE COBB: And Dr. Spade.

DR. DAN SPADE: Here.

DR. GEORGE COBB: And Dr. Wolf.

DR. DOUGLAS WOLF: Present.

PANEL MEMBERS: FOLLOW-UP ON PREVIOUS DAY

DR. GEORGE COBB: All right. Seems like we have most of our folks here -- almost all. I do want to circle back. A couple of people sent emails last night or this morning about a couple of clarifying questions. So I'd like to open it

up to the Committee to see if there are clarifying questions about the presentations from yesterday.

DR. CHRISTINE CHAISSON: I've got a comment. I can't find it.

DR. GEORGE COBB: Oh. Go --

DR. CHRISTINE CHAISSON: (inaudible 00:05:18) Here's the little hand, here we go.

DR. GEORGE COBB: -- go ahead, Dr. Chaisson. Please, go ahead.

DR. CHRISTINE CHAISSON: Everything seems to change positions on my computer. Anyway, thank you very much. Let me just pull up -- just a moment please. Okay. Thank you.

I've collected together, from our different Committee individual reports, questions that have come up that I don't think we've discussed yet, so there are several of them. I'll just go through this.

One was from line 351 of the report -- "The CEM model has been peer-reviewed. Could EPA provide a reference for this? Is it public? Is that peer-reviewed report publicly available?

The only peer review that was mentioned online was from 1999, presumably, since EPA is using a 2023 version. There must be others. So could EPA please provide for the Committee whatever is publicly available about that peer review?"

And the same question arose from the Exposure Handbook because values taken from that were an issue that EPA commented on regarding current weights of people as an example. "When was the last update on those kinds of factors?"

The next question is -- I'm sorry, just a second. "A CEM was not used for dermal exposure. And in the separate spreadsheet, did the HC use degrading absorption and transfer coefficients with repeated exposures? So that meant repeated exposures to the same medium.

Are the dynamics of leaching understood for different plastics and other matrices, such as cellulose, which is in increased use for the phthalates -- with the phthalates -- from which the different phthalate skin escape

under conditions of aging, structural stress, and temperature.

What were those things factored into the exposure scenario? Could EPA summarize how that was represented in the Draft Consumer Exposure Analysis?"

The next question was related to that. It has to do with chemical migration rates, in Section 5, derived from surrogate data. "Could you point to where the surrogate data are identified and extracted for use here?"

A similar question is "As migration proceeds over time, if migration dynamics change and the distribution of values of the migration rates can be front-loaded in relation to plasticizer concentrations in product -- but also degradation of product plastic in aged toys, et cetera -- this is an important factor in exposure assessment, particularly to workers and the public exposed as bystanders -- could this be delineated for us?

If in fact, by the way, what I'm asking for is already in the documents, and we just missed it -- which is possible -- if the EPA could just give specific directions to where it's at -- assuming that the questions are fully clarified in those"

The clarification came up several times from different people, asking for clarification about the domain of FDA for regulation. Do the FDA risk assessments consider the exposure scenarios mandated by TSCA.

For example, for food uses, would the exposure risk scenarios of manufacturing, distribution, transportation, disposal, et cetera, be considered in the same way that FDA -- as EPA would do under TSCA? Is task identification part of the FDA regulatory consideration? If not, can EPA assess the scenarios not covered by FDA?"

DR. GEORGE COBB: Wait. Chris --

DR. CHRISTINE CHAISSON: Yeah?

DR. GEORGE COBB: -- please ask questions and don't provide direction. We need to ask questions that the --

DR. CHRISTINE CHAISSON: Right.

DR. GEORGE COBB: -- EPA can answer, not --

DR. CHRISTINE CHAISSON: Right. Well, I'm at --

DR. GEORGE COBB: -- not expound on that.

DR. CHRISTINE CHAISSON: -- I thought I was. Sorry, Dr. Cobb. I thought that was what this was.

"Are medical devices covered under TSCA in the same way or just FDA?" Also, the same question came up for cosmetics. And "Are phthalates used in food context zones? There was a regulatory action in 2006, but subsequent information does not seem to be consistent with that."

Let's see. "EPA based confidence in weight fractions for different products, using the

comment that it is more current or less current. Is there a generalizable trend that EPA uses in the rate of DINP use across product categories that could be used to deduce some certainty?"

And the last question is "Are phthalates used in hydraulic fracturing for oil and gas, and if so, where is this included?" And I think I've summarized all of our questions. So, Dr. Cobb, thank you.

DR. GEORGE COBB: Thank you, Dr. Chaisson. And EPA, we'll turn it over to your response. I also understand that you have some responses to previous questions. And you can start at either place at your discretion.

DR. CHRISTINE CHAISSON: Are you speaking to EPA?

DR. GEORGE COBB: Yes, to EPA.

DR. CHRISTINE CHAISSON: Oh. Okay.

DR. GEORGE COBB: They were going to respond to a question that you and Dr. Fenner-Crisp -- or questions that you and Dr. Fenner-Crisp had yesterday, I believe.

DR. CHRISTINE CHAISSON: Okay.

DR. ANNA LOWIT: So good morning, everyone. Anna Lowit, Senior Science Advisor. So Tony, if you can get on and start --

DR. GEORGE COBB: Dr. Lowit, we can barely hear you.

DR. ANNA LOWIT: Thanks. Sorry. Tony Luz, if you can get on, let's start with the ones from yesterday. So Dr. Chaisson, we appreciate all those questions. It's a fairly lengthy list of questions.

DR. CHRISTINE CHAISSON: Mm-hmm.

DR. ANNA LOWIT: And I'm afraid you were going so fast that we probably missed some. It looks like you're reading off of something. Is it possible to share what you were reading off with Dr. Kamel, and then --

DR. CHRISTINE CHAISSON: Certainly.

DR. ANNA LOWIT: -- we can transmit that and have our team work on those and get back to you later?

DR. CHRISTINE CHAISSON: Absolutely. I'll send it right away.

DR. ANNA LOWIT: Okay. And just recognize -- some of the FDA questions, we're not going to know the answer to. But we'll do our best.

DR. CHRISTINE CHAISSON: I know you will. Thank you.

MR. ANTHONY LUZ: Thank you Dr. Chaisson and Dr. Cobb. This is Tony Luz with EPA. I just want to read into the record a couple of EPA's responses to questions that were asked to EPA yesterday, and we didn't have the information about one on the spot (inaudible). So I'm just going to read our response into the record.

So first, in response to a question from Dr. Fenner-Crisp regarding the study by Cho et al 2011 of Wild Type and RAG H2 -- transgenic mice exposed to DIDP for 26 weeks.

So pertaining to dose selection in that study, Cho et al 2011 states "As a prelude to conducting the 26-week carcinogenesis study on

DIDP, a 4-week repeated dose toxicity study was carried out on RAG H2 wild type mice to survey the target organs and sock the doses to be used for a 26-week carcinogenicity study.

As a result, the MTD was limited to 1 percent DIDP in diets, as there were deleterious effects on body weight, organ weights, and clinical chemistry in higher doses.

Therefore, 1 percent of DIDP was selected as the high dose level, where a certain level of toxicity was expected. The low dose was set at 0.1 percent with the estimation to provide information on the NOAEL. The mid-dose level of 0.33 percent is approximately the geometric mean between the low- and high-dose levels.

Also, in response to the second question from Dr. Fenner-Crisp, EPA discusses the study by Cho et al 2011 on several sections of the Draft Human Health Hazard Assessments for DIDP in Appendix C.2 of the Draft DIDP Hazard Assessments.

In that section, we state "Cho et al fed male and female wild type mice diets

containing 0.0 or 1.0 percent DIDP, the equivalent to approximately 1500 milligrams per kilogram per day in male and female transgenic RAG H2 mice: 0.0, 0.1, 0.33, and 1.0 percent DIDP, equivalent to approximately 150, 495, and 1,500 milligrams per kilogram per day for 26 weeks.

The most significant effects on survival were reported at any dose for wild type or RAG H2 mice of either sex, and wild type mice terminal body weight was reduced by 27 and 12 percent in male and females, respectively. Liver effects included an increase in relative liver weight in male and female mice -- 59 to 72 percent increases.

Lesions of increased incidence included a podocyte hypertrophy with eosinophilic granules in both sexes and parenchymal inflammation, pigmented hepatocytes, pigmented Kupffer cells, and prominent Kupffer cells in males. That's provided in Appendix Table C-10. A non-displacing significant increase in the

instance of (inaudible 00:16:45) focal necrosis were observed in males as well.

Similarly, in RAS H2 mice, terminal body weight was reduced by 31 and 15 percent in males and females, respectively. Relative liver weight was increased 15 to 52 percent for mid- and high-dose males and 35 percent for high-dose females.

Lesions with increased incidence included parenchymal inflammation in females, hepatocyte hypertrophy with eosinophilic granules in both sexes and philcamatroceous pigmented hepatocytes, pigmented Kupffer cells, and prominent Kupffer cells in males. That incidence data is provided in Appendix Table C-10.

We also want to respond to another question from Dr. Chaisson, who requested additional information regarding the COUs being evaluated for other high-priority phthalates.

So in the draft proposal for cumulative risk assessments of phthalates under TSCA, EPA presents an overview of COUs for DINP,

DEHP, DBPD, DIBP, DBPN, PCHP -- as presented in the final scope documents for each -- phthalates in Table 6-1.

These aren't final, but provide a good overview of COUs in the Draft Phthalate Cumulative Proposals available in the docket. And that's the end of EPA's response to those two earlier questions from yesterday.

DR. GEORGE COBB: Thank you, Dr. Luz. I really appreciate you taking the time -- you and your team taking the time -- to pull those answers together and presenting them here early in the morning today. And I gather that the response to Dr. Chaisson's questions will be forthcoming as you are able to pull those responses together. Is that correct?

MR. ANTHONY LUZ: Yes. Yeah. No, I appreciate you being able to provide them and narrating to -- to Alaa and the rest of the team involved. We do our best to get responses as quickly as possible.

DR. GEORGE COBB: Thank you. I appreciate that.

MR. ANTHONY LUZ: Yes. Thank you.

DR. GEORGE COBB: Dr. Chaisson, your hand is still up. Is that a residual, or do you still have a question?

DR. CHRISTINE CHAISSON: Sorry. I'll get it down.

DR. GEORGE COBB: Don't worry.

DR. CHRISTINE CHAISSON: Fair, since I figured out how to do that. Thank you.

DR. GEORGE COBB: Don't worry. So are there any other questions? Uh, Dr. Heiger-Bernays.

DR. WENDY HEIGER-BERNAYS: Yes, thank you.

DR. GEORGE COBB: Yep.

DR. WENDY HEIGER-BERNAYS: Yes. Thank you. This is a straightforward one. In the COUs, were nail salon workers -- or in the occupational exposures -- were nail salon workers considered? That's all.

DR. GEORGE COBB: I think we're waiting for a response.

MR. ANTHONY LUZ: Hi, this is Tony with EPA. Thanks for your question, Dr. Heiger-Bernays. For DIDP, that did not show up in the surrogates.

DR. WENDY HEIGER-BERNAYS: Well, thank you very much.

DR. GEORGE COBB: Are there other clarifying questions from the EPA's presentation? All right. Being none, I think it is time to move into the charge questions. And we are at Charge Question 1.a, related to the DIDP assessment. And I'll turn it over to EPA to read the question into the record.

CHARGE QUESTIONS FOR DIDP RISK EVALUATION

1. EXPOSURE ANALYSES

MR. ANTHONY LUZ: Thank you, Dr. Cobb. This is Anthony Luz with EPA. So now we're reading in Charge Question 1.a. So EPA relied on

data from several sources to derive consumer exposure estimates that include products representative of the conditions of use, as described in Section 1, 2, and 3 of the Draft Consumer Indoor Dust Exposure Assessments for DIDP. EPA anticipates that the exposure methodologies demonstrated in the Draft Risk Evaluation for DIDP will be applicable to DINP exposure scenarios.

CHARGE QUESTION 1.a.i

Charge Question 1.a actually has five subparts. So I'll now read the first subpart. So "Please comment on the strengths and uncertainties of deflective data and methods used in consumer products in indoor air exposure analyses." Thank you.

DR. GEORGE COBB: All right. And we have a team of discussants evaluating this question, and Dr. Chaisson is the lead. So we'll go to her, and then we'll go through all the

discussants, and then we'll go to the full Committee for comments. Dr. Chaisson.

DR. CHRISTINE CHAISSON: Dr. Cobb, could you -- I have to excuse myself for one second. There's construction going on. I'm going to ask these people to stop it for a few minutes. Hold on one second. Hey guys, you have to stop pounding. You have to stop.

DR. GEORGE COBB: So folks, I apologize. And we could go into another charge question, but Dr. Chaisson is the lead for several charge questions in a row. So we just have to pause for a second. Ah, you're back. Hey, Chris, you --

DR. CHRISTINE CHAISSON: My apologies. My apologies. There was some major noise going on -- I just stopped it -- from construction. Of course, they didn't start until a few seconds ago. So okay, let's see here. Okay. Dr. Cobb, can you hear me? Hello?

DR. UDAYAN APTE: Yes, we can hear you.

DR. CHRISTINE CHAISSON: Okay. Thank you. First of all, our community commends EPA for their professionalism in creating and presenting the phthalate assessment, recognized as the effort to consider perspectives of the public comment or -- and those of SACC. Dr. Freedhoff's message strengthened our resolve to provide our best instructed advice to these scientists and the EPA leadership. Our Committee has not yet finished organization and detailed articulation of our comments. Our written reply will contain more detail on our points and references.

The strengths that we noted -- we appreciated that EPA calculated ranges -- low, medium, and high -- in lieu of more -- in lieu of other methods. This is a good substitute -- much better than considering only a single value.

However, it does not deliver a most likely value -- akin to a median exposure -- for different age groups or view and use of skewed distributions -- a common situation for exposure assessment factors.

Also, see Section 4.4 -- issues of assumptions, deterministic methods -- such as using only single values to represent a distribution of plausible values -- and other issues show, indeed, the limitations of estimates from the CEM.

Note, it's excellent that EPA did this analysis and showed it transparently -- discussed the sources of the differences. We certainly don't want to discourage EPA from that kind of conversation.

The differences were 1 to 2 orders of magnitude, which needs attention. This shows the importance of the use of modeled distributions for each value, especially where highly skewed distributions are realistic for life changes, or venue changes, or even activity level differences. And this emphasizes the need for a different kind of modeling methodology, which can handle full distributions of the values.

We commended EPA on its consideration of children in the dust exposure.

We thought that was quite good. Section 5, pages 115 to 116 -- this was a discussion of rat versus human dermal absorption.

Elements of variability were noted here, but also, there will be differences in human dermal absorption because of the area of the body being exposed, temperatures, age of some of the humans, et cetera.

EPA used conservative estimates, which were reasonable under these circumstances. We invite others in the SACC, beyond our subcommittee, to comment on this, as there are -- maybe -- additional information they could provide.

It's excellent that indoor dust inhalation was carefully considered -- and the ingestion. But note that dermal contact is also important. This is discussed again in other sections. The same should also be done for people in vehicle environments.

Values used in the calculations and frameworks for the dose rate calculations were

reasonable for time in integrated doses, given model limitations to utilize such data. And the professional judgments of the scientists seemed reasonable.

Although this doesn't deliver actual distributions of likely exposures -- newer exposures for all routes are actually computed for each exposure opportunity -- the exposures presented are likely representative, assuming all of the COUs are actually considered and groupings of products into each COU scenario didn't "disguise a sentinel COU situation."

Uncertainties presented in these documents -- the scenarios included in this assessment may not reflect all of the conditions listed in the review mandate.

For example, there is no mention of exposure related to product transportation and market dynamics of today -- and tomorrow -- for product delivery to consumers, including handling of massive quantities of the products, newly minted and wrapped in phthalate-rich materials to

contain and stabilize products on slabs in the distribution centers.

Thousands of workers in these centers are touching the materials, breathing the dust, taking the dust home -- that's a track-back issue -- and experiencing long durations of exposures daily.

The next point was -- phthalates are used extensively in all electronics and printers and inks. At least two scenarios of exposures may be relevant -- large office areas and computing centers -- including the air evacuation systems operating to vacate working areas, covering about a million square feet each, for dust removal and cooling systems for those massive centers.

At least a qualitative discussion -- a recognition of the need for data in these major new exposure scenarios across the country -- would be good to have in a report like this.

Experts on those facility designs and phthalate use in electronics could be contacted to consider this. Even if the EPA

decides there's little likely exposure, including the environment and nearby residents -- and the dust in those homes -- a conversation about this is recommended.

This new reality in our market system is imposing new environmental challenges to both rural and urban areas and are so big that they deserve attention and regulatory science and reflection on the regulatory covering transportation and distribution activities.

More detail and references will be in the written report -- in our written report. The point is that the EPA documents seem to overlook the stated scenarios required in the review.

Next point -- as with previous SACC reviews -- oops, excuse me; I'm sorry -- as with previous SACC reviews, we appreciate the efforts EPA scientists make with the deterministic spreadsheet approaches to these assessments.

But we implore EPA to provide state of the art statistical and modeling tools,

including Bayesian statistics, which can easily handle full distributions of data -- any exposure duration that is appropriate to hazard metrics and provide aggregated exposure estimates reporting relative contributions from different exposure opportunities over different conditions of exposure and to different subpopulations.

We recognize this can't be completed for the phthalate regulatory assessment and decisions, but hope the EPA leadership will seriously consider this issue as has been raised before. As previously stated, exposure estimates are likely representative of the general population, assuming all of the COUs and resulting scenarios are actually considered and groupings of the products don't disguise the sentinel.

This issue for exposures via water -- both drinking and full body -- from water contamination, including down-the-drain releases to environmental media and into water sources -- was only qualitatively assessed.

But even that discussion did not address exposures consequential to the contamination of particles and sediments of water bodies. Or we didn't understand that to be the connections -- such as fishing, crabbing, and oyster consumption -- in a quantitative way for these biota.

This was discussed in more detail by Dr. Barton's public comments submission.

While fish consumed by Native Americans may indeed be worthy of a separate consideration, other substances -- I'm sorry -- other subsistent populations derive a significant amount of their food from shallow surface water bodies -- brackish water sources.

Consider the coastal regions of the Gulf of Mexico. Pest communities there are not all tribal, but their foods include all types of birds in swampy areas -- shrimp, fish, and other aquatic animals, including alligators -- as typical foods.

Consider the coastal communities of the Chesapeake Bay, for example, and equivalent communities in Northwest and Northeastern coasts, where consumption of bivalves is constant and significant. Bivalves are filtering those waters.

A contaminant that becomes sequestered into the water body sediment cannot be considered to be inconsequential to human or environmental risk or permanently sequestered. Consider the opposite issues of the Hudson River, which was extensively studied over decades by EPA.

Today's realities may impose additional issues, including some areas where daily freshwater flooding takes place, displacing sediment into newly exposed venues in the environment and foods -- and let me see -- exposing biota in all forms of animals.

The next point in line 315 and 316 -- - "EPA did not perform quantitative assessments of the COU summarized in Table 2.2 due to lack of recently available information, monitoring data, and modeling tools." This is such a big

possibility for widespread and significant exposure via dermal and ingestion. It should be explored further.

Next point, we commend EPA for considering the Rivian DU Netherlands and IPH (phonetic 00:34:32) and ECCA evaluations for sub values. However, an overall comparison of the exposure assessment conclusions -- the product groupings across these regulatory authorities -- were not provided and are likely to be somewhat different.

In a related issue, data quality -- as a function of possible differences between U.S. and Canada -- was cited as a potential problem regarding monitoring data for DIDP in residential indoor dust -- that's page 126, lines 2181 to 2190 -- but no perspective given about why EPA suspects the problem denigrates the use of the information.

Were there regulatory positions on the use of the phthalates over that time period as compared to U.S. regulations? Or what information

-- not assumptions -- led to the concerns about U.S. Canadian product use for phthalate content?

It could be assumed that these products and uses are very similar, even provided by the same manufacturers in many cases -- so why the downgrade? Also, for evaluations done by these other authorities, including Canada, were product groupings the same as EPA, as that will certainly affect the exposure scenarios.

There were other methodological issues detailed. I've collected these together. Lines 1131 to 1141, on page 45, Section 3.1, EPA calculated dermal absorption of DIDP in consumer products or articles first migrating into the layer of aqueous phase on the product or article surface to form a saturated solution.

And two, the human skin absorbs DIDP from this saturated solution. This is the reason that EPA used to equate in 2-24, which was originally designed to calculate dermal exposure to chemicals in water by the EPA's risk assessment

guidelines for Superfund Volume I Human Health Evaluation Manual.

DR. GEORGE COBB: Okay.

DR. CHRISTINE CHAISSON: However --

DR. GEORGE COBB: The last one?

DR. CHRISTINE CHAISSON: Yeah.

DR. GEORGE COBB: Good. We're still indoor air -- consumer products and indoor air exposure. Is this still on that charge question?

DR. CHRISTINE CHAISSON: Yes, I think.

DR. GEORGE COBB: Okay. Just -- okay --

DR. CHRISTINE CHAISSON: As far as I know.

DR. GEORGE COBB: -- please continue then. Please continue.

DR. CHRISTINE CHAISSON: The member who submitted this has several pages of these methodological problems. If it's okay with you, Dr. Cobb, I think we've gotten -- made the point.

DR. GEORGE COBB: Please.

DR. CHRISTINE CHAISSON: How about I just include this in the written part? Would that be okay?

DR. GEORGE COBB: You can proceed. I started hearing about the dermal exposure, which is another question. And I wanted to make sure that was -- if you --

DR. CHRISTINE CHAISSON: Well, this came up in CEM model --

DR. GEORGE COBB: It's all good. Please proceed.

DR. CHRISTINE CHAISSON: -- which we interpreted as part of this question. So --

DR. GEORGE COBB: Yeah. Surely. Please proceed.

DR. CHRISTINE CHAISSON: -- okay. Well, nevertheless, there's a very detailed discussion of these factors used in CEM models user guide. Would it be appropriate -- should I read this into the record? Or would it be appropriate to just include it in the written part?

DR. GEORGE COBB: You don't have to read each issue in, but you can broadly state what those are. And I'm not trying to shortcut the discussion. I simply wanted to make sure it was on this particular charge question.

DR. CHRISTINE CHAISSON: Well, this all has to do with calculations for human skin absorption as used in CEMs. So I'll submit this as -- these details -- as part of the written record, recognizing that we -- I'm not trying to diminish the importance of this. It's just very detailed, as we think that this relates very much to the weighted calculations that were made in the CEM.

DR. GEORGE COBB: Okay.

DR. CHRISTINE CHAISSON: So I'll skip forward on that.

Regarding biodegradation, a more thorough explanation of half-life is needed in these discussions. Half-life does not indicate a time to decrease toxicity by 50 percent. To what extent has the transfer information of DIDP to

model isodecyl phthalate been assessed in the context of this fox trail of events of half-lives and the influence of a half-life or availability of toxic transformation products?

Next, on page 12, lines 204 to 205, the major concern is that there are no NOOS data upon which to base environmental releases for DIDP. This lack of information is inconsistent with the call for expedited review of the two compounds. Any chemical deserving expedited review should have ample supporting information in the publicly available domain.

Alternatively, the users and producers should be required to provide the needed data. This is appropriate for other data uncertainties and gaps, given the policies for EPA decision-making. The requester should provide the information.

The evaluation of releases to water was a single study of phthalates in a single river in China. This is insufficient information upon which to make any reasonable assessment of the

environmental exposures that would be expected for people or non-human organisms.

If there are more data describing DIDP releases to water, they need to be documented. Excuse me. There is a study from 2023 that would add some breadth to this evaluation. That's Belroy Kinkera (phonetic 00:41:04) et al 2023.

Anticipated exposure estimates should be developed for scenarios where people and animals, especially those hunted or fished -- including bottom dweller depth shellfish -- are exposed. The assessments can be constructed as sentinel with factors derived from past consumption values. See the Barton comments as sentinel exposures -- Plausible and Probable Exposure Scenarios Today.

The same should be done for selective sentinel representative scenarios for the consequence of flooding. We'll expand on this in our written comment. Notably, even if EPA thinks that this will not be a risk concern, the

calculations should be done and presented to the public.

Bottle liners, water bottles, and other food containers should be specifically noted, given their high use in the United States. Migration factors, recognizing product age, plastic bases, heat environments, frequency of shape distortion, using -- repeated uses -- this comment is consistent with the discussion on the other phthalates as well.

We asked earlier a question about the hydraulic fracking that's come up, but without much explanation. If phthalates are actually used, the extent of that use and its possible impact on exposure needs to be considered.

The Committee is concerned that there are gaps in the overall approach in selecting products to model and parameters for modeling that may result in a failure to capture the high exposure pest theories.

This will be discussed in detail in our written report, but it will always include the

overall responsiveness to the TSCA elements for review -- absence and pathway related to product distribution and transportation, particularly.

Some Committee members found the pathways for chemicals to enter -- the three dust compartments of the CEM -- are poorly described, especially for abraded particles. This doesn't appear that modeled products contributed any mass to the dust through abrasion mechanics.

The generation of dust particles come from tracking in outdoor dust, dander, smoking, and cooking in the model. These comments very well reflect the CEM capabilities more than the assessments approach.

Product and article selection -- EPA should explain and substantiate how consumer products or articles containing DIDP were selected from the group representing each COU. A brief explanation, given in lines 275 to 278, "selected for large surface area" is not sufficient for COUs with large numbers of products and articles.

Please provide clear rationale that the products and articles moved forward for quantitative exposure modeling are those best-suited to capture and quantify the upper-range potential consumer exposures and result in a healthy, protective evaluation. This will apply to DINP and the other high-priority phthalates as well.

Generally, the exposure assessment needs to be more clearly articulated, especially on how DIDP is considered to enter dust compartments in the modeling. It is difficult to tell whether volatilization through air is the only route for chemical migration out of the products and articles.

Is direct migration to a dust layer considered? Do articles contribute to the mass of that dust through degradation or abrasion? Please discuss why and how this happens.

Specific comments on routes of exposure in products -- Table 2.1 -- one, automotive products other than fluids --

automotive interiors were dropped from the analysis without clear rationale. Vehicle interiors are a significant use of DIDP and represent a potentially route exposure scenario. EPA should evaluate and document the data for this COU.

Next, adhesive sealants and related products are intended to be held in place for long durations after application. The cured products have the potential to wear and abrade and contribute to dust, as well as to emit high levels of DIDP to air.

Is that noise interfering? Hold on one second. I really apologize for this. I didn't realize this was going to happen.

DR. DOUGLAS WOLF: I don't hear any background noise.

DR. GEORGE COBB: Yes. Chris, go ahead. Dr. Chaisson, hi. We don't hear anything.

DR. ALAA KAMEL: I think she's using earphones. She's aware that she has to come back.

DR. DOUGLAS WOLF: Uh-huh.

DR. ALAA KAMEL: Yeah. I don't hear anything either.

DR. GEORGE COBB: Dr. Chaisson, we did not hear any background. You're muted. But we did not hear any background when you were worried about that. Dr. Chaisson, you're muted.

DR. CHRISTINE CHAISSON: My sincere apologies. It sounds like they're knocking the whole wall down.

DR. GEORGE COBB: We couldn't hear anything on this side.

DR. CHRISTINE CHAISSON: Oh, my goodness. Oh, that's good. Again, my apologies. Products -- you can hear me, Dr. Cobb?

DR. ALAA KAMEL: Yeah.

DR. GEORGE COBB: We can.

DR. CHRISTINE CHAISSON: Okay. Products selected for modeling in some COU subcategories, such as arts and crafts and hobby materials -- and playground sports equipment -- seem limited. EPA did not include a product for arts and crafts and hobby, and use of a single

fitness ball in a residence does not seem adequate to capture exposures that may occur, for example, in a gym, for the sports equipment COU.

And then we have a listing, which I won't go through, of formatting for just editorial or typos, things like that, which we will submit. We invite other members in the SACC to address some of these issues where we know that expertise exists on some of the things that we brought up. And with that, we conclude.

DR. GEORGE COBB: All right. Thank you very much for that summary. And I know you had lots to do with the first question and the short timeframe with the revised charts question. So I do truly appreciate that.

And there's quite a bit of -- probably crosstalk -- between the questions based on the complexity of the types of analyses being done. So I do appreciate that. I was not trying to shortchange your -- or shortcut -- your discussion. I simply wanted to make sure that we were in this charge question.

DR. CHRISTINE CHAISSON: No. I think your comments were good. Thank you, doctor.

DR. GEORGE COBB: So I'll turn it over to the other discussants on this -- the associates. And the first one is Dr. Li.

DR. LI LI: Okay. Good morning, everybody. So I just want to cover two things that have not been read off during the summary. So the first point is a very technical one. But I want to read a short version so that you can record it.

So the first point is, according to the reports, dermal absorption seems to be one of the highest exposure routes. However, considering that DIDP is lowly volatile and lowly water soluble, it's hard to understand the significant contribution to dermal exposure.

The Committee raised a concern about how EPA assessed the dermal absorption of DIDP in consumer products. First, the current calculation considered DIDP absorption from a saturated

solution on consumer product surfaces, which may lead to an overestimation of exposure to DIDP.

Second, this approach overlooks absorption from dust on this scheme. So in the written report, I will provide a more detailed explanation of these observations.

And the second point is line 1253, on page 48 -- a water solubility of 0.33 milligram per liter is mentioned here, which is 2000 times higher than the water solubility of 0.17 microgram per liter, as used in the environmental media modeling. See Section 4.2.1 of Draft Environmental Media and the general population exposure for DIDP.

However, 0.17 microgram per liter also appears as a "selection value" in the Excel spreadsheet, DIDP Draft to Consumer Risk Calculator, publicly released May 2024. So we were wondering which number was used. Yeah, that's my thing.

DR. GEORGE COBB: Thank you.

DR. LI LI: Yeah. Thanks.

DR. GEORGE COBB: And then our next discussant is Dr. Fanning.

DR. ELINOR FANNING: Good morning. Thank you. And thanks to Dr. Chaisson for representing as many of our comments as possible. I have one quick clarifying question. Chris, are we -- I understand that was our -- that was just 1.a.i. Correct?

DR. CHRISTINE CHAISSON: Correct.

DR. ELINOR FANNING: So we're still going to -- okay. In that case, I believe that my comments were -- you know, the points that I particularly wanted to make on 1.a.i were included and represented well. Thank you.

They have primarily to do with the fact that, as a general comment, I believe EPA has handled modeling of consumer and dust exposures to selected products in a reasonable way.

What I don't see are a clear rationale and transparency for whether these particular products are able to capture the full exposure distribution and ensure a health

protective assessment. So I think that comment was clearly read in by Dr. Chaisson.

And I would also add that the -- well, actually, I am going to pause because I think some of the other comments fit better under 1.a.ii and we're still coming to that. So thank you. I'll pass to the next.

DR. GEORGE COBB: Thank you, Dr. Fanning. And I guess I'd like to point out, since you mentioned that specifically -- the universe of products that would be chosen -- that yesterday I asked a question about toys that were intended for pets that perhaps children would be chewing on -- toddlers. So perhaps that can be part of the listing of things that should potentially be considered.

DR. ELINOR FANNING: Yeah. We've included a number of -- I think Dr. Chaisson was reading them in -- some of the scenarios that we had concern about. I think in-vehicle uses are particularly important -- vehicle interiors.

We talked about other modeling scenarios for some of the products. And we will get -- in the next section -- to some of our concerns about the dust. So I think products is a general comment.

DR. GEORGE COBB: Yeah. Great. Excellent. So thank you. And Dr. Reif is our next discussant.

DR. DAVID REIF: I have no additional comments.

DR. GEORGE COBB: Thank you. Dr. Ottinger.

DR. MARY OTTINGER: I have just a couple of comments. One is that, for the estimates of children's toys, they need to have a time-related element to them to see if there's any kind of change in the release of the compounds.

And also, the question of any sequestering -- I know that there is information about the lack of bioaccumulation -- but I wondered if there was a change in body burden and if that would affect the age-related exposures.

And then, finally, the inhalation -- the small -- which, of course, trapped the chemical -- the small size of particles are considered inhaled, and the larger ones are considered oral. And I'd like more definition about how that actually affects exposures.

And that's it. I had other recommendations, which I'm sure Dr. Chaisson will incorporate this in our written report. Thank you. And thank you, Dr. Chaisson, for putting all these comments together. That was heroic.

DR. CHRISTINE CHAISSON: Thank you.

DR. GEORGE COBB: All right. Thank you to the discussants. Now I'll turn it over to the Committee -- the full Committee -- for comments that you may have related to Charge Question 1.a.i. If there are no further comments, we will return to Dr. Chaisson for Question 1.a.ii. Oh, wait. I see a hand; I see Dr. Heiger-Bernays' hand.

DR. WENDY HEIGER-BERNAYS: Yes.

DR. GEORGE COBB: It disappeared.

DR. WENDY HEIGER-BERNAYS: Thank you. Yeah.

DR. GEORGE COBB: Ah.

DR. WENDY HEIGER-BERNAYS: Got it. Thank you. Dr. Cobb, this is one of the first questions, I think, with regard to that risk characterization. But it really focuses on 1.a.i, so I'll put it here.

So for workers -- so one of the known ongoing exposures of phthalates, including this chemical, is to young nail salon workers. I'd asked EPA whether that was considered. And I'd just like to put it here.

This population relies on income from poorly ventilated -- long hours, poor salaries -- in nail salons across the country. The majority of these populations are women of childbearing age. There's no evidence there are new publications on these with the knowledge that DIDP and the other phthalates are developmental toxicants.

This exposure scenario should be considered. EPA doesn't consider this. And if EPA chooses not to include this population -- which I would suggest is pest population -- then justification is needed. Thank you.

DR. GEORGE COBB: Thank you, Dr. Heiger-Bernays. And I was writing that in my book. I wasn't not paying attention to what you were saying.

DR. WENDY HEIGER-BERNAYS: I will send you my -- the write-up.

DR. GEORGE COBB: Okay. So thank you for that comment. And now, are there other comments? Okay. Seeing none, we can go to EPA to see if there are clarifying questions or if you prefer to read Charge Question 2 into the record.

MR. ANTHONY LUZ: Thanks, Dr. Chaisson and the rest of the Committee. This is Tony with EPA. We really appreciate your thorough response to our charge question. This time, we don't have any clarifying questions for you. So I think we can move on to part two of the charge.

DR. GEORGE COBB: Thank you. Please, do proceed.

CHARGE QUESTION 1.a.ii

MR. ANTHONY LUZ: Sorry -- okay, there's the charge question. Thanks. Okay. So part two of Charge Question 1.a. -- please include, in consideration of the consumer exposure model assumptions for analysis of suspended and surface dust through inhalation -- ingestion -- routes of exposure.

DR. GEORGE COBB: All right.

DR. CHRISTINE CHAISSON: Should I --

DR. GEORGE COBB: Yeah. Dr. Chaisson --

DR. CHRISTINE CHAISSON: Okay.

DR. GEORGE COBB: Yeah. Dr. Chaisson is our --

DR. CHRISTINE CHAISSON: Okay.

DR. GEORGE COBB: -- lead discussant.

DR. CHRISTINE CHAISSON: Thank you. Once again, I hope EPA will be patient. And so we got all of our comments into a much more tidy form. But I will -- I've collected them together here to show you the issues that we're focusing on.

Section 4.4, on page 112, in terms of DIDP exposures through the dust ingestion, the EPA found their model results of 50 to 700 times higher than estimates based on monitoring data. EPA wrote "The sum of DIDP intakes from dust and CEM modeled scenarios were, in all cases, considered higher than those predicted by the monitoring approach."

The difference between the two approaches ranged from 50 times in infants less than one year old to a high of 704 times in teenagers -- 16 to 20-year-olds. Our observation is that the method used by the CEM may have overestimated the DIDP concentration in dust by a factor of 100.

The CEM model uses an equation of 56 -- equation number 56 in the CEM Models User Guide -- that expresses a chemical's partition coefficient between dust and air as being proportional to a chemical's equilibrium -- octanol-air partition coefficient -- the KOA.

The underlying assumption is that the model treats dust as being equivalent to 40 percent octanol and assumes equilibrium partitioning between the dust and the air. However, more and more evidence shows that this equilibrium partitioning assumption is no longer valid for lowly volatile chemicals, especially for chemicals in KOA greater than 1 to the 10th.

This is because lowly volatile chemicals need an extremely long time to reach equilibrium between the air and the dust, which is often orders of magnitude longer than the resident's time of the dust within the interior environment.

In other words, dust disappears before a chemical reaches equilibrium between the

air and the dust. So for lowly volatile chemicals, the chemical concentration in dust -- I'm sorry, just a minute -- predicted by equilibrium models may always be higher than those measured in reality.

For example, Wechsler and Nazaroff 2010 collected measurements of more than 60 organic chemicals from 19 published studies. Their analysis shows that equilibrium models may overestimate chemical concentrations in the dust by a factor of 5 for a chemical with KOA of 1 to the 10th and by a factor of 100 for a chemical with KOA 1 to the 13th.

You can find this relationship in Figure 2 of Wechsler and Nazaroff's SVOC partitioning between the gas phase and settled dust indoors, published in the journal, "Atmospheric Environment." We'll provide the full reference.

As we know, DIDP is an extremely lowly volatile chemical, and the Draft Physical Chemistry Assessment for DIDP uses a KOA of 1 to

the 13th from this chemical. Therefore, it's likely that the DIDP concentration in the dust has been overestimated at least by a factor of 100.

Our recommendation is to either replace the default C (phonetic 01:03:00) in a method with more realistic numbers to consider the non-A polar (phonetic 01:03:03) being partitioning of DIDP between dust and air, or if this is not feasible, articulate this overestimation in a report.

Other issues included lines 6 -- 1463 to 1467, Equation 3-1, on page 56 and 57, and it's confusing why EPA sought to back-calculate the ingestion rate of dust -- or the ingestion rate of DIDP among Canadians -- reported by UC and Health Canada.

First, this black -- back-calculated ingestion rate of dust was not used in EPA's own calculation, as the EPA indicated later that the data for their calculations were taken from Oksana et all 2022.

Second, the way Health Canada calculated the ingestion rate of DIDP is by multiplying the acute p (phonetic 01:04:00) chemical concentrations and the ingestion rate of dust. So the ingestion rate of the dust is actually the input, not something that needs to be back calculated.

Other comments -- the CEM is generally appropriate for purposes of assessing indoor dust exposures for use patterns and receptors. However, CEM assumes a home environment, and EPA should not limit exposure scenarios for the COUs to in-residence.

In order to address exposure scenarios, such as vehicle interiors or gyms, as mentioned, some CEM defaults may be adaptations. EPA has to ensure that upper bound exposure scenarios are included and carried forward to the risk evaluations. This comment is relevant to DINP and other high priority phthalates.

Carpeting in homes does not appear to be a CEM input, but the presence of carpets may

alter dust fate and chemical loading of dust. It should be considered as a source of variability, uncertainty, and modeling, perhaps. And the others added that the issue about carpets can be handled, as it would be the medium that is providing the exposure.

We appreciate the detailed technical information from CEM. It's not all rewritten in the exposure assessment. The equations in Tables 2.7 through 2.12 are helpful. However, some additional information on dust size fractions and fate pathways into the dust would be appreciated.

Time periods for acute, intermediate, and chronic exposures seem appropriate, as does the daily model doses to compute the intermediate exposure durations that are based on professional judgment.

Section 2.2 -- dermal modeling -- this section explains EPA's logic, though we need further consideration on the aqueous layer as part of the dermal exposure, particularly given to the low solubility for DIDP.

There does not appear to be consideration of the dermal to oral pathway for DIDP. This may be important for some articles and for some pests and should be added. This is a concern for the other phthalates as well. An example is a young child using synthetic leather furnishing while sucking a thumb or eating snacks with unwashed hands.

Section 3.2 -- indoor dust modeling -- Gubuaveaux (phonetic 01:16:00) et al -- reference to be provided -- is an appropriate comparator given the limited data for DIDP.

However, EPA should note that production and use of DIDP has increased since the Canadian house dust study -- which was performed in this 2013 publication on dust in Canadian homes -- may underestimate current exposure levels for dust in the U.S.

It's also worth noting that the maximum concentration of DIDP in house dust was 14-fold higher than a median, indicating a

substantial difference between -- or a great variability -- in the DIDP dust.

Regarding other phthalates, there are considerably more dust monitoring studies for lower molecular weight phthalates. We'll include other references. The dust ingestion rates -- Noskenya (phonetic 01:08:00) et al -- and EPA -- appear to be incorporated and applied.

That's the end of our comments for that section.

DR. GEORGE COBB: Thank you, Dr. Chaisson. And we have a similar list of discussants. Dr. Li.

DR. LI LI: I don't have anything to add. Thanks.

DR. GEORGE COBB: Thank you. Dr. Fanning.

DR. ELINOR FANNING: Thank you. Let's see -- as my camera's not working. Oh, there we go. Thank you. Just a short addition to the comment that Dr. Chaisson read in concerning

modeling of potentially non-residential exposure scenarios.

So one of the assumptions that is made in this modeling is that residential exposures capture the high-end consumer exposures. And we think that, despite shorter exposure time durations in other microenvironments, EPA has not clearly assured the public that exposure levels couldn't be higher in some of those microenvironments.

And so we recommend that EPA explore and present some specific exposure scenarios for selected COUs -- and particularly those COUs with numerous products -- such as -- I don't have my document open -- but a COU that is plastic products generally.

And I think the important piece I wanted to add is that high exposure scenarios should aggregate across exposure levels across numerous contributing products. So for example, on the car interiors, we don't -- we're not interested in just hearing about exposure from car

mats. It needs to integrate across all the plastic products in the car. Thank you.

DR. GEORGE COBB: Thank you for that comment, which reminds me -- alumni from our university and others have published information related to phthalates in things like carpet dust and found that they are certainly equal to, if not higher, in places like daycares and places of worship and work environments -- like office environments, not manufacturing environments. So that is an important point. Thank you for bringing that up. Now, our next discussant is Dr. Reif.

DR. DAVID REIF: I have no additional comments. Thank you.

DR. GEORGE COBB: All right. And then we have Dr. Spade.

DR. DAN SPADE: Thank you for the summary. And I think the only comment that I have that wasn't in the summary is just a question for clarification from EPA.

If the model dust concentrations -- if that model includes the assumption that DIDP has to enter the vapor phase before it can become associated with dust -- I think in the previous charge question, there was a request for clarification about whether abrasion or other pathways could lead to DIDP entering dust without having entered the vapor phase. And so I think that is a relevant question to how dust concentrations of DIDP are modeled.

DR. GEORGE COBB: So is that a question to EPA today? Or is that a question you're suggesting should be addressed in their report?

DR. DAN SPADE: I guess that's a question I'm suggesting should be addressed in their report.

DR. GEORGE COBB: Okay.

DR. DAN SPADE: Yeah.

DR. GEORGE COBB: Thank you. Dr. Fanning is back.

DR. ELINOR FANNING: Yeah. I just wanted to follow up on Dr. Spade's comment there. That was an important piece of conversation that we had in the Committee.

And I also wanted to put in the record the discussion that we had with staff yesterday about the volume of dust in the model that is considered available for exposure to DIDP. And what we thought we heard from staff was that it's only the dust that settles on the article in question.

So that, I think, is actually a question to EPA. Can EPA please clarify for us whether dust that enters -- DIDP in dust that enters into the model -- is the entire reservoir of house dust available for exposure? It was very hard to tease that apart yesterday.

DR. GEORGE COBB: Okay. All right. Thank you. And we will go to EPA for clarifications on some of that after we go to the remainder of the Committee. So are there comments

from the remainder of the Committee? Okay. I don't see any.

But I do have a -- maybe a question for those who commented on the partitioning and equilibrium of DIDP between vapor phase and dust. And there was a discussion about -- since the partitioning couldn't come to equilibrium, that the concentrations in dust were overestimated.

The question then becomes -- does that not imply that the concentrations in air are underestimated? And if so, is that not a large underestimation, given the partitioning coefficient? So does the group -- or the person that made that dust overestimate -- what do you think about that?

DR. LI LI: So this is Li Li speaking. So I made a comment on the dust and air partition coefficient. So maybe I can provide some more information about this. So let me find this. Okay.

So the CEM model actually made an assumption that it is the chemical first getting

to the air phase -- which is the vapor phase -- from the product material and then partitioning to the dust. So that's why the dust air partition coefficient is very important.

So if this partition coefficient has been -- overestimate -- and then, with the same level of air concentration, you can get a higher concentration in the dust -- so that's why the concentration of dust would be overestimated.

So I have to point out that a limitation of this method is -- they ignore the abrasion or other ways of release of chemical in the environment because the chemical can be released into the environment through the abrasion and the dust generated from this one.

So in that case, the starting point of the chemical partitioning would be the chemical in the dust, not the chemical in the air or in the vapor phase. So in that case, if the partition coefficient is -- underestimate -- then the concentration in air would be a overestimate. And

then the concentration in dust would be still okay. Yeah.

DR. GEORGE COBB: So even more complicated than my question.

DR. LI LI: Oh, yes.

DR. GEORGE COBB: Okay.

DR. LI LI: Yes.

DR. GEORGE COBB: So thank you for that discussion. And I think that will be helpful. Are there other comments from the Committee before we precede back to the -- turn it back to EPA? All right. So thank you to everyone.

And we'll turn it back over to EPA for -- to see if you have clarifying questions for us and perhaps to see if you can answer Dr. Fanning's question about the dust deposition. If not, I understand it's on the spot.

MS. LAURA KRNAVEK: Hi, this is Laura Krnavek. Responding to -- just to rephrase the question and make sure I can understand it -- the question was whether the entirety of the

surface area for the article -- and then all of that is covered in dust -- that would become available for -- and it depends on the exposure route that we are pursuing, of course -- so for inhalation, for example, that dust would become available, suspended, and then would become available for inhalation.

So Dr. Li's description of the complexity of the dynamics of dust and vapor are correct. The model does provide the inhalation of both -- of the dust particulate and gas phase without decoupling both. So when we get inhalation, it's both a particulate -- the dust then suspended, and the vapor. I hope that sort of clarifies a little bit of that.

And then there is some ingestion from some of that suspended as well. That's also part of the ingestion assessment. A lot of the ingestion assessment is also done as suspended on the settled dust. So that would be the bulk of that assessment -- whatever was settled. So we do

assume that the bulk of that dust would be available for ingestion, which is --

DR. GEORGE COBB: Okay. Dr. Fanning, does that answer your question?

DR. ELINOR FANNING: Sorry -- trying to get off mute. I think that that is -- I think we have the information that we need to proceed with preparing comments about the handling of dust in the models. Thank you so much.

DR. GEORGE COBB: Yep.

DR. CHRISTINE CHAISSON: Yeah. Dr. Cobb, we'll be taking the information EPA has provided -- or if they want to give us more information about the specifics of those comments -- and then I'll be asking Dr. Fanning and Dr. Li to try to put together a thorough, coherent conversation of this --

DR. GEORGE COBB: Okay.

DR. CHRISTINE CHAISSON: -- along with the recommendations.

DR. GEORGE COBB: Yeah. I'm confident in that. So thank you to EPA for

providing that response. And now we'll move to our next charge question.

DR. LAURA KRNAVEK: Anthony.

CHARGE QUESTION 1.a.iii

MR. ANTHONY LUZ: This is Anthony Luz, EPA. So I'm now going to read Charge Question 1.a, part three. Please also comment on mouthing behavior input parameters related to estimating chemical migration to saliva for infants and toddlers. Thank you.

DR. GEORGE COBB: Okay. And Dr. Chaisson is our lead discussant again. And I will remind everyone -- this is George Cobb speaking -- we are supposed to identify ourselves. And so please do that. I'm introducing Dr. Chaisson, so I'm not sure that's essential. But when you do speak, please identify yours- --

DR. CHRISTINE CHAISSON: This is Dr. Chris Chaisson. In general, the Committee accepted the EPA approach for assumptions for this

to be representative for the exposure assessment. However, the approach described in lines 851 and onward and in Table 2-10 appear to contain a slough (phonetic) that could lead to underestimated exposure.

To set high, medium, and low exposure scenario for mouthing values, EPA used the mean mouthing time from the exposure factor manual for ages 1 to 3, 3 to 6, 6 to 9, and 9 to 12 months.

However, by setting the high exposure scenario mouthing time as the longest mean time from those four subgroups, the model is listing approximately the upper 50th percentile of the distribution for that highest subset. This could lead to underestimates of exposure.

We note also that this lack of looking at the full distribution overlooks the possibilities of the -- of such distributions being skewed either to the left or to the right. It also may underestimate the effects of age of

the materials and of the effect, if you will, on distortions from "chewing."

Parameterization of the mouthing behavior and migration to saliva appear to have been thoughtfully done. The resources were identified. The Danish EPA report on migration of phthalates into saliva support the use of this document generally, as well as using the DINP migration rate as a surrogate for DIDP.

Mouthing behavior inputs from the exposure factors handbooks seems reasonable. We ask you to consider the inclusion of pet toys, as has been brought up before, and was in the dynamics of the release factors that have been mentioned before.

That was an uncharacteristically short report from us.

DR. GEORGE COBB: So thank you, Dr. Chaisson. And, you know, there probably was crosstalk between a lot of these questions. So maybe some of the response to this actually was captured in 1.a.i a bit as well. So I appreciate

that. So our discussants are again fairly similar. So, Dr. Li.

DR. LI LI: I don't have anything to add.

DR. GEORGE COBB: And Dr. Fanning.

DR. ELINOR FANNING: No additional comment; thank you.

DR. GEORGE COBB: Dr. Reif.

DR. DAVID REIF: No additional comments; thank you.

DR. GEORGE COBB: And Dr. Spade.

DR. DAN SPADE: I have no additional comment; thank you.

DR. GEORGE COBB: So thanks to that group of discussants. And the rest of the Committee -- are there additional comments from the remainder of the Committee? If there are none, we can turn this back to EPA for clarifying questions and then reading in the next charge question after that.

MS. LAURA KRNAVEK: Hi, this is Laura Krnavek asking in a clarifying question on

one of the comments and making sure that the comment on the age routes and the mouthing parameters used were not just related to the indoor monitoring assessment analyses that were performed, but they're also looking to the dosing parameters for the overall modeling mouthing that we did in -- just clarifying that.

DR. GEORGE COBB: Dr. Chaisson or the discussant group?

DR. CHRISTINE CHAISSON: I'm not sure I know the answer to that. Maybe somebody else on the subcommittee can clarify that.

DR. DAN SPADE: This is Dan Spade. So I think part of the comment is a question about how a high-exposure scenario or a low-exposure scenario is properly defined. So if you are defining a high-exposure scenario for the entire age -- 0 to 1 year's age group -- by selecting mean data for subsets of individuals that fall under that 0 to 1 age group --

DR. GEORGE COBB: Yeah.

DR. DAN SPADE: -- does the high exposure scenario properly define -- to have to account for some portion of the upper tail of the distribution? And if it does, then I think the question is -- does the selection of the highest mean of the four means leave out a significant portion of the upper tail of the distribution?

DR. CHRISTINE CHAISSON: Okay. I misunderstood the question fully. Within the Exposure Factors Handbook, the references for the data that actually was used by the group to derive those means is usually included.

I haven't looked up these numbers in a long time. But that is where I usually go to look for two things, and one is if -- why did they pick the mean -- and did they report the median? And what is the distribution of the exposures that were used?

The people who put the Exposure Factors Handbook together really took on a heroic task because sometimes the data that were being used was this snuck hole (phonetic 01:27:00)

ideal. And so they did the very best they could, from my point of view, to come up with usable factors that are generally employed.

In situations like this, I think it might be well worth going back to look at the original information and see whether or not those distributions can be exposed, if you will -- no pun intended -- and whether or not there are better information available today than were cited in the exposure.

This was actually the reason why we asked for when the latest update was done on some of these factors in the book. Because some of those data are a couple decades old. So I understand that the Agency uses exposure factor handbooks, which is an outstanding tool, but in this kind of circumstance where -- it might be worth looking for more recent information, specifically showing the distributions.

DR. GEORGE COBB: Dr. Krnavek, does that answer your question?

DR. LAURA KRNAVEK: Yes. I think so. I think they are talking in general, not just the one analysis. So yeah. Thank you.

DR. GEORGE COBB: It's good to get these things clarified. And I know it helps you prepare before we can get our final report drafted. So now we can turn to reading in the final charge question for 1.a.

MS. CHARLENE ASP: 1.a.iv, Dr. Cobb?

DR. GEORGE COBB: Are we on 1.a.iv? We --

MS. CHARLENE ASP: I think.

DR. GEORGE COBB: Yeah. I'm laughing because Charlene was trying to help me not make this error, and I've already made it. So yes, 1.a.iv -- we're not quite to the final charge question for this -- for 1.a.

CHARGE QUESTION 1.a.iv

MR. ANTHONY LUZ: This is Tony Luz with EPA. I'll now read in part four of Charge

Question 1.a. So in light of comments on charge questions 1.a.i through 1.a.iii, please comment on the latest scientific evidence and its conclusions for the consumer in indoor dust assessments -- both Section 5 of the Draft Consumer Indoor Dust Exposure Assessments.

Please include in these comments a discussion of the clarity and transparency of the data used and EPA's interpretation of the exposure results. Thank you.

DR. GEORGE COBB: Thank you for reading that into the record. And Dr. Chaisson is the lead discussant for this question as well.

DR. CHRISTINE CHAISSON: Thank you. This is Dr. Chaisson. We had a series of comments. First one -- use of Canadian data, as well as data from other countries, was sort of downgraded. And, in our opinion, it looked rather severe. Unless there are reasons to expect the COUs or other significant factors of manufacturing, environmental conditions, use,

populations involved, or such, the geopolitical status does not seem relevant for downgrading.

This is especially true for information from Canadian and the EU countries, where the scientific and regulatory attitudes about research, monitoring, data quality, regulatory use of information, et cetera, are at least equal to those of the U.S. regulatory and research bodies.

We need to compare reviews on these chemicals across other regulatory authorities. By the way, we noted that the way that this was done -- in looking at the toxicology information -- I think was really excellent. And we will strongly encourage a similar approach to be used for the data and information in general used in the exposure assessment.

This is important for a variety of reasons, including comparisons of data use, approaches, and ultimate exposure assessments and risk assessment metrics. In such comparisons, the details about the options and utility of data,

approaches and methods and models can be understood by the EPA scientists, SACC reviewers, stakeholders, and the public.

EPA evaluations now seem to be isolated reviews on an international level, although the products and chemicals are often internationally distributed, used, and regulated. A presentation of what other authorities offer for scientific reviews and/or regulation of the chemicals -- including internationally, by U.S. state, under scientific authorities -- would be a good starting point.

Data used depends on contextual factors such as -- are the products grouped in the same way for review -- are other data information used by other authorities -- the era of the reviews -- and are aggregated exposure and risk assessment used -- either to assess multiple scenarios or to highlight relative contributions of different exposure scenarios, such as those we're considering -- and products to the aggregated risk?

What are the differences among the answers, exposure of populations exposed, et cetera? These kinds of comparisons are very, very helpful and very, very important for credibility of the Agency's review.

Such considerations of other thoughtful evaluations serve to provide context around the answers and highlight areas of significant differences, which can be discussed and can improve confidence in the EPA's assessment methods they've used -- models -- et cetera.

Scientists, stakeholders, and the public can see differences in conclusions -- regulatory differences, et cetera -- from other authorities and regulators. Without such discussions by EPA, these readers will logically wonder what yielded the differences and possibly question the reviews. Indeed, that situation can be exploited.

The clarity and transparency of EPA's reports are impressive for a regulatory assessment across such broad necessary sciences.

Comments in the previous sections may assist with additional improvements. The most significant issue is probably one of apparent omission rather than improvements of existing reviews.

In particular, the overall construct of the document -- parsing into consumer use -- only one of the review topics in the TSCA mandate, we've pointed out, seemingly ignored completely topics as we discussed before -- and their related exposure scenarios. We will detail that, of course, in our written report.

The explanations for assignment of slight, moderate, and robust confidence for weight fractions, product use patterns, and article surface are transparent. Selecting stay-at-home activity patterns and approaches to mouthing behavior are reasonable, but we, of course, have already suggested some improvements on that.

Dermal absorption is an area of high uncertainty in the assessment, and it needs to be highlighted for the risk evaluation chapter. Use of upper bound exposure estimates in risk

evaluations for the COUs, including dermal absorption, is warranted due to the considerable uncertainty. Thermal to oral routes should also be addressed.

In Tables 5.1 through 5.3, due to the issues raised previously -- without construction products contributing to exposure after use as they age and wear and endure environments -- we recommend reducing the overall exposure confidence until that's corrected.

Further, as mentioned previously, the COU -- automotive and other fluids -- needs to be fully represented. That absence and lack of discussions lend to other potentially high exposure scenarios. And non-residential scenarios reduces the overall confidence in the report.

Confidence estimates derived from the Canadian house dust study monitoring -- from moderate to slight -- there are numerous uncertainties in comparison to the modeled measure estimates. We will detail this further in the written report.

Lines 2120 to 2113, on page 116 -- a calculation of the aqueous permeability coefficient -- Kp -- in this assessment may be highly uncertain. The Ken Burch approach was used, which considers the resistance to permeation caused by three components in the imminent skin -- the lipid medium and proteins in the stratum corneum, and the aqueous boundary over the skin, also known as the water layer.

This EPA calculation was looked at -- and found that since DIDP is highly hydrophobic, the majority of resistance comes predominantly from the aqueous boundary layer. It does not matter how the lipids and proteins are considered or prioritized in the model. The key is ensuring the permeation across the aqueous boundary layer is well-characterized and calculated.

However, a chemical's permeability across the aqueous boundary layer is currently understudied for highly hydrophobic chemicals. We simply don't have enough data. Therefore, the calculated Kp may also be highly uncertain, and we

do not know whether the calculated Kp overestimates or underestimates the actual permeability across the aqueous boundary layer.

In line 2114 to 2115, on page 116, EPA states "However, EPA is confident the selected approaches represented upper bound dermal absorption from DIDP from solid articles." However, there is no explanation for why the EPA is so confident.

And -- mentioned before -- the EPA's estimate of dermal absorption may have substantially overestimated dermal exposure because it does not consider rate limit by mass transfer within the product material. If this overestimation is considered a sign of conservativeness in risk assessment, then the EPA can state that this confidence is based on that principle.

However, leaving to question the entire SACC and EPA, overestimation can be caused by either using inappropriate assumptions in the calculation or by selecting the higher end values

for individual variables. Conservativeness in risk assessment can be achieved through both -- and this needs to be clarified.

And I believe that's our entire presentation. Thank you, Dr. Cobb.

DR. GEORGE COBB: Thank you, Dr. Chaisson. You're doing yeoman's work here for these charge questions. I'd like to turn it over now to the individual discussants. Dr. Li.

DR. LI LI: No additional comments.

DR. GEORGE COBB: Thank you. Dr. Fanning.

DR. ELINOR FANNING: No additional comments; thank you.

DR. GEORGE COBB: Dr. Reif.

DR. DAVID REIF: No additional comments; thank you.

DR. GEORGE COBB: And Dr. Spade.

DR. DAN SPADE: No additional comments; thank you.

DR. GEORGE COBB: Excellent. Thank you to that team. Now we'll turn it back over to

EPA to see -- one, if there are clarifying questions -- and if there are none, we will proceed to the reading of the next charge question.

MR. ANTHONY LUZ: Dr. Cobb, this is Tony Luz with EPA. There's no clarifying questions at this time. So maybe we can move on to the next charge, as you mentioned.

DR. GEORGE COBB: Excellent.

CHARGE QUESTION 1.a.v

MR. ANTHONY LUZ: Okay. So now I'm going to read part five of Charge Question 1.a. So for the remaining phthalates, i.e., DEHP, DBP, DIBP, BBP, DCHP and DINP, EPA anticipates potentially needing to refine the exposure assessment for consumer indoor dust exposure.

We suggest exposure data sources, models, and narrated (phonetic 01:41:00) methods for estimating dermal inhalation and ingestion exposures to chemicals from consumer products that

are reasonably available and can be conducted in a timely fashion that allows EPA to meet statutory timelines for TSCA risk evaluations. Thank you.

DR. GEORGE COBB: Thank you for reading that question in. And we will turn again to Dr. Chaisson.

DR. CHRISTINE CHAISSON: Yes. Dr. Cobb, can you give me just a moment to pull that up, please?

DR. GEORGE COBB: Certainly. And while all that's being read in, one thing that came to mind that I did not mention that is pertinent to this particular charge question is -- with the advent of a lot of modern high-resolution mass spectrometry, research groups have gone to using high-resolution mass spectrometry to capture virtually all the chemical signature from a sample and archive the data rather than archiving the samples -- archiving the mass spec data that could be queried for this type of information.

Now, that said, finding that information -- that specific information -- I'm

not prepared to make a suggestion for that. Now, just to realize that there are research groups throughout the world that are collecting samples of the types we're discussing and analyzing them basically for all the organic materials that their data processor will gather.

And then they're archiving the data rather than the samples. So there may be ways to obtain those types of data. But again, I don't have specific sources for that right now. So, Dr. Chaisson, did that --

DR. CHRISTINE CHAISSON: Yeah.

DR. GEORGE COBB: -- get you enough time?

DR. CHRISTINE CHAISSON: Yeah. Thanks for that. I appreciate it.

The risk assessment for these chemicals individually rely on exposure and hazard information that carefully align. At least one of the phthalates -- DBP -- is thought to be acutely potent, which means that the exposure scenarios,

habitational factors, and subpopulation emphasis will likely be uniquely important.

Such scenario components are different from those designed for chronic exposure scenarios. Attention on the statistical handling of data informing the exposure models must be appropriate for acute exposure scenarios. DIDP is relatively data-poor in comparison to the other high-priority phthalates.

As a general comment, EPA should be prepared to thoroughly evaluate products and scenarios to model to ensure that the selected items and scenarios will provide reasonable assurance of including upper bound exposures and most highly exposed as biologically simple populations -- and as pointed out above, consideration for use in acute exposure.

EPA may need to model some scenarios outside of the CEM with readjustments to the CEM if those scenarios represent high exposures that may be a concern for a given COU. Just a moment. More complete attention to how chemicals can enter

the household air and dust through a generation of dust particles from articles and products will be important for the broader COUs and the number of products and articles for the DIDP.

As suggested before, degradation of plastic polymer products and articles should be included in the dust exposure modeling. We have also noted before that the dynamics of the polymer in which the phthalates are included are a key point for all of these evaluations and that apparently cellulose is also a non-plastic component that needs to be covered.

The DINP exposure assessment should be reviewed by the SACC, in our opinion. The current review exposure methods for DIDP does not adequately cover issues that were likely to arise with the DINP.

We will include a list that details many of the specifics, including how the additional exposure scenarios that we discussed in early parts of our review will impact these other phthalates and how some of the specific issues

that we have found should be considered for these specific -- especially where we expect that the type of plastic or type of polymer, in general, in which it is embedded -- becomes an issue across all of these.

This is a very abbreviated review here in this section, but I think we've captured the key topics that we will expand upon and, wherever possible, provide references.

DR. GEORGE COBB: Thank you.

DR. CHRISTINE CHAISSON: And that completes it.

DR. GEORGE COBB: Thank you. And let's go to the other discussants. Dr. Li.

DR. LI LI: No additional comments; thank you.

DR. GEORGE COBB: Dr. Fanning.

DR. ELINOR FANNING: I do have one additional comment. Thank you for reading in the compilation, Dr. Chaisson. I wanted to add to the record the opinion that, as EPA assesses exposure to DINP and the other high-priority phthalates,

attention to cumulative consumer exposures and risks will become especially important.

Some of the broader conditions of use for the phthalates include conditions of use where there are multiple products that can contain different phthalates. What that means is that those conditions of use need to be evaluated for the potential or cumulative exposure and risk.

So pests -- based on either high-exposure or susceptibility -- are particularly important. On this, I want to recognize the Committee is aware that the cumulative risk approach is not yet finalized, yet we still urge EPA to provide some context for those COUs with multiple phthalates, as EPA is conducting evaluations for the individual phthalate chemicals. Thank you.

DR. CHRISTINE CHAISSON: Dr. Cobb?

DR. GEORGE COBB: Yes.

DR. CHRISTINE CHAISSON: Adding to Dr. Fanning's comments, there have been discussions about how, when doing aggregation and

doing cumulative assessments, it appears to us that the entire concept of distributional exposure factors and probabilistic approaches will have to be employed.

So we're not jumping the gun, I hope, on that assessment. But that substantiation of the comments I just made will also be included in our remarks.

DR. GEORGE COBB: Okay. Great. Thank you. Now, Dr. Reif.

DR. DAVID REIF: No additional comments for me.

DR. GEORGE COBB: All right. Thank you. Return to the balance of the Committee -- are there additional comments about the broader phthalate question in the exposures? I see Dr. Fenner-Crisp.

DR. PENELOPE FENNER-CRISP: It has to do with the comment that was made about the acute stuff. And that reminds me of a cautionary tale about expectations of what cumulative risk assessment might look like. I think it may be an

expectation on some people's part that that would be one thing -- just one assessment.

But the fact that the comments that were made just now might well be that there will have to be multiple ones based upon durations of exposure -- not simply one that would cover everything.

But Dr. Chaisson noticed some of the acute effects vary, and they aren't the same ones that are right now targeted -- or at least have been discussed with respect to the human risk assessment.

You may have to have different endpoints and all that kind of thing. So I think one should be cautioned to understand that the Agency has more work to do in a cumulative risk assessment for these phthalates than one might have expected.

DR. GEORGE COBB: Excellent point. Yeah. Thank you very much. Are there other comments? Okay. Seeing none, we can move to the

EPA to see if there are clarifying questions related to this charge question.

MR. ANTHONY LUZ: (auto skip 01:51:37) EPA -- no clarifying questions. I'd just like to thank the Committee for all the thoughtful discussion and recommendations to the Agency for DIDP Charge Question 1.a. Thank you.

DR. GEORGE COBB: Well, and we appreciate your dialogue with us today here. All right. We are at a lunch break, and we're ten minutes early. I think perhaps we can -- is it okay with the Committee and the Agency if we go to lunch now and take an hour and ten minutes?

MS. CHARLENE ASP: That would be great.

DR. PENELOPE FENNER-CRISP: Some of us have teed up a breakroom session during lunch.

DR. GEORGE COBB: Well we can --

DR. PENELOPE FENNER-CRISP: Do we want to do that now or later?

DR. GEORGE COBB: -- you know what -- the lunch break is not scheduled until an hour

from now. I misread the schedule. I really apologize. Dr. Chaisson, are you prepared with 1.b.i?

DR. CHRISTINE CHAISSON: Yeah. We sure are.

DR. GEORGE COBB: Okay. Well then, EPA, if you can read 1.b.i into the record, that would be great. And if that's Dr. Luz, I apologize for continuing to call you EPA, but --

MR. ANTHONY LUZ: That's okay.

DR. GEORGE COBB: -- I don't have a list of who's going to be asking the question.

CHARGE QUESTION 1.b

MR. ANTHONY LUZ: No problem, Dr. Cobb. This is Tony with EPA. I'll be reading Charge Question 1.b. And this has four parts.

As described in Section 2 of the Draft Environmental Media and General Population Exposure for DIDP, EPA used sentinel exposures to conduct a screening approach for the DIDP exposure

assessments. EPA anticipates that the exposure methodologies demonstrated in the Draft Risk Evaluation for DIDP will be applicable to DINP exposure scenarios.

CHARGE QUESTION 1.b.i

And so part one of Charge Question 1.b -- please comment on the strengths and uncertainties of the selected data and methods employed in the use of sentinel exposures in the screening approach.

DR. GEORGE COBB: Okay. Thank you for reading that in. And we will turn to Dr. Chaisson as our lead discussant.

DR. CHRISTINE CHAISSON: This is Dr. Chaisson. Right now, we're going to detail for you a listing of issues that we've come up with in our report. We will further discuss these in terms of strengths and challenges within that report.

The issues included relevance of the medium. DIDP in water is assumed to partition into particulates that settle to the bottom or lower part of the water column.

And therefore, waterborne chemicals would not be available for exposure opportunities -- humans or other organisms in food chains, et cetera. This may overlook food chain issues and consumptions by other types of fish or yield food chain exposures, especially to pest communities -- subsistence communities.

The water bodies are not all clear in reality, often when it's murky -- or constant turbulence. That condition provides opportunities for exposure by swimming, surface water consumption, or use in foods by subsistence communities. This is discussed in references from the public submissions, by the way, and was discussed previously with EPA.

If concentrations are above -- this was a point of some confusion about the calculation -- if concentrations are above 27,000

-- no advance per kilogram -- that's like 2.7 percent by weight -- that level of contamination, even if adhering to particulates, needs to be explored in detail. EPA presumes that to be of no consequence, as it is written up, whether or not they meant to portray it that way. We will detail that a little further.

Flooring scenarios -- mobilizing media containing the phthalate, including on the ground and dry surfaces and the sediment in shallow bodies of waters -- rivers and creeks -- should be further discussed.

The general approach of sentinel is good. We have no argument with that -- see page 8, lines 272 to 281. But execution of the approach could profit from a more structured deliberation. And we would like to present where we see that could be included in the overall approach for the TSCA evaluations.

Again, the concept of just general population seems to be used with less consideration, in a structured way --

consideration for pest. Although EPA mentions it, it just usually says we don't find any pests -- in that conversation. Given the vigorousness of phthalates, it seems to be understated -- details to follow.

The assessment could benefit from further exploration of exposures from dirt. What about construction workers, gardeners, landscapers, and the track back into the home by general dirt in them -- both from occupational and from general environments -- and the daily exposures to broad groups of people?

The concept of the use of sentinel exposures to test for exposure scenarios of potential consequence, as discussed in EPA's document for exposure assessment -- as discussed in Section 2 -- is a valuable approach, especially when monitoring data where new exposure scenarios are being discussed with limited record of actual exposure of media resident.

The Committee agrees on this. However, the assumptions described in Section 2 --

especially lines 368 to 375 -- at the highest end of an exposure path -- it begins with industrial releases -- it should be chronicled and defended somehow because it drives the entire sentinel assessment paradigm on which these analyses rest.

The industrial releases may indeed yield high-end exposure pathways. But there may be other exposure pathways for phthalates which are also generating high-end exposure and potentially, also, sentinel.

And given there are no monitoring or resident data to declare which sentinel is the biggest, all potential high-end pathways may be legitimate to include in this assessment process.

The EPA assessment of phthalate exposure and subsequent risk does not include the world of distribution of products nor the products through the wholesaler, retailer, or online -- distributed to the consumer. That pathway has a lot in common with the logic that is used for industrial releases.

The pathway involves wrapping individual products and whole plats of products -- movement, stacking, storage -- in massive warehouses. Workers in these facilities are in constant proximity to phthalate-rich wrapping materials, insulation materials, packing materials, and the dust in the buildings' shelves and on interior structural components of the buildings.

Just as in the residences, the exposures could be significant. And for these workers, one can assume long daily exposures -- periods over a five or six day per week working schedule.

The track home residents may not be sentinel, but could also be significant to the contamination of home spaces and the multi-generational people living there. Hence, unlike the industrial fugitive release into outdoor spaces, here we have the potential of exposure to phthalate-rich dust for chronic exposure scenarios.

In other words, the dust either stays in those big warehouses for exposure to the workers, or it gets sucked out through the ventilation, where exposure pathways look a lot like the industrial kinds of emissions.

Perhaps in addition to the pathways proposed by EPA, in Table 1-1 of Section 2, page 11 -- distribution in commerce -- it is listed, but is apparently not discussed in the assessment -- or not found, at least by this reviewer.

Section 2.2 and other sections state "General population exposures occur when DIDP is released into the environment, and the environment media is then a pathway for exposure." While this is most likely true -- but is the evidence or body of evidence that this specific scenario is always the progenitor of the sentinel exposure?

If this is to be the only progenitor scenario considered by EPA -- as a practice of science, if not a policy -- then the evidence for it should be at least cited in the document,

especially if other initiating scenarios are not to be considered.

I believe that's all of the -- no -- there are others. There is also an issue about the use of fish consumption that, of course, is very important for the calculations in the sentinel exposure scenarios, as other types of animals may also be.

Since DIDP has a high KOW and a high KOA, it's anticipated that fish consumptions -- more so than maybe other terrestrial food sources -- makes the highest contribution to the total chemical intake because such chemicals are more bioaccumulative in aquatic animals than in terrestrial animals. That may also be true for the other species that we've mentioned in this review.

And with that, I conclude.

DR. GEORGE COBB: All right. Thank you for providing that summary. And now we can turn to our other discussants. Dr. Li.

DR. LI LI: No additional comments; thank you.

DR. GEORGE COBB: Thank you. Dr. David.

DR. RAYMOND DAVID: No additional comments.

DR. GEORGE COBB: Dr. Reif.

DR. DAVID REIF: No additional comments on this.

DR. GEORGE COBB: Thank you. And then, Dr. Gentry.

DR. ROBINAN GENTRY: (audio skip 02:03:44) additional comments.

DR. GEORGE COBB: Was that no comments?

DR. ROBINAN GENTRY: No additional comments; thank you.

DR. GEORGE COBB: Okay. Thank you very much. All right. So now we can turn back to EPA to see if there are clarifying questions. And if not, we can move to Charge Question 1.b, which would be led by Dr. Li.

DR. CHRISTINE CHAISSON: Excuse me. Dr. Cobb, are there comments from the rest of the Committee? We hit on some points that others might have expertise on.

DR. GEORGE COBB: Yep. You're exactly correct. And I did not go there. So let's go to the rest of the Committee to see if there are other comment- (audio skip 02:04:24) --

DR. LI LI: Thank you for reminding us, Dr. Chaiss- --

DR. GEORGE COBB: Yeah. Dr. Ottinger.

DR. MARY OTTINGER: I just want to bring up a theme that's going to keep coming back over and over again, which is that there's a bit of a disconnect in terms of the assessments that are made for aquatic levels and that there were effects at lower than environmentally measured concentrations. But the question became -- was it a physical rather than chemical effect -- and just to read that into the record so we can have further discussion on that point.

DR. GEORGE COBB: I think that's a good point. That's one that I brought up yesterday. And I think that's an important point that needs to be addressed. And we can either do that here or in the later discussion of how that cascades into the risk. But yeah, I agree that there were effects that were discounted and not considered. So do you want to expand on that any, Mary Ann?

DR. MARY OTTINGER: Yeah. I think it's going to come up again in 1.b.ii. And it's also going to be revisited when we talk about more of the environmental effects in the charge questions later today and tomorrow.

But I think it's important to make sure that we look at the data that are available because they are sometimes dismissed for various reasons -- and just make sure that the reasoning for dismissal is very clear and warranted, and supported by the available literature. Beyond that, I just think it's going to be a continuing

discussion and question, especially for the eco side.

DR. GEORGE COBB: Yeah. I agree, fully. Thank you. Dr. Fanning.

DR. ELINOR FANNING: Yes. Thank you. I think this is the appropriate charge question for this comment. It can be -- there is some overlap. It appears to me that contributions to environmental releases are only considered as coming from facilities.

I would like to comment that it is possible for releases to surface waters to come from DIDP -- and relevant to other phthalates -- from phthalate-containing products in the environment as well.

An example for DIDP that was given in conditions of use is, for example, large awnings -- so stadium covers. And degradation of these plastics -- emissions to the environment -- could conceivably contribute to surface water concentrations via a storm water route. I would encourage EPA to ensure that related contributions

to environmental concentrations from product use be considered. Thank you.

DR. CHRISTINE CHAISSON: Dr. Cobb --

DR. GEORGE COBB: Go ahead, yes.

DR. CHRISTINE CHAISSON: This is Dr. Chaisson. I'd like to just add a little extra onto Dr. Fanning's comments. This whole issue about increased non-storm flooding that's occurring more and more across our country is exaggerating, if you will -- or magnifying; let me use the word magnifying -- the issue that Dr. Fanning just brought up.

And the whole idea of washing out various streets and residences, and warehouses and all kinds of things like that into local water is an issue that's being experienced, not just along the coast -- in fact, there has been more daily non-storm flooding in the interior of the United States than all of the coastal regions combined. And those are from mostly small creeks and the tributaries into major water and major rivers throughout the United States.

So the issue Dr. Fanning brought up is really critical, I think, for EPA to begin to be including in these kinds of reviews. This is a problem that's going to obviously be with us for -- - hopefully not decades, but it's certainly here now.

DR. GEORGE COBB: Good. Thank you for that question. This is George Cobb. Dr. Chaisson, by non-storm, do you mean non-hurricane or do you mean non- --

DR. CHRISTINE CHAISSON: Nope. Non-storm. It just not a --

DR. GEORGE COBB: Just not a big storm --

DR. CHRISTINE CHAISSON: These are -- -

DR. GEORGE COBB: So it's a rain event, but not a big storm.

DR. CHRISTINE CHAISSON: Nope. It's not a rain event. They are listed under "sunny day flooding events". And this is when whole residential -- commercial -- areas frequently

flood because of a variety of factors. But one of the events that happens is that you get sort of a washing off of the surfaces of huge areas -- and back into the waterways nearby.

DR. GEORGE COBB: Okay.

DR. CHRISTINE CHAISSON: And obviously, it also includes rain and storm events. But it's certainly not limited to that.

DR. GEORGE COBB: Yeah. Got it. Okay. Turning back to the remainder of the Committee, are there other comments? All right. Then we can move to EPA for clarifying questions. And after we're done with that, we can move to our next charge question.

MR. ANTHONY LUZ: I'm sorry. This is Tony Luz with EPA. There's no questions this time.

DR. GEORGE COBB: Great.

CHARGE QUESTION 1.b.ii

MR. ANTHONY LUZ: Okay. We can move on to Charge Question 1.b, part two. Please include the consideration of the strengths and uncertainties associated with methods related to calculating surface water concentrations for DIDP that's in Section 5. Thank you.

DR. GEORGE COBB: All right. And our lead discussant for this is Dr. Li.

DR. LI LI: Okay. So this is Li Li speaking. So first I will read some overview of the general comments from the subcommittee. So the subcommittee appreciated EPA's efforts to integrate both model predictions and environmental monitoring evidence for calculating surface water concentrations. However, it's unfortunate that all water monitoring data came from outside of the U.S. and that no water monitoring data were available for the U.S. water bodies.

The Committee also raised their concerns about a model of DIDP concentrations in water and the sediment. The model concentration

in water exceeded the DIDP water solubility by nearly 100,000 times.

Of course, it's not uncommon to see the model concentrations exceeding the water solubility to some extent because the model concentrations represents a total concentration which combines the fraction freely desorbed -- and the fraction absorbed open to suspended particles -- rather than freely absorb the concentrations.

However, such a huge difference cannot be rationalized by the difference between the total and the freely desorbed concentrations. So EPA may wish to consider the reason behind this -- for example, whether the release scenario or the scale of the assumed receiving water bodies is reasonable.

However, if EPA determines they have high confidence in these extremely high concentrations, they should be aware that these numbers already exceed the aquatic effects level by 20 to 400 times, indicating significant risk to aquatic ecological researchers.

Although the Committee understands that commanding ecological effects and the ecological risk is not part of the questions asked here, the Committee believes that the risk issue needs to be addressed during this review meeting. So I also saw Dr. Ottinger and Dr. Cobb mention the ecological facts just now, so maybe this would be a good place to comment on this issue.

So now I will show identified issues one by one. I will first show some minor issues -- most are for clarification. So lines 722 to 724, on page 29, the sentence reads "Sediment associated with urban storm water runoff collected within an underground sedimentation facility in Gothenburg, Sweden, represents the highest concentration of DIDP within sediment at 60,000 microgram per kilogram."

The nature of this sedimentation facility is to isolate and retain sediments from storm water runoff within a treatment facility -- and not representative of the sediments associated with the surface waters.

So one of our Committee member comments -- discounting the 60,000 microgram per kilogram -- that is 60 milligram per kilogram -- of DIDP in storm water sediment is troubling. The distribution of concerns in this study could be used to compare with the acute sediment toxicity data. The same study contains the values of DIDP and DINP in storm water discharge, which could be used in comparison to acute toxicity values for ecological researchers.

And then, Table 5-3, on page 33 -- provides estimated acute dose -- 80 hours for different age groups. In the footnote, it states "Table 1-1 provides the cross work of OES to COUs to indicate how different scenarios were made." The sentence in line 849 to 850 reads "Using the acute dose based on the highest model -- the 95th percentile -- the MOEs are greater than the benchmark of 30."

So comments -- provide more explanation of the MOEs greater than the benchmark study -- Table 5-3. Also, the assumptions made

for the 80 hours with different age groups needs further references to link the data to the information -- beyond Table 1-1.

The next one -- on line 1015, on page 39, the sentence reads "However, DIDP is not expected to be bioavailable for uptake by aquatic organisms due to a strong absorption to organic measures and the hydrophobicity."

So comment -- the statement that DIDP is not expected to be taken up by aquatic organisms is directly contradicted by monitoring data present in the Draft Environmental Exposure Assessment. In fact, EPA used an empirical BASF to compute uptake to animals. All these types of language need significant harmonization across an assemblage of the report in these documents -- in this docket.

Next one -- line 1024, on page 39, -- comment -- the values in the surface water column all need citations. The monitored surface water data seem to be the means from a single

study. This single study can be noted in the caption.

The mean must be changed to a high sentinel and perhaps from a system with higher aqueous concentrations. Higher sentinel values from this study would produce a value of 73 milligram per liter.

And next one -- Table 11-2, on page 66 -- so comment -- the 30 cubed 5 (phonetic 02:18:39) concentration of 100 microgram per liter is not the same as the concentration of 500 and the 47 microgram per liter reported for lubricants and the function of fluids in Table 5-1-1 and the other tables in that section.

Why is there a difference? Or is one of them incorrect? If the 547 value from Table 5-1-1 is correct, then the MOEs are lower, but still acceptable for humans. These predicted concentrations do raise the question about protection of ecological researchers.

And then I will raise some main issues. So number one -- the absence of U.S.

water monitoring data -- so line 66 -- sorry, 67 to 60 -- 6, 7, 8 (phonetic 02:19:45), on page 28, the sentence reads "Eight studies within the pool of reasonably available information reported DIDP concentrations within surface water."

No U.S. studies were identified. Comment -- the lack of U.S. data is somewhat surprising. Please make clear why this is the case. And how does this fit with the WWTT data -- the Wastewater Treatment data?

And two -- overestimation of DIDP concentrations in water and the sediment -- comment -- Tables 4 and 5 and the related text on page 26 and 27 -- using the WW- -- sorry, using the VVWM model, with the Point Source Calculator 2, the EPA predicts DIDP concentrations to range from 1.7 -- sorry, 1.47 to 10,200 microgram per liter if no wastewater treatment techniques were applied.

Table 4-4 -- the concentration is 547 microgram per liter. Even -- it is assumed that 94 percent of DIDP is removed during

wastewater treatment -- Table 4-5 -- this predicted concentration far exceeded water solubility of DIDP, which is 0.17 microgram per liter, by up to 100,000 times.

Of course, it's not surprising to see the concentrations slightly higher than the water solubility in environmental monitoring. This is because the monitoring concentrations are the total concentrations in water rather than the concentrations of freely dissolved chemicals in the aqueous phase. And the chemicals may be absorbed onto suspended particles in water.

However, it's unlikely for the total concentration to be 100,000 times higher than the water solubility at a normal level of suspended particle contact -- this in the case that predicted concentrations may not be that reasonable.

We're not comfortable with using these predicted concentrations for further exposure assessment, especially for drinking water

exposure assessment because risk assessments requires a reasonable worst-case.

As described in Section 4.1 -- that is lines 575 to 576 -- the modeling was based on the generic modeled water body parameters, which has a standardized width of 5 meters, a length of 40 meters, and a depth of 1 meter.

Actually, this represents a very small volume. This means that EPA assumes the order that DIDP releases from a site is confined to such a small swimming pool. In reality, chemicals may be diluted and will not be confined within this small area.

If the modeled water body is a part of a larger water body -- for example, a lake or a river -- if the modeled water body represents an entire lake, then the DIDP must form a pure phase separated from the water phase.

And if this really happens, then aquatic animals are exposed to a pure phase of dense liquid DIDP. In either case, the assumed

emission rate or the scale receiving environment may not make sufficient sense.

In addition, regarding Tables 4 and 5 and the related text on page 26 and 27, EPA estimates that the beneath sediment concentration of DIDP were up to 27,600 microgram per -- sorry, milligram per kilogram. As I mentioned above, since assumed emission rates or the scale of the receiving environment may not be realistic, we are not comfortable using this number for further exposure modeling.

So our recommendation is that EPA may either, one, use a large or more realistic volume of water body -- or two, scale the release rate based on the portion of receiving water body in a large water body.

And another comment on this is -- in Table 5-3, the model concentrations are 547 microgram per liter, and 9,110 microgram per liter -- with or without wastewater treatment -- respectively. These numbers exceed the aquatic

effect level of 20 or 40 microgram per liter by 22,400 times.

So if EPA determines these numbers -- the predicted concentrations -- are reasonable, these predicted concentrations raise concerns about protection of ecological researchers. So maybe I need to pivot this to Dr. Cobb because I believe he can elaborate this much better than I do. Yeah. That's everything from my side.

DR. GEORGE COBB: So thank you, Dr. Li. This is George Cobb. I think we'll turn to the other discussants for additional comments before I can address the specific things that you mentioned that you would turn over to me. But I think some of the other discussants want to get their perspectives in. And thank you for that very nice summary.

DR. LI LI: Thanks.

DR. GEORGE COBB: And I see Dr. Ottinger is on screen, so we'll go with you first.

DR. MARY OTTINGER: Thank you, Dr. Li. That was a very complete and very accurate

representation of all the input that we all gave you. All I want to do is emphasize again the disconnect between some of the measurements.

If the assumption is that the wastewater removal -- the treatment plants -- were very effective and therefore means that nothing is really getting out in the environment, that is not a good assumption, and it means that we need to be very cognizant of rainwater and other sources of potential contamination that have been discussed in the previous charge question. So all those factors need to be integrated together.

The other thing I want to bring up again is the idea that there is a absorption assumption and documentation that is evidence for potential higher exposure in some areas, especially if the chemicals -- the phthalates -- are adhering to particulate matter in the sediment and therefore available to aquatic species.

And that can go beyond -- and you'll hear more from me later about this -- but that can go beyond the fish and other organisms that are

usually considered and into dabbling ducks and all sorts of other, generally terrestrial-considered animals.

So -- just want to bring up that disconnect of exposure potential and risk to these organisms, and the assumption that no effect or no data means that they're just fine, which I think is in error. Thank you.

DR. GEORGE COBB: Thank you, Dr. Ottinger. And I'll follow up on that in a second. I see Dr. David has a comment as well.

DR. RAYMOND DAVID: No. I have no additional comments. Sorry?

DR. GEORGE COBB: Oh, I apologize. I saw your screen. So I will -- Dr. Heiger-Bernays, do you have your hand up?

DR. WENDY HEIGER-BERNAYS: But I'm not on this question, so I need to wait until you go through all the respondents, and then I can talk.

DR. GEORGE COBB: Okay. All right. So I'll add -- for what Dr. Heiger-Bernays

mentioned -- that there are monitoring data that are not even in industrialized areas where there is wastewater treatment from a municipal wastewater treatment plant where the measured concentrations far exceed the concentrations that -- I shouldn't say far -- they exceed the concentrations that produce toxicity in the laboratory studies.

So I think EPA really cannot discount those laboratory studies and has to include those. There may be differing perspectives on this Committee. But I don't see how you can say that there is no effect and just throw those data away when you've got measured concentrations in the environment that exceed those concentrations in the aquatic testing.

I'll also say that there is a possibility that you can use the maximum acceptable toxicant concentration -- MATC -- for Daphnia, across a couple of different phthalates, and compare that to the observed effect for the DIDP, and come up with a ratio that may actually

allow you to use some of those other phthalate data to predict toxicity in sensitive fish species like trout.

And if you do that, you will find out that the trail is probably similarly sensitive in the chronic state -- but those data do not exist. Now, I'm not an aquatic toxicologist, per se. I have worked on aquatic toxicology studies with others.

So I'll be happy if someone thinks that's not an appropriate approach -- happy to hear if that's not an appropriate approach. There are lots of details in this, and that'll be in the report. But I did want to voice those.

So we do have other discussants on this question. And Dr. Chaisson is first.

DR. CHRISTINE CHAISSON: I have no other comments; thank you.

DR. GEORGE COBB: Thank you. Dr. David.

DR. RAYMOND DAVID: No. As I said before, I have no other comments.

DR. GEORGE COBB: Dr. Reif.

DR. DAVID REIF: No other comments.

DR. GEORGE COBB: Dr. Ottinger.

DR. MARY OTTINGER: No other comments; thank you.

DR. GEORGE COBB: I do want to circle back to my comments because they are substantial relative to the risk assessment -- and make sure that anybody who thinks that's not -- that including the toxicity data for the Daphnia is not warranted -- that we hear that because that would be a pretty substantial difference in the way EPA has approached this ecological assessment.

Dr. Heiger-Bernays, is your hand still up? Nope.

DR. WENDY HEIGER-BERNAYS: Yes. Well, I just put it down. But, yes, my hand is still up.

DR. GEORGE COBB: All right. So let's --

DR. WENDY HEIGER-BERNAYS: Okay.

DR. GEORGE COBB: -- see what you have to say.

DR. WENDY HEIGER-BERNAYS: So should we hold off on Daphnia -- on the tox data -- for a sec? To go back to Dr. Li's point, I want to add something additional which I think we did discuss when we did the 1,4-Dioxane assessment, which is with regard to surface water and the assumption of removal of DINP via wastewater processes that was raised and discussed.

And even if we assume that wastewater treatment is as effective as stated, for now, EPA reports, as of January 2023, that there are around 700 communities in the United States that experience combined sewer overflows. These communities are mostly in the Northeast, the Great Lakes, and the Pacific Northwest and service around 40 million people.

Much of those waters are used for drinking water sources, not to mention the impacts to the ecological species that are living in the receiving water bodies. So I want to make sure

that that is a specific example of why this assumption of adequate wastewater treatment is problematic.

With regard to Dr. Cobb's point and Dr. Ottinger's point with regard to film on the water and whether those data from the laboratory studies should be used, I absolutely concur. If you think about the way the experiment perhaps is set up, there is that insoluble component on the top of the water. But the concentrations are lower beneath that area.

I think that is where it's concluded that there is a sort of smothering -- physical impact -- to those organisms. And I think if we think about the way the chemical is partitioning, it behooves EPA to justify why those data are excluded. And I concur with others who suggest that it should be included. Thank you.

DR. GEORGE COBB: Thank you for those comments. Are there other comments from the Committee? Dr. David.

DR. RAYMOND DAVID: So just in response to that suggestion of that for experimental data where the concentration was above water solubility -- and there is an obvious film of undissolved material -- having dealt with Dahlias for a long time, even though I'm not an ecotoxicologist, I remember this was an issue for many years.

And in fact, the OECD has guidance on how to evaluate substances that are clearly not very water soluble. I don't think the agency has such a document, but OECD does. And my understanding is that it is generally accepted that a film on top of the water -- where the Daphnia have to come up -- represents -- not an inherent toxicity of the chemical -- it is more of a physical property that causes the mortality -- especially for Daphnia.

And so that is why ecotoxicologists have argued that those data are really not relevant for understanding inherent aquatic toxicity. Because if it's a mechanical problem,

then it really is a totally different issue. And I'm happy to invite EPA to chime in on this if you allow that, or if that makes sense.

DR. GEORGE COBB: Yeah. I think that's entirely appropriate. I think we started this conversation a little bit yesterday. And I kind of pushed this to the Committee because it would be a pretty big change in the assessment for what I'm suggesting.

And I do want to point out that, in the studies by Adams et al -- and most of those people are friends of mine and very good scientists, I will point out -- they mentioned that the Daphnia were kind of entrapped in DIDP and floated to the surface -- not that there was a surface film that they became entrapped in but that they were somehow encountering the DIDP -- perhaps as microdroplets -- in the water column and then floating to the surface, which is somewhat different than the scenarios that we've been hearing about so far.

And I believe that the Rhodes study on occasion observed films. But I haven't looked at that particular paper in a couple of days, so I don't remember specifically. So are there other thoughts about this from the Committee? I see Dr. Ottinger has her hand up.

DR. MARY OTTINGER: Yeah. this brings up an issue that I've been wrestling with throughout this review, and that is the potential mechanisms of action -- or modes of action. And I think the issue becomes over invertebrates, other vertebrate organisms, including -- other than mammals -- that there may be very similar modes of action which could apply across the board, meaning that there could be measurements to see if that's the case.

The other issue that you bring up is -- are they suffocating, basically -- or denied oxygen because of that layer of film -- which is what was implied -- or is there a direct effect on these organisms due to exposure? And that remains somewhat unclear to me.

DR. GEORGE COBB: I think I agree.

DR. MARY OTTINGER: I didn't know if you wanted some further explanation. I have some papers that I will provide on some of these modes of action as well.

DR. GEORGE COBB: Okay. That sounds great. Dr. Fenner-Crisp.

DR. PENELOPE FENNER-CRISP: I probably should have brought this up sooner, but I just thought of it now as you were talking about wastewater -- and wastewater treatment. Wastewater treatment comes with a byproduct -- sludge. And often the sludge -- except that now EPA calls it biosolids -- is applied to agricultural areas broadly.

Is the agency considering that particular source route of exposure in any of its assessments -- not just with this chemical but for any one of them? We may be getting re-exposed to them through agricultural use.

DR. GEORGE COBB: I do not remember that. There's a soils question later, and maybe

some folks that were a part of that can respond. I don't recall that. And the EPA can perhaps answer that question when we turn it back over to them.

DR. PENELOPE FENNER-CRISP: It came to mind because it's such a seminal point -- now, with another category of chemicals, obviously.

DR. GEORGE COBB: Exactly.

DR. PENELOPE FENNER-CRISP: Yeah.

DR. GEORGE COBB: Are there other comments from the Committee? Dr. David, did we adequately capture your thoughts and have that discussion thoroughly?

DR. RAYMOND DAVID: Relative to --

DR. GEORGE COBB: To the question of the toxicity in the laboratory studies.

DR. RAYMOND DAVID: Yes. Yes.

DR. GEORGE COBB: Okay. All right. If there are no further questions -- Dr. Li, and discussants, and others who have spoke up here -- I appreciate that dialogue. And now we can turn it back over to EPA for clarifying questions. And

I think if there are no clarifying questions, it may be about time for a lunch break. But let's get through the clarifying questions first.

DR. ANNA LOWIT: Dr. Cobb, can you hear me? (inaudible 02:41:49 video).

DR. GEORGE COBB: We're having a hard time hearing you, Dr. Lowit.

DR. ANNA LOWIT: Take off the headset. I'll see if that works better for you.

A couple things -- on the conversation that the Panel just had around the Daphnia studies, it would be most helpful to us to see the broad swath of the opinions to ensure that all the opinions on this topic are represented in the report.

Because I'm hearing a differing set of opinions, and I'd like to make sure that's reflective in the report so that we can look at the totality of the input to decide how to move forward on that -- is -- that's possible.

DR. GEORGE COBB: I totally agree. And that's why I was asking for comments more than

once, just to make sure we had cap- -- I'm sorry, my unmute button was not working --

DR. ANNA LOWIT: I heard you.

DR. GEORGE COBB: Okay. I want to make sure that all of these comments are captured. And I think Dr. Li will certainly do that. And I know that Dr. Ottinger had some comments. And Dr. David is on a related question -- he's actually on this question. So I'm sure we're going to capture everybody's comments there.

DR. ANNA LOWIT: Okay.

DR. GEORGE COBB: As well as the Committee, if they start reading the report, they'll be able to comment as well.

DR. ANNA LOWIT: Okay. Excellent. And a quick thing on -- Dr. Fenner-Crisp -- the biosolids, when this question comes back up, we did look at biosolids in the Environmental Media Technical Support Document, Section 3.1. So when that circles back around, make sure that that's part of that conversation.

But I just did want to put in sort of a plug and maybe a request. So today has been amazing. I can't tell you how much we appreciate the detailed, thorough comprehensive comments on 1.a and where we -- so far in 1.b.

The kinds of comments that we're getting are just amazing. I love the specificity of the line numbers and the table numbers and the single numbers. Those are the most useful kinds of comments because it gives us specificity on how to improve.

But I would request, as part of the write-up, that, if you all can do two things for us -- first, there's a lot of stuff in there. Set some priorities of the things that are most important, related to whether it's DIDP -- or the other ones for that matter -- understanding the time and resource limitations we have.

So not necessarily in rank order, but if there are some that are particularly important to the panel that really need to be

addressed more than other things that may take longer to address -- that would be really helpful.

And then, secondarily -- related to that -- it's also helpful in the comments to help us understand how a particular recommendation impacts the risk -- or the exposure, for example. So if a particular comment suggests that we're underestimating risk, I'm really interested in those.

If we can be more explicit about those where the Panel thinks we're underestimating risk as opposed to maybe we're overestimating risk in other places -- and the suggestions -- albeit really valuable -- will help us refine those. And so that will also help us make choices about how to use our time and our resources and how it'd impact the other phthalates for that matter.

If I can just put in those two requests -- because there's so much -- we'll do our best, but we have limitations, so --

DR. GEORGE COBB: Yeah. Thank you for the clarifications and for that request of

order. We try to do that, but we don't always get to that point either. So were there other clarifying questions about this?

DR. ANNA LOWIT: No, I don't think so, unless my -- the team in North Carolina wants to jump in. But I don't think so.

MR. ANTHONY LUZ: Dr. Cobb, this is Tony Luz with EPA. I think Dr. Lowit covered our questions and clarifications. So we're good here.

DR. GEORGE COBB: Okay. So with that, we are not at a lunch break, but we're close enough that I think we should prob- -- and we're relatively far ahead of our schedule -- so I would like to propose that we take a lunch break until 1:00 p.m. -- no, would that be 2:00 p.m. Eastern -- an hour and 15 minutes-ish -- an hour and 12 minutes-ish? Dr. Kamel, is that okay?

DR. ALAA KAMEL: Yeah, sure. One hour from now is okay.

[LUNCH BREAK]

DR. ALAA KAMEL: All right. Is Dr. Cobb back?

DR. GEORGE COBB: Oh, I am here, yes.

DR. ALAA KAMEL: Oh, okay.

DR. GEORGE COBB: I thought you could see me.

DR. ALAA KAMEL: Yeah. Maybe I needed to push that blue arrow to see you. Yeah.

DR. GEORGE COBB: Well, all right.

Alaa, do you need to say anything before we reconvene?

DR. ALAA KAMEL: No. You can proceed with the charge questions.

DR. GEORGE COBB: Yes.

Thanks, everyone. I hope you had a good lunch, and we're back to work through our charge questions a bit.

One thing that we normally do before we resume our work is we will circle back and see if there are any clarifying comments for the things that we covered before the lunch.

I know I need to take the roll, but I wanted to make that announcement so that folks who are ad hocs or new to the Committee will know that we're going to circle back and see if there's any clarifying comments based on what we had said this morning or earlier in the day.

Let's go through the roll.

Dr. Apte.

DR. UDAYAN APTE: Present.

DR. GEORGE COBB: Dr. Baker.

DR. MARISSA BAKER: Present.

DR. GEORGE COBB: Dr. Chaisson.

DR. CHRISTINE CHAISSON: Present.

DR. GEORGE COBB: Dr. Eick.

DR. STEPHANIE EICK: Present.

DR. GEORGE COBB: Dr. Fong.

Dr. Gentry.

DR. ROBINAN GENTRY: Present.

DR. GEORGE COBB: Dr. Graham.

DR. CYNTHIA GRAHAM: Here.

DR. GEORGE COBB: Dr. Heiger-Bernays. Oh, okay.

Ms. Jenkins.

MS. ALLISON JENKINS: Present.

DR. GEORGE COBB: Dr. Li.

DR. LI LI: Present.

DR. GEORGE COBB: All right. Dr. Merced-Nieves.

DR. FRANCHESKA MERCED-NIEVES: Present.

DR. GEORGE COBB: Dr. Ottinger.

DR. MARY OTTINGER: Present.

DR. GEORGE COBB: Dr. Przybyla.

DR. JENNIFER PRZYBYLA: Present.

DR. GEORGE COBB: Dr. David.

DR. RAYMOND DAVID: Present.

DR. GEORGE COBB: Dr. Fanning

DR. ELINOR FANNING: Present.

DR. GEORGE COBB: Dr. Fenner-Crisp.

DR. PENELOPE FENNER-CRISP: Present.

DR. GEORGE COBB: Dr. Howdeshell.

DR. KEMBRA HOWDESHELL: Present.

DR. GEORGE COBB: Dr. Martinez.

DR. JEANELLE MARTINEZ: Present.

DR. GEORGE COBB: Dr. Shuman-Goodier.

DR. MOLLY SHUMAN-GOODIER: Present.

DR. GEORGE COBB: Dr. Spade.

DR. DANIEL SPADE: Present.

DR. GEORGE COBB: Dr. Wolf.

DR. DOUGLAS WOLF: Present.

DR. GEORGE COBB: I see you.

All right. Let's circle back really quick and see if there are any clarifying comments based on Charge Question 1 and the first two parts of Charge Question 1. So, 1.b.a, all of it, and the first two parts of 1.b.ii under any clarifying comments.

I see Dr. Reif.

DR. DAVID REIF: I'm sorry. I only saying present.

DR. GEORGE COBB: Oh.

DR. DAVID REIF: I'm always after Dr. Przybyla, so --

DR. GEORGE COBB: I think I -- oh, you know what? I was looking forward to someone

who was not here to make sure I captured that, and I missed you. I'm so sorry.

DR. DAVID REIF: No worries, just for the record. Yeah, so --

DR. GEORGE COBB: Are there any clarifying comments from the charge questions we've covered so far today?

Okay. If not, we'll turn it over to EPA to read in the next charge question, which I have as 1.b.iii.

DR. ANTHONY LUZ: Hi. This is Tony Luz here at EPA. I'll read in Part 3 of Charge Question 1.b.

CHARGE QUESTION 1.b.iii

In light of comments on Charge Questions 1.b.i and 1.b.ii, please comment on the weight of scientific evidence and its conclusions for the general population exposure assessments on Subsection 11.3 of the Draft Environmental Media and General Population Exposure.

Please include in these comments a discussion of the clarity and transparency of the data used, and EPA's interpretation of the exposure results.

Thank you.

DR. GEORGE COBB: Thank you for getting that on the record.

Our lead discussant is Dr. David. He'll summarize for the group, and then we'll proceed to their comments as well.

DR. RAYMOND DAVID: Thank you.

DR. GEORGE COBB: Go ahead.

DR. RAYMOND DAVID: In its concluding statements concerning the exposure to the general population to DIDP, the Agency expressed robust confidence in the model exposure levels that resulted in no pathways of concern. This confidence was supported by a comparison to the model exposure levels to exposure data calculated from the NHANES data by a monitoring data, which provide an aggregate exposure. That comparison indicated that the NHANES data were

below the model exposure levels, suggesting that the model levels overestimated the actual exposure.

The reviewers support the Agency's conclusion with the understanding that reverse dosimetry, the calculation, has some limitations. So, firstly, that the urinary excretion factor for DIDP, or it's metabolites, have not been determined experimentally, and so the Agency used the excretion factor for MCOP, a metabolite of DINP. Although this is certainly likely to be a reasonable substitute, as EPA proposed, it seems unlikely that there would be big differences in the excretion amounts. But that is a limitation or an uncertainty.

The other is that the NHANES samples are from a limited population, although the Agency has noted on page 57, Section 10.2, that the data set is considered representative of a national sample or representative of the entire civilian population. Certainly, NHANES represents an aggregate exposure, so it would be very

comprehensive. The EPA also cited that other regulatory agencies have used NHANES data or biomonitoring data, and so there is some consistency in the approach that EPA has taken.

There were comments provided on some of the transparency and clarity questions within the document, and those will be included in the written reports. I don't think it's necessary to go through them one by one at this point.

I open this up to the other discussants to add any additional comments if they have them.

George?

DR. GEORGE COBB: Thank you for that summary. I'll turn it over to the discussants now.

Dr. Chaisson?

DR. CHRISTINE CHAISSON: No further comment. Thank you.

DR. GEORGE COBB: Ah. Thank you.

Dr. Li?

DR. LI LI: No additional comments. Thanks.

DR. GEORGE COBB: Dr. Reif?

DR. DAVID REIF: No further comments.

DR. GEORGE COBB: Dr. Gentry?

DR. ROBINAN GENTRY: No further comments.

DR. GEORGE COBB: All right. Well, thanks to everyone there.

I think that from my perspective, there were a few sources that could have been better handled, but I believe we covered those in Charge Question 1. I agree with the first dosimetry approach that Dr. David really captured quite well there.

What about the rest of the committee? Do we have comments from the rest of the committee?

Seeing none, we can turn this over to the EPA for clarifying questions.

DR. ANTHONY LUZ: Thanks, Dr. Cobb.

This is Tony of EPA. No questions from us.

DR. GEORGE COBB: Okay. So, we can get into the next charge question then.

DR. ANTHONY LUZ: Okay. Now I'll read into the -- now I'll read in Part 4 of Charge Question 1.b.

CHARGE QUESTION 1.b.iv

For the remaining phthalates (i.e., DEHP, DBP, DIBP, BBP, DCHP, and DINP), EPA anticipates potentially needing to refine the exposure assessment to the environment and general population.

Please suggest exposure data sources, models, and related methods for estimating concentrations and environmental media paying special attention to those media most relevant to phthalates, e.g., water, sediment, and soil. In your consideration, please keep in mind that methods, data, and approaches should be

reasonably available and can be conducted in a timely fashion that allows EPA to meet statutory timelines for TSCA risk evaluations.

Thank you.

DR. GEORGE COBB: Thank you for getting the charge question on the record.

Dr. Chaisson is our lead discussant.

DR. CHRISTINE CHAISSON: Thank you, Dr. Cobb.

This is Dr. Chaisson.

Many comments about the approaches for exposure assessment and risk assessment have been offered in previous comments today. These will be accrued into this charge question's written report with details and references, including for the exposure scenarios not yet considered by EPA.

Below is a specific example of issues expected to reappear for EPA as they utilize their current models with the choice of parameters for incorporation into their algorithms for the environmental media. These issues, with

methods and applications of data, can magnify when multiple chemicals are considered cumulative exposures to the cumulative risk assessments.

The Committee noted a major issue regarding EPA's use of different models targeting different environmental media, such as the variable volume water model for surface water and the air mode for air swopes deposition. This may be acceptable or even ideal for chemicals that primarily reside in a single medium such as PFAS in water or volatile organic compounds in air.

However, it may not appropriately consider the multimedia behavior of DIDP. Chemicals with a high Kow and a high Kon. Therefore, there may be inconsistent considerations when assessing different environmental media. For example, when calculating the chemical concentrations in water, the EPA considered the deposition of chemicals from the air, which is a process that is not directly considered by them a variable volume

water model. The EPA relied on atmospheric deposition rates derived from AERMOD.

However, it should be noted that the two models used different environmental settings and spatial scales. AERMOD considers there is distances from the source from 10 meters to 10,000 meters in a large area, but the variable volume water model considers placing only a small water body like that swimming pool size with a five meters length of 40 meters and depth of 1 meter in a place adjacent to the source.

In this case, we can imagine that the calculated water contamination is unrealistically higher than the calculated soil contamination. Therefore, it's clear the separate considerations in water and soil contamination lead to inconsistencies. Therefore, the U.S. EPA may consider using multimedia mass balance models for semi-volatile organic chemicals like the phthalates.

We must acknowledge that single-medium models are advantageous because they focus

on a single medium at a time, which allows them to use sophisticated representations of individual media and detailed characterization on individual physical chemical and biological processes.

Since multimedia mass balance models need to accumulate -- or sorry -- accommodate multiple environmental media, they have to use relatively coarse spatial resolutions and simplify the algorithms for processes within each medium. But their advantage is that they can integrate multiple environmental media simultaneously, consider the interactions between them.

There are many multimedia mass balance models available ranging from those very simple configurations like unit world level III model built into the EPI Suite to more advanced models like the risk assessment identification and ranking radar model for the PROTACs model or the USEtox model. They contain both aquatic and terrestrial environmental media and support considering multiple exposure pathways at the same time. This may be particularly important when

multiple phthalates are considered in any kind of cumulative exposure assessment or when comparing results across different kinds of phthalates, which are embedded in different plastics or other form of media.

That's my conclusion there.

Dr. Cobb?

DR. GEORGE COBB: Thank you.

Let's see what we can hear from our associates. Dr. Li is our first associate.

DR. LI LI: No further comments.

DR. GEORGE COBB: Dr. David?

DR. RAYMOND DAVID: No further comment.

DR. GEORGE COBB: Dr. Reif?

DR. DAVID REIF: No further comments.

DR. GEORGE COBB: Dr. Przybyla.

DR. JENNIFER PRZYBYLA: No further comments.

DR. GEORGE COBB: All right. Let's see what the rest of the Committee has to say.

Are there further comments from the remainder of the Committee?

I will add that there are several references that I have that we can add to the end of this that will, I think, help. But I don't think it's worth enumerating those, but there --

DR. CHRISTINE CHAISSON: Yes.

DR. GEORGE COBB: There are --

DR. CHRISTINE CHAISSON: That's great.

DR. GEORGE COBB: They are new reference.

DR. CHRISTINE CHAISSON: Thank you, Dr. Cobb. That's great.

DR. GEORGE COBB: Let's turn this back to the EPA.

DR. CHRISTINE CHAISSON: Dr. Cobb, maybe the other --

DR. GEORGE COBB: Did I miss someone?

DR. CHRISTINE CHAISSON: No, but the general --

DR. GEORGE COBB: I think we did that.

DR. CHRISTINE CHAISSON: Oh, I'm sorry. I missed that.

DR. GEORGE COBB: I think we did that.

DR. CHRISTINE CHAISSON: Sorry.

DR. GEORGE COBB: Do it in order.

We can turn it over to Dr. Luz or one of his colleagues to see if there are clarifying questions.

DR. ANTHONY LUZ: Thanks, Dr. Cobb.

This is Tony with EPA. Nothing from us. Thank you.

DR. GEORGE COBB: All right. I think we can move on to the next charge question, which is we're going to a new subheading 1.c.

DR. ANTHONY LUZ: Thanks. Now I'm going to read Charge Question 1.c noting that it has two parts.

CHARGE QUESTION 1.c

As described in Section 5 of the Draft Environmental Exposure Assessment for DIDP, EPA conducted a screening trophic transfer analysis to estimate dietary exposure resulting from modeled surface water releases and air deposition to soil, including use of monitoring and biomonitoring data. The resulting dietary exposure estimates were compared to the hazard threshold for semi-aquatic and terrestrial mammals. EPA anticipates that the exposure methodologies demonstrated in this Draft Risk Evaluation for DIDP will be applicable to DINP exposure scenarios.

CHARGE QUESTION 1.c.i

Part 1 of this question: Please comment on the methods and data used for estimating dietary exposures for ecologically relevant species and comparison of the exposure

estimates to the hazard threshold for terrestrial mammals.

Thank you.

DR. GEORGE COBB: Thank you.

Our lead discussant for this charge question is Dr. Li.

DR. LI LI: Okay. Thanks.

Now I am presenting the -- first, I'm presenting the general comments from the subcommittee.

EPA looked into the potential dietary exposure of concerns of terrestrial mammals. They used the models and the available, also, somewhat limited exposure and toxicity information to run a screen level analysis using representative species. They explained why they chose the certain surrogate species, why they picked some exposure fractures and discuss how relevant these choices were, all in a transparent manner.

Overall, the subcommittee believes the method and data the EPA used for estimating

dietary exposures are reliable, reasonable, effective, and relevant. They reflect a conservative approach to estimation. The methods and data are clearly presented. Especially, the Figure 5-1 is particularly helpful. The method makes sense, and they include the likely concentrations and the considerations.

However, there is a major concern about the use of the IDP concentrations in sediment. It seems like that the IDP concentrations might be overestimated by an unknown degree. This estimation is suggested by the prediction that the IDP concentrations in water exceeding the water solubility by a hundred thousand times.

If the EPA has a high confidence in these extremely high concentrations, these numbers can lead to exposure levels that are very close to the NOAEL and the LOAELs from reproductive and developmental studies. So, if we concede it uncertainties in deriving these toxicity threshold, being very close to these levels in the

case, the possibility of reproductive and developmental effects.

Now I'm introducing the many issues identified by the Subcommittee.

The first issue is the overestimation of the IDP concentrations in sediment. So, Section 3.2 shows that the calculation of exposure of aquatic species were based on "conservative modeling approaches that produce high concentrations of DIDP in sediment," which can be "16,560 milligrams per kilogram for the COUs and the OES with the highest of surface water release and resulting sediment concentration."

One comment is: Tables 5-4 and the 5-5 show much lower concentrations from samples taken in Taiwan, Sweden, and Canada. Are there any insights from location or part pollution source that may explain these differences? Do these differences reflect an overestimation? OSHA has the differences in sampling design or analytical methods.

Another comment: As mentioning our earlier discussion, DIDP concentrations in water and the sediment were calculated by VVWM PSC model may be significantly overestimate as additives that by the 100,000 times higher concentration of the IDP in water compared to a water solubility. If the IDP concentration are calculated based on this predicted concentration, then there is also a possibility of overestimation of the ecological effects. The IDP concentrations are asked to be 16,000 and the 560 milligram per kilogram in sediment, which means 1.6 percent of the sediment mass is made by the IDP.

I'm glad to see that the EPA presented two sets of calculations of the IDP concentrations in Tables 3-1, one based on the model's sediment concentration and the other based on the measured concentration. Measured sediment concentration reported in the literature.

However, it is unfortunate to see only chironomid DIDP concentrations based on the model sediment concentrations were used to

calculate the fish exposure as shown in Table 5-2. On the other hand, Section 6 also indicated overestimation of the IDP concentration in sediment.

We got one comment: Section 6 discusses confidence in the model of the concentration being overestimates on the lack of publication from the U.S. involving sampling and the measurement of the IDP reflective of the availability of research or the criteria used to evaluate the quality of the research.

The second issue we identified is the difference between exposed weight, which is dose, and the concentration as shown in Table 5-2 on page 17.

We got a comment: When calculating dietary exposure for American mink, the IDP concentration in mink were per kilogram. In fish, it's needed as shown in Table 5-2. In that table, it's stated that fish concentration is calculated from the IDP contaminating sediment ingestion and that the IDP contaminated pre-injection values

presented in Table 5-4. However, Table 5-4 only presents the calculation fish dietary exposure rate, which is in milligram per kilogram per day.

I was wondering whether the EPA has converted a fish dietary exposure rate, which is a dose, to fish concentration, which is a concentration, and if so, what formula or method was used for this conversion?

A certain major issue identified is the use of representative species as shown in Section 5. So, EPA chose a short-tailed shrew, a black tail horse, a red horse, and American mink as representative species or sentinels for trophic transfer assessment.

One comment is: Are there any biological data from any of these representative species that demonstrate degree of sensitivity to the IDP? What are the measurement endpoints that would be selected to observe effects although not directly relevant to dietary exposure? The selection of representative species should be

further rationalized in terms of predictive response to varied level of exposure.

Another comment is: Modeling the dietary exposure scenario should contain some information about potential related adverse outcome and information from those selected representative species, such as relative sensitivity to comments and the potential exposure to other stressors in the environment that might affect the adverse effect from the dietary exposure.

The last major issue we identified is a potential toxicological effects at the predicted exposure level. Section 7, especially Table 7-1 and 7-2, show both dietary exposure estimates and the DIDP mammal toxicity reference value, all TRV in parallel. EPA concluded that exposure concentration below that the TRV.

The commenters, first: The comparison of dietary exposure estimates to the TRV could also be displayed in the form of a table for increased clarity.

Second: The uncertainty that underlined the derivation of TRV, which used a human health model as a representative of all terrestrial mammals lab to field difference, interspecies variability, et cetera, may not be reflected in the current value as if derived, calculated as a geometric mean with no assessment factor or error.

Third: The dietary exposure estimate for mink, which is 92 milligram per kilogram per day, appears within the range of NOAELs and LOAELs from the studies displayed in Figure 6-1 used to derive the TRV. Exposure estimates also surpassed the non-cancer PODs before application of UFs select from the same pool of rodent studies for human health assessment. Acknowledging the differences in conversion between human health ecological assessments, the EPA may still wish to consider whether these overlap indicating there is a possibility for reproductive and the developmental

effects relevant to terrestrial mammals from the high-end estimates for dietary exposure.

Then I also named a few minor or editorial issues. Line 318 on page 14, the sentence reads, "The IDP is expected to have low potential for bioaccumulation and biomagnification in both aquatic and the terrestrial organic organisms."

Comment: Does this thereby suggest that this is a short-term issue with limited potential impacts?

Then, lines 351 through 352 on page 14, the sentence reads: Because surface water source of wildlife water ingestion are typically in the ferment row, the trophic transfer analysis for terrestrial organisms assume that the IDP exposure concentration for wildlife water intake are equal to soil concentration for each corresponding exposure scenario.

Commenter one: Please clarify if this statement -- it seems to indicate that the IDP exposure via injection of water assumed to be

equal to DIDP exposure via soil injection. If that is the case, simply rephrase more clearly.

Commenter two: I was wondering how the soil concentration is used for equations such as equation 5-1 that required water concentration as input given that they have completely different units milligram per kilogram dry weight versus milligram per liter.

Next one, lines 435 to 441 on page 17, comment: This text is redundant with text in the preceding section.

Then, line 448 on page 18 comment: Contaminated level should be contaminant concentration.

Lines 477 to 478 on page 19, the sentence reads: As a conservative assumption, 100 percent of the American minx diet is predicted to come from fish.

Comment: Does this text mean (inaudible) no sediment in the diet or that organism X compromises 100 percent of non-sediment diet.

Finally, Table 5-3 on page 19: The table states that estimated DIDP concentration in representative soil invertebrate earthworm assume equal to aggregate highest and the lowest calculated soil via air that position to soil.

Commenter one: Can you please clarify how this was done?

Commenter two: Were there any data from measurement concentrations in earthworms?

I think that's everything I got from the Subcommittee.

DR. GEORGE COBB: Excellent. Thank you for that very nice summary. I know there was a lot there and thank you again for doing that.

Let's go to the other discussants now.

Dr. Ottinger?

DR. MARY OTTINGER: Nothing further. That was an excellent summary. Thank you.

DR. GEORGE COBB: Dr. Shuman-Goodier?

DR. MOLLY SHUMAN-GOODIER: Yes. Thank you to Dr. Li. No further comments. Mine were captured.

DR. GEORGE COBB: Thank you.

Dr. Reif?

DR. DAVID REIF: No further comments. He captured everything.

DR. GEORGE COBB: Dr. Apte.

DR. UDAYAN APTE: No further comments.

DR. GEORGE COBB: One thing I will point out, and there was a fair amount there about overestimation of risk. One of the things was comparison of the estimates to measured concentrations in water -- measured the IDP concentrations in water. To my read of the articles that were referenced for that aspect, there were no industrial effluents tested.

There were, perhaps, wastewater treatment effluents, perhaps watersheds -- full watersheds -- perhaps streams or embayments, but there were no industrial outfalls or measurements

near industrial outfalls that were measured. If I misread that, someone can please correct me.

The other point is, all of these data that we're gnashing our teeth over, these effluent data, could have been provided by those applying for this expedited review, and had that been done, we wouldn't be having to worry -- nor would EPA be having to worry -- about these aspects. So, I would humbly offer that perhaps that should be part of the requirements before any more expedited reviews are done that release data, perhaps empirically measured release data, are provided.

Let's go to see if the rest of the Committee has any comments.

Dr. Chaisson.

DR. CHRISTINE CHAISSON: Yes. Thank you, Dr. Cobb.

I see that this includes calculating dietary exposures with recidivism intake for these particular terrestrial animals and, of course, we've had the same conversation with the aquatics.

As I mentioned yesterday, I'm very interested. It seems that we're very nicely -- using these methods, we could get to a presumed representative dietary residue that could be used for dietary exposures to humans from the phthalates.

Considerations might include our bird eggs, especially those nesting near water surfaces known to accrue higher levels of the phthalates than we're discussing here. Should birds consuming terrestrial and aquatic animals be considered as well for sentinel animals?

Now, I'm way out of my league here in terms of knowing about this, but this is tantalizingly close to coming up with some kind of representative levels for estimating human exposure via subsistence diets. We'll probably never have the kind of databases that we would love to have for those kinds of animals, but this kind of information and the use of these models seem to be enticingly close.

We could at least have some representative values, if you will, that we could

look at, estimated human exposure scenarios with the phthalates.

Thank you. I'm hoping that this Subcommittee might at least address this as a -- whether or not it's a plausible use of the data, and if so, advise EPA on how that might be done.

Thank you so much.

DR. GEORGE COBB: Thank you.

Dr. Ottinger.

DR. MARY OTTINGER: I really appreciate Dr. Chaisson's comment. The short answer is, yes, there are some studies available that could be used to get some estimates. I don't know if there are any for this particular phthalate but certainly for other phthalates.

I think in our write-up we'll have more references that can be perhaps utilized by the EPA to see if it's similar to what the risk associated levels might be for at least some of the representative species that are used as sentinels.

DR. GEORGE COBB: All right. Thank you. That would be very helpful information.

Are there other comments from the Committee?

If not, we can turn it back to the EPA, Dr. Luz or colleagues, for clarifying questions and/or the next charge question.

DR. LI LI: We do have two raising hands.

DR. ANTHONY LUZ: Thanks, Dr. Cobb.

DR. GEORGE COBB: Excuse me, Dr. Li, did you have something else?

DR. LI LI: I saw two raising hands.

DR. GEORGE COBB: Oh, well, I think Dr. Chaisson's is still up, but I did not see Dr. Fanning. I'm sorry to miss that.

Dr. Fanning.

DR. ELINOR FANNING: Oh, that's fine.

I wanted to add, in light of what was raised by Dr. Li and his Subcommittee -- very clearly presented. Thank you -- concerning the

limitations of the environmental monitoring data -- and that was reinforced by Dr. Cobb -- I would like to reiterate a comment that I made earlier today about environmental releases. That is that for the modeling of environmental concentrations, all sources should be considered, and that should include in-use products that can contain DIDP, such as large outdoor sources to include vehicles, just to make sure that the inputs to this process are well captured and adequately modeled.

Thank you.

DR. GEORGE COBB: Thank you for relaying that. That is important.

Dr. Li, thank you for pointing out that I missed someone because I had covered part of the screen with my charge questions to make sure I got back to the right one.

Now we can turn to Dr. Luz and EPA for clarifying questions and/or our next charge question.

DR. ANTHONY LUZ: Thanks, Dr. Cobb. Thanks, Dr. Li.

We really appreciate the really thorough and thoughtful discussion response for this charge and all the previous ones.

We don't have any questions at this time, so I think we can move on to the next.

Okay. Next, I'm going to read Part 2 for Charge Question 1.c.

CHARGE QUESTION 1.c.ii

For the remaining phthalates (i.e., DEHP, DBP, DIBP, BBP, DCHP, DINP), EPA anticipates potentially needing to refine the environmental exposure assessments.

Please suggest exposure data sources, models, and related methods for estimating dietary exposures via environmental media paying special attention to those media most relevant to phthalates, e.g., water, sediment, and soil. In your consideration, please keep in mind that methods, data, and approaches should be reasonably available and can be conducted in a

timely fashion that allows EPA to meet statutory timelines for TSCA risk evaluations.

Thank you.

DR. GEORGE COBB: All right. We will turn it back over to Dr. Li, who was our lead discussant again.

DR. LI LI: Okay. Thanks. It's me again.

We got three comments from the Subcommittee.

The first comment talks about possible resources of data: Has EPA pulled data for the phthalates and the going risk evaluation from the Washington Department of Ecology EIN database? Several studies of phthalates have been conducted throughout the Puget Sound and the Washington state with measurements in sediment and the surface water. All these data are publicly available in the EIN database with links to any publications, QAPPs, and reports.

In the return report, we will provide you with the link.

There may be studies that tested for various phthalates in marine and the freshwater organisms that were not captured in the systemic review, a systematic review process available in the recent 2020 review.

In the written report, we will also provide you with this link.

The second comment is about the methods: For the remaining phthalates that were determined to follow a similar mechanism of action or adverse outcome pathway, for example, anti-angiogenic, will future cumulative assessment concede as summing total phthalate exposure to organisms as a worst-case scenario and to acknowledge the reality of mixtures?

EPA could also concede that evaluating how often DEHP, DBP, DIBP, BBP, DCHP, DINP, or their primary metabolites are detected together in organism or the environmental media, such as sediment to inform the future cumulative assessment.

The third comment is: According to the charge questions, the following phthalates will be reviewed and included. Five other phthalates: BBP, DBP, DCHP, DEHP, DIBP. These remaining phthalates will be reviewed. Do you think the method that is similar for each individual phthalate? However, their potential difference in hazard value and, consequentially, individual risk profiles. As such, each of these additional phthalates must be considered on an individual basis for their characteristics. If several of these phthalates exhibit similar characteristics and information on sources indicate that they are expected to be collected, then exposures will be most likely to be concurrent and reflective of nature in the environment.

It may be appropriate to combine the predicted concentration for exposure assessment. The predicted adverse outcome from exposures must be based on the exposure data from the literature if possible. If this data are not available, then

develop models based on the chemical characteristics and the predicted concentrations in the environment.

There appear to be many uncertainties that complicate environmental exposure assessment, including availability of data on relative concentrations of the remaining phthalates in water, sediment, soil, and if deposition from air is a significant source.

Our recommendation is to prioritize the remaining phthalates: DEHP, DBP, DIBP, BBP, DCHP, DINP beyond the DIDP and the DINP as to the following criteria: Likely concentrations in soil, land, air; potential sources from pond pollution and the chemical releases; volatility and other chemical characteristics, and potential adverse effects on wildlife, both aquatic and terrestrial. This is in acknowledgment that analytical and modeling approaches are going to be similar in approach to these already used for the IDP and the DINP.

This additional evaluation will be added to DINP into accumulative risk assessment for review in early 2025.

Okay. This is everything I got from this Subcommittee.

Thanks.

DR. GEORGE COBB: Okay. Let's turn to our other discussants now.

Dr. Shuman-Goodier.

DR. MOLLY SHUMAN-GOODIER: Thank you. My comments are captured. No further comments.

DR. GEORGE COBB: Thank you.

Dr. Ottinger.

DR. MARY OTTINGER: Likewise. Thank you very much for a very complete summary.

DR. GEORGE COBB: Dr. Reif.

DR. DAVID REIF: Yeah. No further comments on the section.

DR. GEORGE COBB: Dr. Baker.

DR. MARISSA BAKER: Nothing further from me. Thank you.

DR. GEORGE COBB: All right. Excellent. We're making good progress.

Do we have comments from the remainder of the Committee on Charge Question 1.c.ii? Okay.

If not, I'll point out that we are actually where we're supposed to be at the end of the day today. We are going to proceed into charge questions that are scheduled for tomorrow. I just want to give people a heads up on that.

If I can, I did want to go back to one of the discussions we were having about the toxicity studies and the types of toxicities that were observed in those toxicity studies. I want to read a couple of passages from the two papers that tested Daphnia, among other species, but in which Daphnia were seen to be very sensitive species.

I'm just going to read a couple of sentences. This is from Adams et al. 1995: "The floating Daphnid problem resulted in test solutions" -- excuse me -- "in several tests being

repeated. The findings presented here are based solely on immobilization and not entrapment."

That particular study did not consider entrapment as part of their toxicity. That's the Adams '95 study.

If you go to the Rhodes '95 study, which was an allied large study that was actually well conducted in my estimation -- I'm sorry. Yeah. Here we go.

They did observe entrapment, but they note, "Daphnids became entrapped at the surface of control chambers in only one of fourteen studies."

Now, it does not say how many chambers in that one study, but they were also observing entrapment in their controls. There are a couple of things there that I think are important to note, specifically that Adams et al. did not include entrapment in their toxicity estimates. That's the endpoint.

Having read that in, are there comments from the Committee about that, or we just

let that go and move on to further discussion of other topics?

Is Dr. David trying to make a point?

DR. RAYMOND DAVID: Yes. I was about to raise my hand, but yes.

If we're reading from documents, I wanted to refer to the OECD document --

DR. GEORGE COBB: Yeah.

DR. RAYMOND DAVID: -- that discusses what to do, how to adjust the aquatic toxicity testing for poorly water-soluble materials.

One of the comments that they make -- and again, the caveat is, I'm a mammalian toxicologist. I've never done these, but I've read a little bit about it, so take it with a grain of salt.

One of the recommendations is to not use a static test system. Either renewal or flow through, which, to me, makes some sense because that way the poorly soluble substance doesn't have the opportunity to partition to the top.

It recommends things like reducing the ratio of test organisms, the biomass, to the test solution. There may be -- so especially for a chronic study where the organisms have to be fed during the course of the study, particularly a 21-day Daphnid test. Feeding the animals can, in some cases -- the material may absorb onto the food and remove chemical, actually, from the exposure concentration.

I'm not going to go through all of these, but it's just to point out that there are ways around which one can adjust the test system. If, in fact, those were done for these studies, then, okay, maybe we're talking about inherent toxicity.

If not, I really do think there is a valid argument to say that this is not inherent toxicity. This is something that is a mechanical one.

DR. GEORGE COBB: I'll just say, this is an important discussion to have because we want to capture the different perspectives and the

different reads of these documents and how to best utilize this data for making regulatory decisions.

I will say I really appreciate that comment. That's a very important comment.

Are there other comments?

All right. I'm seeing a request for a break.

Dr. Reif, let me ask you, do you feel like you can go through this next charge question before we take a break? Then maybe we take a break right after 1.d?

DR. DAVID REIF: For 1.d? I embarrassingly sent out a draft kind of based on the other one a little bit probably too late for people to have replied back. So, I'd prefer if we waited a little bit on 1.d.

DR. GEORGE COBB: Okay, 1.d.

DR. DAVID REIF: Were you asking --

DR. GEORGE COBB: No. I was asking if you were ready for 1.d.

What about Dr. Baker? Are you ready with 1.e?

DR. MARISSA BAKER: Yeah. We could do 1.e.i and .ii.

DR. GEORGE COBB: Okay. Let's try to get through 1.e.i for sure and try 1.e.ii, and then we'll take a break, and then we'll come back to 1.d. Yeah.

DR. MARISSA BAKER: They seem short and straightforward, so we might be good.

DR. GEORGE COBB: Okay.

DR. DAVID REIF: Yeah. I think it's doable. I was struggling to separate out 1.d from -- I mean, it was the made-up one from the other ones --

DR. GEORGE COBB: Yeah.

DR. DAVID REIF: -- so yeah. It might --

DR. GEORGE COBB: Okay. If we --

DR. MARISSA BAKER: Just give me a second to pull it up.

DR. GEORGE COBB: Okay. If that does not work -- well, we're going to have to get it read into -- if that doesn't work, we can,

perhaps, move on even further and come back to you, David.

Okay. Dr. Luz, do you have clarifying questions for us, or would you like to read in 1.e.i?

DR. ANTHONY LUZ: Dr. Cobb, this is Tony with EPA. There's no clarifying questions. I think we can move on to 1.e.i.

Okay. Then I'll read in Charge Question 1.e.i. Again, this has two parts.

CHARGE QUESTION 1.e

As described in Section 3 of the Draft Environmental Release and Occupational Exposure Assessment for DIDP, production volumes for Manufacturing and Import/Repackaging OES were determined using Chemical Data Repository, or CDR, information. The production volumes for the other OES came from CDR and/or percent production volume percentages -- so that's percentage of manufactured DIDP used for a particular OES --

reported in the European Union, or EU, Risk Assessment on DIDP since the use rate of DIDP is similar in the USA and EU.

EPA anticipates that the exposure methodologies demonstrated in the Draft Risk Evaluation for DIDP will be applicable to DINP exposure scenarios.

CHARGE QUESTION 1.e.i

Part 1 of this charge question: for environmental release assessments, please comment on the strengths and uncertainties of using EU production volume percentage to estimate production volumes for DIDP.

Thank you.

DR. GEORGE COBB: Thank you for getting that into the record.

Dr. Baker.

DR. MARISSA BAKER: Yes. This is Marissa Baker.

Overall, respondents to this charge question felt comfortable with the proposed estimated production volume and percent, which was cited in the Draft Environmental Release and Occupational Exposure Assessment.

A respondent raised the point that U.S. law prohibits sharing information within and between industry groups about production volumes or market shares, but that information is provided to the American Chemistry Council, the ACC, panel coordinators so that they can determine company dues to each panel. The European Union has no such restrictions, so for this reason, obtaining production volumes from the EU are likely to be accurate.

Since the ACC, compromised of the manufacturers of DIDP, indicate that the use rate of DIDP in the EU is similar to the use rate in the U.S. -- and I have a reference -- the respondents felt it appropriate to use the 2003 DIDP risk assessment published by the EU to estimate production volume for the various

sectors. The EU and U.S. market are also likely to be comparable.

A respondent posited that the only other option would be to obtain data on global production, but those will not reflect the U.S. market accurately.

A respondent also found it appropriate to split the production of non-polymer uses equally between paints and coatings, adhesives and sealants and inks since the industry has not given a more specific breakdown. However, the reviewer recommended having these estimated production volume breakdowns reviewed by industry to ensure that the potential releases are estimated correctly.

One respondent noted that production volumes for several sectors were reported as a range, some of which were extremely large. A question was raised as to whether it is possible to estimate a narrower range for these sectors or provide context as to why the ranges are so large.

The examples will be given in detail to the EPA, but many of them were ranging from the hundred thousands to over a million kilogram per year ranges.

Exxon indicated a half-year production schedule. Therefore, respondent recommended that an attempt should be made to obtain production schedules for other manufacturers and formulators. EPA states that import and repackaging facilities operate 24 hours a day, 7 days a week, multiple shifts. However, EPA capped the total number of operating days so as not to exceed estimated site throughputs. That came directly from the document.

However, EPA did not identify chemical or site-specific information on site throughputs. Site throughput information was estimated through Monte Carlo modeling with a 50th to 95th percentile range, a 46 to 55 kilograms per site day; again, pulled from the document.

One respondent indicated estimating on an estimation creates more uncertainty, which

may also create a higher estimated occupational exposure potential. But another respondent says that they appreciate EPA modeling on the higher percentiles to represent the worst-case occupational exposure, which would be more protective of workers.

That concludes our remarks.

DR. GEORGE COBB: Excellent. Thank you for that summary.

Now we can turn to our associate discussant, Dr. David.

DR. RAYMOND DAVID: I don't know -- actually, I do have something to add, but I will wait till after the other discussants because it's not -- it doesn't address the question specifically.

DR. GEORGE COBB: Okay.

DR. RAYMOND DAVID: Although, I would like to ask the EPA: What information are you getting in the CDR if you're not getting this kind of production information? I mean, I thought that was the whole idea.

DR. GEORGE COBB: Perhaps we can wait to answer that question after we get --

DR. RAYMOND DAVID: That's fine.

DR. GEORGE COBB: -- through. But that's a really good question.

But let's see what Dr. Reif has to say if he's not busy compiling.

DR. DAVID REIF: No. I don't have any additional comments on this one. Thank you.

DR. GEORGE COBB: Then, Dr. Graham.

DR. CYNTHIA GRAHAM: All of my comments were included. Thank you.

DR. GEORGE COBB: Excellent. Thank you very much.

Okay. Dr. David, do you have the other comment that you had?

DR. RAYMOND DAVID: Well, yes, because I noticed in the charge questions there were no charge questions that asked about occupational exposure. Yet, the risk assessment for DIDP identifies an occupational exposure

scenario in which the exposure level exceeded the margin of exposure that they set.

I was a little disappointed in that. It prompted me to go back to the document on occupational exposure. There were a couple of things that struck me about it.

For example, in Section 3, there's a repeated referral by the EPA to exposure to vapors of DIDP during transferring of drums or other operations, and I found that an odd statement to make given that DIDP has a very low vapor pressure unless someone is standing next to the extruder where the hot plastisol or PVC is coming out. It doesn't seem like there would be a lot of opportunity for exposure to vapors as such.

The other thing that struck me is that the Agency indicated that they didn't have any idea of engineering controls or use of PPE. Again, that struck me as odd because safety data sheets certainly would have recommendations for PPE. We heard from one of the presenters yesterday about engineering control. Why is it

that the Agency isn't getting that information? Are they not asking the right questions, or is it simply not available?

The last point I want to make was that the exposure scenario where there was concern was in a paint application where DIDP is used as a solvent, basically, in paint. It was generating aerosols for -- I think it was actually auto painting or repainting. The concern was that there would be inhalation exposure primarily, not only to the primary worker but secondary workers who might be present during the operation. That exposure scenario just seemed unrealistic to me.

I'm sure there are paint operations where they don't enclose the car as it's being painted. I've not seen too many but probably so. But for an operator to aerosolize a liquid and not have on at least a dust mask, I find that very odd.

These are questions that I think it would be a good idea for the Agency to go back and revisit. I will -- I've asked Dr. Baker to

include my written comments into her write-up so that the Agency can have them down on paper.

Thank you.

DR. GEORGE COBB: Thank you for those comments. I will say that a lot of the things that you are commenting on and questions that you're raising are questions that the Committee has wrestled with for a while with the Agency, especially availability of data and the willingness of industries to provide those data or to proactively produce those data so that we can make better decisions.

The only other thing I'll say is that this Committee's been pretty clear with the EPA that PPE is a risk mitigation consideration -- risk management situation -- rather than a risk assessment situation, and so that's probably why there's that apparent disconnect with the way that you are thinking.

DR. RAYMOND DAVID: I understand that the Agency is -- I believe it is their

mandate to determine the risk in lieu of any PPE that might be used, and that's fine.

DR. GEORGE COBB: Yeah. I think that if there were data demonstrating how that proceeded, perhaps they could consider that. They may differ, but I do not think those data are available. But we'll let the Agency respond to those questions instead of me.

DR. RAYMOND DAVID: Perhaps that is part of their -- when it comes to identification of an unacceptable risk, perhaps that's one of the opportunities to mitigate the risk.

DR. GEORGE COBB: Exactly. Exactly.

Are there further clarifying comments -- not just clarifying, but comments from the Committee about the discussion we just had or anything else?

I see -- are you there?

DR. UDAYAN APTE: Yeah. Okay. You cut out for a second. You're asking me, right?

DR. GEORGE COBB: Yes. Please proceed.

DR. UDAYAN APTE: Okay. This is Udayan Apte.

I just wanted to comment on the discussion you had where it is pretty clear that there is a data gap, right? We are -- as a committee, when we make recommendations, we are kind of refraining from asking the Agency to do studies because that's not what this whole thing is about, or the Office of Pesticide is concerned that. But putting those data gaps that are so concerning in the report is I think probably very important. I'm hoping somebody reads them, and it is conveyed to the right people who are charged with obtaining new data. It may not be this office, but somebody else might get that information down the road once the reports are done.

I think we should highlight those as a committee is my recommendation.

DR. GEORGE COBB: Yes. Thank you for that.

Are there other comments?

I will say that in a couple of -- at least one instance -- I shouldn't say a couple. In one instance where the Committee was making recommendations for different kinds of data availability, that one of the industrial groups did step up and provide some of those data that were very helpful in the risk assessment process. I do not remember the chemical. I'm sorry. But I mean, that can very easily be the solution to use data that may actually exist or that may easily be attainable.

Okay. Let's go back to the Agency, to EPA, and see if there are clarifying questions, and then we can proceed to the next question, which Dr. Baker, by the way, is the lead discussant for it.

UNIDENTIFIED MALE: (Audio distorted Inaudible) from EPA. One of the questions was whether we used production volume data from CDR. We used all the available data that we had from CDR to calculate production volumes for four years, except the (inaudible) teams and the where

we needed extra information to sort of fill in the blanks or fill in the gaps. We also used information from other sources that we found through systematic review.

DR. GEORGE COBB: Thank you.

Will someone from EPA read in the charge question? I believe it's 1.e.ii.

DR. ANTHONY LUZ: Hi, Dr. Cobb, this is Tony Luz here with EPA.

I can read in the second part of Charge Question 1.e.

CHARGE QUESTION 1.e.ii

For the remaining phthalates (i.e., DEHP, DBP, DIBP, BBP, DCHP, DINP), EPA anticipates potentially needing to refine the environmental release assessments.

Please suggest additional data sources, models, and related methods for determining production volumes that are reasonably available and can be conducted in a timely fashion

that allows EPA to meet statutory timelines for TSCA risk evaluations.

Thank you.

DR. GEORGE COBB: Thank you.

Dr. Baker, would you please --

DR. MARISSA BAKER: Yes.

DR. GEORGE COBB: -- provide the response.

DR. MARISSA BAKER: Yes. This is Marissa Baker again.

Respondents had a few ideas to pass along to EPA. Respondents recommended EPA explore the feasibility of compiling information from purchase records or manufacturing that can serve as inputs in conjunction with TRI data, which is already being used.

In particular, the modeling to predict indirect surface water deposition and land deposition can be strengthened, particularly in regions of highest production. A respondent suggested that waste stream identification and monitoring is critical and using estimates from

sewage outfalls. But the Committee did not have specific recommendations as where to access these data.

Another respondent indicated it is preferable to rely on industry data or primary exposure data collected by a qualified hygiene professional as opposed to relying on modeling data. This perspective was informed by comparing the modeling data to the actual monitoring data from Exxon that was in the draft document.

The use of industry-supplied data can be confirmed and used to determine production volumes. Therefore, the use of the CDR appears to be appropriate.

But a respondent also indicated that using modeling data is an appropriate way to estimate higher-end exposures, which can result in more protective exposure estimates.

That concludes my response.

DR. GEORGE COBB: Excellent. You were correct that we might be able to get through these parts quickly.

Let's go to the remainder of the group.

Dr. David?

DR. RAYMOND DAVID: Just an additional thought to make sure that EPA does not look at EU production levels for these particular phthalates because several of them are restricted in the EU, and so the production levels would not reflect U.S. production.

DR. GEORGE COBB: That's a very good point. Thank you.

Dr. Reif?

DR. DAVID REIF: No comments from this.

DR. GEORGE COBB: All right. Thank you.

I think Dr. Heiger-Bernays had to step away unless she's gotten back.

DR. WENDY HEIGER-BERNAYS: Here. I'm here.

DR. GEORGE COBB: Oh, you're here. Aha.

DR. WENDY HEIGER-BERNAYS: I'm here. Yeah.

Thank you, Dr. Baker. That was everything.

Dr. David made the comment I was going to make about careful about using production from the EU since many are restricted.

Thank you.

DR. GEORGE COBB: All right. Thank you.

To the Committee, are there comments from the Committee related to this charge question?

If not, Dr. Baker and team, thank you for that good summary of these last two questions.

Let's turn it over to EPA for a couple of clarifying questions.

DR. ANTHONY LUZ: Thank you, Dr. Cobb. This Tony of EPA. Nothing from us.

DR. GEORGE COBB: All right. Well, at this point, I think it's best if we maybe take

a ten-minute break, and then we can come back to perhaps Charge Question 1.d if Dr. Reif is ready. If not, we may move on to -- would you think you're ready, Dr. Reif?

DR. DAVID REIF: Yeah. I hadn't heard affirmation from all of the discussants on the latest draft, but we can present it and circle back.

DR. GEORGE COBB: Okay. Let's go with a ten-minute break, and then we'll pick up with 1.d and then maybe move into 2.a as well.

All right. We'll see you folks back in about ten minutes.

[BREAK]

DR. GEORGE COBB: All right. Welcome back after the break. At this point, I -- welcome back after the break.

At this point, I think we can go to EPA and get our next charge question read in, which we're going back up to 1.d, please.

DR. ANTHONY LUZ: Thanks, Dr. Cobb.

Tony Luz here with EPA. I'll read in Charge Question 1D.

CHARGE QUESTION 1.d

In light of comments on charge question 1.c.i, please comment on the weight of scientific evidence and its conclusions for the environmental exposure assessment (Subsections 6 and 7 of the Draft Environmental Exposure Assessment).

Please include in these comments a discussion of the clarity and transparency of the data used, hazard values, and EPA's interpretation of the results.

Thank you.

DR. GEORGE COBB: Thank you.

Dr. Reif is our lead discussant.

DR. DAVID REIF: Yep. Just because we're backing up, and also because this is an emergent question that came out of discussions,

remember this question here is based on comments to 1.c.i. I'm trying to collect information that hasn't already been presented elsewhere.

In general, in response to the question that the conclusion that risks are not underestimated is supported by the weight of evidence presented. While the use of data from articles rated at least medium- or high-quality is appropriate, the lack of data available for several levels of trophic transfer warrants reconsideration of cells noted in Table 6-1 as moderate confidence. Further, the overall confidence level for the modeled concentrations as being representative of actual releases is characterized as slight in several places, whereas many of the component data sources are characterized as moderate.

For trophic transfer, the lack of metabolic transformation makes plain more of the discrepancy between modeled and observed concentrations than currently noted. This source of uncertainty could be addressed with emerging

methods for probabilistic estimation of metabolism.

Overall, the disconnect between the modeled calculations and measured concentrations should be discussed in greater detail, especially given the relatively few U.S. measurements available. Further, the TRV is key to conclusions, and to support clarity transparency, a more detailed justification for the selection of the TRV should be provided.

The assumptions for proportion of diet in the concentrations available to the predators seem reasonable and based when available on available data -- empirical data, rather. But the choice of sentinel representative species is appropriate associated with their feeding profiles and location.

Particular detail points particular lines or sections for models estimated concentrations for locations near hypothetical facilities releasing DIDP to surface water is appropriate due to short half-life in the

environment. However, the difference in models and observed concentrations -- this is on line 604 to 605 -- is justified by sampling of aquatic species distant from DIBP release sites. This is reasonable, but perhaps too simple, given the complexities of half-life metabolized chemical forms and potential other adverse effects from mixtures and chemicals present in the sediment and other media.

Second, as pointed out in line 618 to 620, the lack of metabolic transformation within prey items reduces the completeness of the biological relevance, and this would limit assessment of exposure and present an incomplete view of potential exposure effects.

Lastly, these are the comments related to Charge Question 1.c, the use of conservative screening values and approaches may result in overestimation of potential adverse effects related to exposure. However, this does not seem to be the case with all areas.

DR. GEORGE COBB: All right. Thank you for that summary.

Other discussants?

Dr. -- wait a minute. I'm in the wrong charge question.

Dr. Shuman-Goodier.

DR. MOLLY SHUMAN-GOODIER: Thank you. No further comments.

DR. GEORGE COBB: Dr. Ottinger?

DR. MARY OTTINGER: No further comments. Thank you very much.

DR. GEORGE COBB: Dr. Li?

DR. LI LI: No further comments.

DR. GEORGE COBB: Dr. Apte.

DR. UDAYAN APTE: No further comments. Thank you.

DR. GEORGE COBB: That's a good summary. So, maybe your concerns were not so much as you thought.

DR. DAVID REIF: Yeah. A lot of this is related to other comments that have been

brought up and perhaps raised, so yeah. That's good.

DR. GEORGE COBB: Yeah. With the complexity of this evaluation, totally understand. Thank you for that really good summary.

Now, let's go to the -- let's go to the rest of the Committee. Are there comments from others on the Committee about Charge Question 1.d?

All right. Well, let's go the -- excuse me -- go to EPA to see if there are clarifying questions because I think this gets us to the end of Charge Question 1.

EPA, are there clarifying questions about this last charge question or any of the others?

MR. CHRISTOPHER GREEN: Well, this is Christopher Green with EPA speaking.

Thank you, Committee, and thank you, Dr. Reif, for that input.

I did have just a little bit more -- pulling a little bit more from you for that last

point you made in terms of conservative assumptions, and I believe you had language where it was appropriate but maybe not in all cases.

I was wondering if just for our own notes to get ahead of things right now, can you be a little bit more specific or just draw a little bit more from that last point you made?

Thank you.

DR. DAVID REIF: Yeah. I think that the spirit of that comment was that choosing conservative over and over I would expect to result in overestimation of potential adverse effects. But that's not guaranteed. I think it would -- that's really a statistical comment based on the other -- based on the other considerations that, while that's the expectation, it's not necessarily a guarantee and just to make sure the language didn't make it sound like in all cases when one does this, the output is this.

MR. CHRISTOPHER GREEN: Okay. This is Christopher Green from EPA again.

Thank you for that. I think that was really helpful.

Again, thanks.

DR. GEORGE COBB: All right. If there are no questions from EPA, this is a little bit unusual. Usually, we do this at the end of the day, but I think we're at the end of a charge question right now, and it's towards the end of the day. I want to just circle back to the Committee to see, based on what we've heard in the totality of Charge Question 1, are there any additional comments that anyone wants to bring up before we proceed to Charge Question 2, which is ecological hazard?

Dr. Ottinger.

DR. MARY OTTINGER: Just want to emphasize as we go into ecological hazard, there's going to be many measures that are commonly held in the sense that they're applicable to both, and so the more we look at conserve mechanisms and how there may be adverse effects that are conserved, again, that that's a really important thing to

keep in mind as we move to the other charge questions.

DR. GEORGE COBB: Agreed.

Other comments? All right. Seeing none, we can wrap up Charge Question 1.

Thank you, Dr. Reif and your team, for finishing that up for us.

Then, let's move into the ecological hazard and have Dr. Luz or one of his colleagues read that Charge Question to us.

DR. ANTHONY LUZ: Thanks, Dr. Cobb.

This is Tony Luz here. I'll now be reading Charge Question 2.a.

2. ECOLOGICAL HAZARD

CHARGE QUESTION 2.a

As described in Section 4 of the Draft Environmental Hazard Assessment for DIDP, EPA had a limited empirical toxicity data available for terrestrial mammals and therefore relied on data from controlled laboratory animal

studies using human health animal models to derive a toxicity reference value, or TRV, to evaluate risk from chronic dietary exposure to DIDP.

Please comment on the strengths and uncertainties of the methodology and data used to derive a toxicity reference value, or TRV, for DIDP.

Thank you.

DR. GEORGE COBB: All right. Thank you for getting that charge question into the record for us.

Dr. Ottinger is our lead discussant for this question -- sub-question.

DR. MARY OTTINGER: First of all, I'd like to thank the discussants because you all have made very, very valuable and interactive contributions, so hopefully this reflects everything.

I'm going to start with general comments. Aquatic invertebrates, fish, algae considered for toxicity with non-observed with

sediment or poor water exposure, no toxicity -- excuse me -- observed.

Second point: No hazard data were available for wildlife. Laboratory rat data were used to derive hazard values for terrestrial animals. The TRV of 28 milligrams per kilogram per body weight per day. DINP data from one earthworm hazard study is used for the read-across for DIDP. There are 13 studies used for toxicity quantitative assessment for fish with two studies using DIDP concentrations higher than solubility. EPA's choice not to use predictive toxicity data from ECOSAR is defensible given the description that the log KOW exceeds the model domain.

The TRV derivation process in general does not appear to include a means of accounting for uncertainty as would be used to drive a concentration of concern. This seems prudent for a screening-type analysis with limited experimental data. The assessors may want to consider quantifying inter and intra study variability and uncertainty in the assessment and

in applying an AF or adding their descriptions of uncertainties that are not accounted for.

The following two points might end up as recommendations and read as follows: It is unfortunate that no data were available or requested for terrestrial plants or avian. Given DIDP poses a potential hazard to mammals, could EPA consider read-across data as they did for earthworms or request testing to complete the rest of the terrestrial assessment?

The second point: Has EPA considered using a new approach methodologies data for phthalates that is publicly available from EPA's ToxCast program with added lines of evidence in the environmental risk assessment? Considering mechanistic effects in data from multiple levels of biological organization, this could be justified for the phthalates. Methods used to derive activity concentrations and cutoff from ToxCast data and exposure activity ratio and subsequent comparisons to the primary apical endpoints would provide additional line of

evidence that could be considered, for example, applications for the screening use in WOE and other references.

There are a number of strengths, including the approach that uses an experimental rat model. That provides good estimation of effects on DIDP in mammals and then by transmission to wildlife.

The strength is that the data come from medium quality studies in rats, and that there are similar values for NOAEL and LOAEL for reduced body weight that were generated from the two different studies.

A potential uncertainty is that wildlife mammalian populations might be less sensitive to exposure due to being more genetically diverse, but there are no data available for DIDP or DINP to suggest that this is the case.

EPA identified two reproduction studies, three growth studies, and two survival studies all in rat models containing relevant data

for DIDP hazard assessment in terrestrial mammals. The rat model is established, and there's reason to believe that it's adequate and responds to phthalates; similarly to other terrestrial mammals.

There are two different rodent species that were used, and so there is the question of whether these inbred rodent models provide more consistency in response, and so as such may not capture all the variability in wildlife.

Another point: EPA did not include data from other phthalates in this section consistent with EPA's determination. The DIDP does not follow the same toxicity mode of action or adverse outcome pathway as the lower molecular weight phthalates.

The EPA appropriately has charge questions focused on data from other phthalates that are deemed high priority in the other charge questions. The spectrum of effects was similar across the identified studies, which increases

confidence that these are reproducible toxic effects of DIDP.

A couple of weaknesses: There are relatively few studies on this chemical, and the reported NOAEL and LOAEL values diverge significantly, sometimes more than log 1. Although there is significant qualitative similarity, the sediment's potentially high quantitative variability in inter-individual response. Additional studies that are available, but not deemed high or medium, could be reevaluated for utility of the information. These data could be reevaluated for the consistency in the draft report.

Recommendations: Rodent models for human health evaluations being transferable to a wildlife TRV is rationalized with detail on why this is conservative, yet no adverse effects are predicted.

Please add information on potential adverse effects that would occur in wildlife and their utility for applications in assessing risk.

Additional data are available for phthalate exposure effects, which should be included in assessment factors and formulation of the TRV, and we will provide some examples.

EPA's choice to use laboratory rodents from human health studies to derive toxicity reference value is well justified and logical. However, the derivation of the TRV does not include a means for accounting for the added uncertainty of using only laboratory rodents as human health models.

The overall conclusion the DIDP has low hazard potential for aquatic species does not agree with the data reviewed. The predominant endpoint in Table 3-1 is mortality with little information on sublethal effects. Acute and chronic studies on fish appear to be highly flawed with fish hazard data based on an acute study with high-control mortality and a chronic study with no-dose response and limited to development on reproductive measurement endpoints.

Please explain why these studies are highlighted and deemed acceptable. Similarly, the aquatic invertebrate, benthic invertebrate, amphibian algae and algae hazard studies were not rated as high- or medium-confidence. However, would some of the lower rated studies be useful in estimated hazard with proper weighting of results?

Another recommendation: The TRV estimated for terrestrial mammals must consider potential sensitivity or the rats' strain and their use in toxicity testing, and the range of endpoints must include nonlethal endocrine disruption as a short- and long-term potential effects as in Waterman et al. 1999 or Hushka 2001 or Exxon Biomedical 2000 and 1998 studies. However, basing the TRV on these rodent studies still must consider transferability and relevance to wildlife at the concentrations that will be potentially encountered with the following questions: Are there measurements of environmental concentrations, and which species are likely to be most exposed?

Lines 269 to 274, these studies also noted significant decreased body weight in survival in both males and females. Is this a palatability or treatment issue? Females also experience reduced number of offspring. Is this effect due to reduced food consumption or potentially associated with palatability? Finally, are there sufficient controls to evaluate accurate NOAEL and LOAEL?

A couple more recommendations: Additional terrestrial wildlife including birds must be considered in the wildlife hazard and risk evaluations, and we'll provide some literature pertinent to that.

That would then mean that there should be relevant field measures for wildlife and how the conclusion from weight of evidence determines little or no hazards to wild organisms or if it does.

There are insufficient robust data sets despite high confidence in some of the aquatic assessment as shown in Table 5-1.

Although the approach used in Section 6 for DIDP is reasonable, the underlying data are insufficient to draw these conclusions. EPA needs to include information regarding the cutoff date for the literature identification. This information was included in the DIDP human health hazard assessment, as well as a description of sources used to identify the environmental health studies.

The final recommendation is Environmental Hazard Assessment Section 3.1: Provide clarification detail for the following issue. There are no exposure concentrations to which TRVs are compared. Reviewing the supporting documents provides confusion. The aquatic fate section of the draft environmental fate and transport assessment contains less than 20 lines of text with no tables or figures depicting available or modeled data. The fate assessment acknowledges that measured concentrations in water are above solubility limits and are likely associated with droplets in the water but provides

no further information. Aqueous concentrations are only found in the environmental media and general population exposures document.

There are specific comments and minor comments that I won't read through but will be provided in writing to the EPA.

Thank you.

DR. GEORGE COBB: Excellent. Thank you for that review, Dr. Ottinger.

Now, let's see what the associate discussants that to say.

Dr. Shuman-Goodier.

DR. MOLLY SHUMAN-GOODIER: Hello. Thanks.

Thank you to Dr. Ottinger. I have no further comments. Mine were captured.

DR. GEORGE COBB: All right.

Dr. Spade.

DR. DANIEL SPADE: Yeah. I have no further comments.

Thank you for the summary.

DR. GEORGE COBB: Ms. Jenkins?

MS. ALLISON JENKINS: I have no further comments. Thank you.

DR. GEORGE COBB: Dr. Howdeshell.

DR. KEMBRA HOWDESHELL: Thank you for that summary, Dr. Ottinger.

I would just add that I'm not a big fan of weighting studies, but I certainly would encourage there to be some review of the complete body of the literature to see if those studies that were less than medium- or high-quality had the same consistency of effects.

Thank you.

DR. GEORGE COBB: Right.

Now to the remainder of the Committee, are there comments from the remainder of the Committee related to Charge Question 2.a?

All right. I would like to mention -- this is George Cobb -- that to Dr. Howdeshell's comment, I agree that when we have robust data, you probably can get really high-quality studies and choose from them. It turns out that a lot of times in our ecological assessments, at least in

my reads over the years, the majority of the data were generated decades ago, and the current levels of analytical sophistication for instruments was not there. Detection limits were much higher. Reporting requirements may or may not have been as rigorous as they are now. Some of those things factor in, and then you're left with virtually no studies.

But I first approximation agreed with your assessment, Dr. Howdeshell. We're perhaps in a conundrum with our ecological assessments.

DR. KEMBRA HOWDESHELL: That certainly systematic review practitioners of environmental health literature recognize that reporting methods have changed, you know. A lot of the older literature often gets dinged for not having the details that the current studies do.

But we do find at the Division of Translational Talks that it's helpful to look to see what the body of the literature is showing. I would encourage the EPA to consider that approach.

Thank you.

DR. GEORGE COBB: I totally agree with that -- totally agree.

Okay. I think we've come to the end of Charge Question 2.a.

We can turn it -- thank the discussants, turn it back over to EPA for clarifying questions, and then the next charge question once we get through the clarifying questions.

DR. ANTHONY LUZ: Thanks, Dr. Cobb.

This is Tony Luz with EPA.

We don't have any clarifying question at this time.

Thank you.

DR. GEORGE COBB: Then I think we can move to 2.b.

DR. ANTHONY LUZ: Okay.

Moving on to Charge Question 2.b for DIDP.

CHARGE QUESTION 2.b

DR. ANTHONY LUZ: Fate and transport modeling analyses indicate that when DIDP is released to the environment, it is expected to partition primarily to soils and sediments, and therefore, these media are of high priority for environmental exposure analyses. As described in Section 4 of the Draft Environmental Hazard Assessment for DIDP, no hazard data were identified for DIDP for soil invertebrates. DINP was selected as an analog for read-across of soil invertebrate hazard data as described in Appendix A of the Draft Environmental Hazard Assessment for DIDP.

Please comment on the appropriateness of the methods used to identify DINP as an analog for DIDP.

Thank you.

DR. GEORGE COBB: All right. Our lead discussant for this is Dr. Reif.

Dr. Reif?

DR. ALAA KAMEL: I think he mentioned he will have a meeting between certain hours. Maybe this is the time for his meeting. I can check what time this is.

DR. GEORGE COBB: I was not aware that he had left.

DR. ALAA KAMEL: He sent an email. Okay. I'll check.

DR. GEORGE COBB: Okay. Well, if Dr. Reif has departed, we can't do that particular charge question. I apologize to the EPA. I was unaware that he had already left. I thought we were going to --

DR. ALAA KAMEL: Well, he had said he would assign to one of the discussants.

DR. GEORGE COBB: Okay.

So, discussants, was that done?

Okay. I apologize to everybody on the call. We're going to have to -- Dr. Luz, we're going to have to come back to 2.b.

DR. ALAA KAMEL: He's gone from 3:30 to 4:30 --

DR. GEORGE COBB: Yeah.

DR. ALAA KAMEL: -- afternoon, Eastern.

DR. GEORGE COBB: Okay. We're going to have to skip 2.b and come back to it.

Dr. Howdeshell, did you have a further comment or is your hand --

DR. KEMBRA HOWDESHELL: Yeah. Kembra Howdeshell. This was just a request. I don't think that David has had a chance to circulate the summary among the discussants yet, and I know that the next two charge questions that I'm also involved in, we haven't had an opportunity to see the compilation of comments yet, so I wondered if this would be a good point to perhaps pause the meeting so that the summaries could be constructed so that we would have a more cohesive response for these charge questions.

DR. GEORGE COBB: We can certainly consider that.

I want to ask Dr. Ottinger and Dr. Wolf that you're the folks for 3.a and 3.b, which

were not slated until tomorrow afternoon. What are your thoughts on proceeding?

DR. CYNTHIA GRAHAM: We're ready.

DR. MARY OTTINGER: I'm just checking 3.a. I think I have everyone's initial input. I could do it with the understanding that there may be edits that would appear in the written version later.

DR. GEORGE COBB: Okay.

Dr. Wolf, I saw that you and Dr. Apte were emailing back and forth.

DR. DOUG WOLF: Yeah. We're ready.

DR. UDAYAN APTE: Yeah. We're ready.

DR. GEORGE COBB: What if we do this, as crazy as this sounds. What if we do 3.b first, then go to 3.a, and then maybe we even save 2 -- what is it -- 2.b for tomorrow?

DR. ALAA KAMEL: I think that since everyone is there, it may work.

DR. GEORGE COBB: Dr. Howdeshell, I'm not trying to discount your comment. Feel

free to make your comments, especially if they are divergent from anything that's said here. I want to make sure we capture all of that.

Mary Ann, is that okay with you if we do 3.b then 3.a?

DR. MARY OTTINGER: I'm waiting for some comments from Dr. Howdeshell. I don't know if she would prefer waiting.

DR. KEMBRA HOWDESHELL: I -- okay. I'll double-check. I tried to send those over the weekend, but I'll get those to you now.

DR. GEORGE COBB: All right.

DR. MARY OTTINGER: I may already --

DR. GEORGE COBB: If not, you can just --

DR. MARY OTTINGER: I may have already --

DR. GEORGE COBB: -- read yours in, Dr. Howdeshell. You don't have to --

DR. KEMBRA HOWDESHELL: Okay. Okay.

DR. GEORGE COBB: You don't necessarily have to send them.

DR. MARY OTTINGER: I mean, I may have already incorporated them. I didn't note on the compiled version who I got what from. I was just checking, and I did receive your input, I think.

DR. GEORGE COBB: Let's proceed to --

DR. MARY OTTINGER: I did.

DR. GEORGE COBB: -- Charge Question 3.b, and then, Mary Ann, you and -- excuse me -- Dr. Ottinger, and you and Dr. Howdeshell can align those --

DR. MARY OTTINGER: No. That's actually just fine. I did incorporate your -- well, you sent them to me on Saturday. I did incorporate them into the version that I have going now.

DR. GEORGE COBB: Okay.

Let's --

DR. MARY OTTINGER: Not a problem.

DR. DOUG WOLF: Do you want to do A --

DR. GEORGE COBB: Let's --

DR. DOUG WOLF: -- A then B?

DR. GEORGE COBB: I think let's do B first, give Mary Ann a little bit of time to compile. I know that you guys -- I think you guys are ready.

DR. DOUG WOLF: Yeah. I --

DR. GEORGE COBB: Then we'll do B, then A.

DR. DOUG WOLF: Okay.

DR. MARY OTTINGER: That's good.

DR. GEORGE COBB: EPA, I'm sorry, but, Dr. Luz, you're going to have to read that in -- Luz, you're going to have to read that in again.

DR. DOUG WOLF: 3.b.

DR. ANTHONY LUZ: Great. Thanks, Dr. Cobb.

This is Tony Luz here with EPA reading in DIDP Charge Question 3.b.

3. HUMAN HEALTH HAZARD

CHARGE QUESTION 3.b

DR. ANTHONY LUZ: As described in Section 5.3 of the Draft Human Health Hazard Assessment for DIDP, EPA has preliminarily concluded that there is Suggestive Evidence of Carcinogenic Potential of DIDP in rodents. EPA's preliminary conclusion is based on evidence of mononuclear cell leukemia, or MnCl, in male and female F344 rats and hepatocellular adenomas in male CB6F1-rasH2 transgenic mice. EPA has further preliminarily concluded that MnCl observed in F344 rats and hepatocellular adenomas observed only in male CB6F1-rasH2 transgenic mice are not appropriate for conducting dose-response assessment for human health risk assessments.

Please comment on the strengths and uncertainties of EPA's preliminary cancer classification and rationale for not carrying forward rodent cancers into dose response assessment.

Thank you.

DR. DOUG WOLF: Okay.

DR. GEORGE COBB: Okay. Thank you being patient on that.

Dr. Wolf, I know that you and I were kind of maybe chuckling about we were just going to get to your question, but we weren't quite going to make it, but we actually did make it today, so --

DR. DOUG WOLF: We did make it. Yeah.

DR. GEORGE COBB: So --

DR. DOUG WOLF: Since I can't be here tomorrow and the next day.

DR. ALAA KAMEL: Yeah.

DR. DOUG WOLF: You got to put up with -- you going to put up with me droning on instead of Dr. Apte.

Some general comments, and these relate to organ weight changes that are prominent with peroxisome proliferators.

Peroxisomes are found in all eukaryotic cells. They contain oxidative enzymes such as catalase and urate oxidase. At such high concentrations that in some cells the peroxisomes stand out in electron micrographs because of the presence of a crystalloid core.

Thus, with any compound that is a peroxisome proliferator activated receptor alpha agonist, peroxisomes can increase in any cell or tissue resulting in increased oxidative stress as a byproduct and possibly organ weight with enough expansion of peroxisome numbers. We provided some references to that.

Health Canada states, however, the relevance of hepatotoxic effects of phthalates observed in rodents is difficult to establish due to the species-specific differences in the peroxisome proliferation response. Rodents being significantly more sensitive than humans to PPAR-alpha and mediated induction of peroxisome proliferator. Again, there's a reference for that.

The carcinogenicity conclusions for DIDP: Health Canada has done extensive work to determine cancer risk of DIDP and concluded that the descriptors suggestive evidence for carcinogenic potential is appropriate for DIDP. The analysis performed supports this claim. Studies showed only two types of tumors, including mononuclear cell leukemia, which have high background incidence in the species studied, the F344 rats and hepatic adenomas.

The tumors were not observed in all groups and at all doses. The mode of action suggests PPAR-alpha activation taken together the evidence for carcinogenic risk is towards the lower end. The analysis is detailed, and the conclusions are supported by evidence. Based on the available information, the Agency's decisions do not conduct dose response assessment as justified.

With regard to mononuclear cell leukemia: DIDP exposure in a two-year rat study, in this case -- well, this reference is for that,

which we'll provide -- produced an increase in MCNL. The increase was seen in both males and females. This is likely a strain-specific effect given the historically high spontaneous rates of occurrence in F344 rats. Given this, there appears to be a consensus among the commenters that increases in MnCl rates of occurrence in Fischer rats is not a useful predictor of human carcinogenic potential. This view is supported by several references which we provided.

While a couple of these references are cited in Section 5.3 of the DIDP Draft Human Health Risk Assessment, no mention is made of a couple of the other references -- which we have provided -- including a paper on why the NTP has eliminated the F344 rat from its standard bioassay.

The Committee recommended the inclusion of the King-Herbert and Thayer citations -- which we've provided -- to the Section 5.3 of the document. This paper describes the 2005 NTP initial toxicology program workshop, the

objectives of which were to determine whether the models then used in the standard two-species, two-strain bioassay, the F344 rat and the B6c3F1 mouse, remained appropriate to identify substances that may pose a carcinogenic hazard for humans.

Workshop participants advised the NTP to discontinue use of the F344 rat. Within the next year NTP did that, replacing the Fischer strain with the Harlan Sprague-Dawley strain. Based upon this discussion, the observation of an increased incidence of MCNL in a chronic bioassay using the Fischer rats should not be considered a factor in the determination of the cancer classification for DIDP.

Mononuclear cell leukemia on Fischer rats, also called Fischer Rat Leukemia because it is so common, it was one of the reasons that the F344 rat was no longer the primary rat species by NTP, as we've stated. In 2006, they decided to switch the rats because of not only the background incidence of mononuclear cell but also the spontaneous high incidence of Leydig cell tumors

or interstitial cell tumors in the testicle and large granular lymphocyte leukemias.

The cause of these tumor, particularly in the large granular lymphocytic leukemia similar tumor in humans to the rat situation, is very different in that these are typically secondary to Epstein-Barr virus infections and not been found to be associated with drug or chemical exposure. Though the specific mode of action of MnCl in Fischer rats is not known, it's not associated with a viral infection.

There is a qualitative difference in how these leukemias in humans and rats are initiated. Therefore, despite some commonalities between the pathology of these tumors, MnCl is not a model for human leukemias. In addition, there's no evidence for a genotoxic mechanism of action. Rather, it's due to a yet unknown secondary mechanism. These data indicate there is not a concern for prediction of a side concordance or

non-concordant human relevant tumor type. Again, references supplied.

Most commenters agreed that given the material presented in a retrospective review of MnCl and Leydig cell tumors among other tumor responses in the rat species, they lack relevance in predicting human carcinogenicity.

With regard to the EPA cancer guidelines and use of historical control data, one commenter did agree that the lack of relevant laboratory historical control data and data pertaining to the time to onset of MnCl make it challenging to determine if the increase of MnCl in high doses, which was statistically significant, is trivially related and is a source of uncertainty. To determine whether a chemical does influence incidence of this tumor type, it's important to compare values to the appropriate historical control and use more stringent statistical criteria such as those outlined in Thomas et al. Again, references provided.

There were other recommendations on publications related to use of historical control data and more recent publications on the use of historical control data. A recent one in 2021 by Kluxen et al. in Regulatory Tox and Pharmacology and a review from both government, academic, and others, Keen et al. (phonetic), which best practices for the use of historical control data of proliferative rodent lesions, which was a product of a society toxicologic pathology working group. Those references are provided as well.

With regard to the rasH2 mouse model, it's important to note that the proposed use of the rasH2 mouse drug development. References are provided.

In a pharma-based interpretation, adenomas would not be considered a positive cancer call, whereas in the more precautionary approach for environmental risk assessment, an adenoma is considered a potential concern. Thus, the transgenic mouse models were not designed to address human cancer risk in an EPA setting, but

rather identify potential malignant responses quickly for an FDA setting.

Remember, these mouse models were designed to be susceptibility models, so they're more likely to result in a tumor response. They're no more sensitive than the standard mouse typically, and they're not sensitivity or dose. You don't see tumors at lower doses. You just see them earlier.

In Section 5.3, the suggestive evidence section, the DIDP document also describes the increase in hepatocellular adenomas in male CB6F1-rasH2 transgenic mice at the highest dose tested only, 1500 milligrams per kilogram per day -- we'd like to point out that's well above the typical limit dose of a thousand milligrams per kilogram per day -- but not in female transgenic mice or in wild type male or female mice. It also should be noted the highest dose tested, again, was above the traditional limit dose.

There are questions as to whether this transgenic mouse is an appropriate model to

use to assess and predict human carcinogenic potential in this instance.

For rasH2 dose selection recommendation, it's recognized by the Committee that the dose selection for the rasH2 is discussed based on toxicity effects, where the high dose of 1 percent resulted in reduced body weight; however, following the guidance for dose selection, animal carcinogenicity studies, and the FDA reference will be provided.

We will also provide references on recommended dose selections for typical studies that EPA entertains. Those are OPPTS guidance as well as OECD guidance and also some publications related to using PK models in dose selection.

The Committee recommended the inclusion of a discussion of exposure ratio of rodent to human plasma AUC of parent compound. The pharmacokinetic endpoints for dose selection of low toxicity pharmaceuticals is of interest in light of the recent publication -- again, that'll be provided -- where they conclude exceeding a

high dose level of 50-fold -- I'm not sure what the a.m. -- it's not my text, so my co-discussants can tell me what the 50-fold a.m. is -- in rasH2 transgenic mouse studies does not appear to be of value. Again, we provided some references for that.

As the document describes, DIDP is considered to be a peroxisome proliferator that can activate PPAR-alpha.

Health Canada and ECA have hypothesized that liver tumors in the male rat stage two mouse occur through PPAR-alpha mode of action. However, a complete analysis of the mode of action for liver tumors consistent with the cancer guidelines NIPCs has not been completed and that we recommend and assume that that kind of analysis is underway and will be completed and included in a revised final human health hazard risk assessment.

Depending upon the outcome of the analysis, the Agency may have to consider a different descriptor of carcinogenicity for DIDP.

If the analysis supports the hypothesis that DIDP is a PPAR-alpha activator in intermediate key events and modulating factors are confirmed -- are suggested by the data, and several commenters also recommended using a biological read-across approach in addition to the chemical read-across approach -- then the appropriate choice would be not likely to be carcinogenic to humans since neither tumor type observed is considered predictive of human carcinogenic potential.

As the document describes, DIDP is considered to be a peroxisome proliferator that can activate PPAR-alpha. Again, multiple agencies have hypothesized that these liver tumors are from that.

There's a suggestive uncertainty associated with the mode of induction of tumors. Postulated modes of action have been identified but not fully elucidated, and all the key events haven't been described. But again, they may not be necessary for every particular case, thus the carcinogenic potential of DIDP in humans remains

unclear in this. One commenter suggests that it's unclear, and it provides an uncertainty.

A complete analysis of -- let's see. I already said that. May risk -- a lot of cutting and pasting. There we go.

Some Committee members noted there was sufficient information regarding DIDP as a PPAR-alpha agonist, and again, several Committee members thought not likely carcinogenic to humans based on the fact that MnCl in the rasH2 are neither relevant to human concern. Also, the doses where findings occurred in the rodent studies were high doses above the limit dose, and if tumors do occur, they'd be through a PPAR-alpha mode of action.

They are not relevant for human cancer, and based on the cancer guidelines, not likely as appropriate when convincing and "the cancer guideline when convincing an extensive experimental evidence showing that the only carcinogenic effects observed in animals are not relevant to humans." Again quoting the cancer

guidelines, "convincing evidence that carcinogenic effects are not likely below a defined dose range. Both are true in this case."

Recommendation is that, after a further analysis of mode of action for the liver tumors and also using read-across from biological read-across, that consideration of a simple statement of not likely to be carcinogenic to humans is more appropriate. Again, not all commenters necessarily agree with that, but the majority did.

The other recommendation is the Committee recommends the use of the RISK21 framework approach to enhance communication of conclusions in a sample plot and provided a couple of examples of that for the DIDP. This publicly-available tool developed through Health and Environmental Sciences Institute collaboration of which multiple government scientists were instrumental contributors, including staff from the U.S. EPA.

The RISK21 tool should be considered to help improve communication, both to senior leaders within the Agency as well as to the general public.

The OECD, Health Canada, and the Chinese Food Safety Authority all have endorsed this framework through documents and through regular use. There are a couple references, one on the OECD and one on Health Canada on how they incorporate that.

Those are primary comments and recommendations. I think the other -- yeah. That's all, so I guess I'll turn it over to my other commenters.

DR. GEORGE COBB: Great. Thank you, Dr. Wolf, for getting that in the record for us.

Now we can hear from the associate discussants.

Dr. Apte.

DR. UDAYAN APTE: All my comments were really well captured, and I'm actually

looking forward to hearing any discussion that's there.

DR. GEORGE COBB: Dr. Graham?

DR. CYNTHIA GRAHAM: Well, I thank you, Dr. Wolf. Yeah. All of my comments were included. Thank you.

DR. GEORGE COBB: Dr. Przybyla?

DR. JENNIFER PRZYBYLA: No further comments. Thank you.

DR. GEORGE COBB: Dr. Martinez.

DR. JEANELLE MARTINEZ: Hi. Yeah. I have no further comments. My comments were included. Thank you very much.

DR. GEORGE COBB: Very good.

Well, so, Dr. Wolf, thank you for making those -- summarizing that and getting that done right before you need to depart tomorrow.

Dr. Apte, do you still have a comment?

DR. UDAYAN APTE: Yeah. I just wanted to mention I think that this was kind of here in the report, but sometimes nuclear receptor

agonists will have, at higher doses, mechanisms that are more closer to cytotoxicity, as MRI, and this could be one of the cases of higher doses here.

But I just want to point out that I would personally consider these two different events. The cytotoxicity MOA of the same chemical has probably nothing to do with its PPAR-alpha agonism or nuclear receptor agonism. So, they are dual things.

At high doses in that, as in toxicology we say, dose determines the poison at a certain point in time, so something's going to kill the cell, and the dose comes in, but at that point, it's actual mechanism at lower doses has been superseded, and so they are two different things.

DR. DOUG WOLF: Yeah.

DR. UDAYAN APTE: I just wanted to put that on record and say I think that should be something that we should be very aware of when we talk about this.

DR. DOUG WOLF: Yeah. I think that's really important, particularly in the rasH2 transgenic model because that's one of the reasons why it doesn't support human relevance.

As a pathologist, what you see at these very high doses is you get so much peroxisome proliferation, and then secondary to that, oxidative stress and cells die. You can get cytotoxicity and proliferative regeneration at those very high doses.

But the molecular initiating event, using the AOP framework, is still that PPAR-alpha agonism because that's what's happening at lower concentrations. Then, as you get up to higher, then this overwhelming system where you're just pushing all these other incidental or associated events at a higher dose, which aren't related to the PPAR-alpha traditional mode of action.

DR. UDAYAN APTE: I just think that in cases like that, the only real experiment is to have data on PPAR-alpha knockout animals and see if you still get the cytotoxicity there, which

would be then independent on PPAR-alpha activation.

I don't know whether -- I don't think we have those kind of data here, so all that doesn't matter from the standpoint of what we are trying to do. It's --

DR. DOUG WOLF: Well, plus, you don't see that in the chronic studies --

DR. UDAYAN APTE: Yeah. You don't.

DR. DOUG WOLF: -- at the lower doses, so there's still a point of departure.

DR. UDAYAN APTE: There is a point of --

DR. DOUG WOLF: Even in the HRAS mouse study there's lower doses where nothing's going on, so you still have no effect levels for whatever's happening at that high dose in the HRAS. You can still -- again, these are not genotoxic, so whatever's driving these responses is chronic toxicity, and you can select no-effect levels, whether you do a benchmark response type

of the traditional NOAEL. So I think we're agreeing -- vociferously agreeing.

DR. GEORGE COBB: Dr. Martinez, did you --

DR. UDAYAN APTE: Although it didn't sound like (inaudible).

DR. GEORGE COBB: Yeah. Dr. Martinez, did you have a comment?

DR. JEANELLE MARTINEZ: No. I think they covered it right now. Thank you.

DR. GEORGE COBB: Okay. Then, I do see Dr. Fenner-Crisp has her hand up.

DR. PENELOPE FENNER-CRISP: I want to vociferously agree as well and make the point about the mouse study.

I would suggest for reasons of the significant exceedance above the MPD -- which I've got the data here. It's 31 percent body weight reduction in males and 15 percent in female transgenic mice and 27 percent males and 4 percent in females in the wild mice. If that were a study that it come to the pesticide programs it would

have been thrown out. If it were required study to maintain or approve for registration, they'd have to do it again.

DR. GEORGE COBB: Okay. Thank you. That's important information.

All right. Are there comments from others on the Committee?

All right. Seeing none, thank you, Dr. Wolf. Maybe don't leave us yet. Stick around because EPA may have questions.

DR. DOUG WOLF: I'm still here.

DR. GEORGE COBB: EPA may still have questions about this. We'll turn it back over to Dr. Luz.

DR. ANTHONY LUZ: Thanks, Dr. Cobb.

Tony Luz here from EPA. No questions for clarification. Thank you.

DR. GEORGE COBB: Yeah. Now I think we migrate to 3.a. So, we're shuffling the deck here.

Dr. Ottinger will be our lead discussant when this gets read in.

DR. ANTHONY LUZ: Great. Thank you, Dr. Cobb.

Yes. DIDP Charge Question 3a.

CHARGE QUESTION 3.a

DR. ANTHONY LUZ: As described in Section 6.1.4 of the Draft Human Health Hazard Assessment for DIDP, EPA has preliminarily concluded that the HED of 9.0 milligrams per kilogram, which is a NOAEL of 38 milligrams per kilogram per day, from the two-generation study of reproduction of Sprague Dawley, or SD, rats based on reduced F2 offspring survival on post-natal day 1 and post-natal day 4 is appropriate for calculation of non-cancer risk from acute, intermediate, and chronic durations.

Please comment on the strengths and uncertainties of EPA's preliminary conclusion.

Thank you.

DR. GEORGE COBB: Now we'll turn it over to Dr. Ottinger, and if you'll read the response into the record.

I want to point out to the associates that you're certainly welcome to comment at any time as well as anyone on the Committee if all the comments are not captured.

Dr. Ottinger, please proceed.

DR. MARY OTTINGER: Okay. I'm going to start with general comments.

The NOAEL of 38 milligrams per kilogram per day was estimated from two 2Gen study and converted to a human equivalent dose, HED, of 9 milligrams per kilogram per day. Supporting literature up to 2018 was included for epidemiology, and there were additional literatures added up to 2023.

The metabolic pathway for DIDP is important for potential bioactive metabolites during excretion. The radioactive transfer study indicates most clearance over two to three days following oral route. Lines 813 to 815 DIDP does

not appear to have antiandrogenic effects similar to DEHP.

The Wistar rats, the oral exposure during pregnancy showed increased skeletal abnormalities. CD-1 mice dosed with higher concentrations of DIDP showed no adverse effect on pups or viability. However, the Sprague Dawley rats in one and two generation tests showed developmental abnormalities and reduced viability with decreased pup weight and also effects on the body weight of the female.

The mammal model in the in vitro studies did not reveal activities for estrogen or androgen responses. Rather, the mechanism of action seems to be PPAR-alpha activator. Thyroid and corticosterone were not examined.

The two-generation test did not include hormone measures, only survival sperm parameters and other downstream indicators that generally requires substantial issues in order to see effects. No effect on fertility strengthens the assertion that the primary target window is

developmental for the reproductive as well as for other systems, like kidneys and liver. However, one study suggested effects on the dam's ability to maintain pregnancy. The body weight of males, females, and pups was not really factored into the results, although significantly reduced.

Interestingly, a cross fostering post-natal study with controlled dams did not improve survival again supporting evidence for adverse developmental effects.

There is limited evidence, besides a previous study by the same author supporting decreased F2 survival on the postnatal day one and postnatal day four, while other studies suggesting developmental toxicity additional two-generation data are lacking.

EPA is considering a 2Gen test as acute exposure. However, it's unclear what EPA's policy is to take into account indirect exposure of the F1 generation. EPA states the following: "EPA considered reduced F2 offspring survival to be potentially relevant for both acute and chronic

exposures," page 55. It is not clear how an exposure can be both acute and chronic. Although not direct exposure to developing fetuses, the developmental toxicity endpoints were not observed in the F1 generation indicating indirect exposure to F1 animals did not influence the F2 animals.

The exposure time frames outlined throughout the document are inconsistent. Starting on page 32 in the Draft Human Health Hazard Assessment for DIDP, EPA uses the term short-term for 1 to 30 days, subchronic greater than 30 to 90 days, and chronic greater than 90 days but then uses the term acute and intermediate starting on page 49. Are short-term and acute the same exposure time frame? Same question with intermediate.

It is unclear why EPA designated the liver toxicity studies intermediate exposure scenario, Table 6.2, when they would fit in the definition of short-term. The longest exposure indicated in Table 6-2 is 28, which should be considered short-term. If upon reexamination, EPA

considered the liver toxicity studies to be acute exposure, EPA should consider deriving the POD for risk assessment using liver toxicity because there's a greater weight of evidence given that liver toxicity is observed at several durations and across species.

There's an agreement with EPA's assessment not to use increased incidence of spongiosis hepatis and microgranuloma as the POD for chronic exposure given the limitations described in the document.

Strengths include the preliminary conclusion to use an equivalent dose of 9 milligrams per kilogram with a NOAEL of 38 milligrams per kilogram per day, and that's based on the results of the 2Gen study in the Sprague Dawley rats compromised of two studies, study A and B.

In study A, the lowest dose was the LOAEL, and in study B, the lowest dose, the 38 milligrams per kilogram per day was the NOAEL. Furthermore, there are additional studies

principally of liver endpoints that had similar NOAEL value that translated into a comparable HED.

The main uncertainties were identified by the EPA. The mechanism by which DIDP inhibited survival is not clear. Nor is it clear whether the effect is caused by a single dose or repeated dosing.

Finally, the EPA's preliminary conclusion is consistent with hazard characterization of several other regulatory and authoritative bodies that do risk assessment around the world. We're providing examples and literature.

The treatment related developmental toxicity is associated with DIDP exposure, and the HED based on the NOAEL for reduced F2 offspring survival is the most appropriate and lowest HED. The slightly lower POD HED from Cho et al. studies has too many uncertainties to be used. That POD is based on a LOAEL for increased incidence of spongiosis hepatitis and microgranuloma.

In addition, EPA states that BMD modeling showed that the HED of 9 milligrams per kilogram is more sensitive than the HED from the Cho study.

There is good evidence for developmental effects of DIDP in animal models. In addition, there is evidence of developmental effects from the limited epidemiologic studies. The basis of the HED of 9 milligrams per kilogram from the two-generation rodent study follows GLP process from which the NOAEL is based. These are strengths to serve as the POD for the HED. Let's see. The HED -- sorry. Repeating things.

There are some uncertainties in the absence of inhalation and dermal DIDP data. It would be good to have additional text in Section 6.1.4 describing major uncertainties and issues with using the oral HED for DIDP to extrapolate to inhalation and dermal routes.

Using a NOAEL as the basis for the POD has associated uncertainties, including the fact that the NOAEL is a function of study design.

Hushka et al., 2001, has good study design, but in 2001 we were not examining the low-dose region of the curves. Endocrine disruption was an emerging field, and the study design is limited to identify the potential for low-dose non-monotonic effects.

By extension, measures of signaling molecules at postnatal day one and four are not as complete as they would be if this study was done today.

EPA did not conduct benchmark dose modeling on Hushka et al. or any of the other candidate PODs, except for the Cho et al. as per EPA's own guidance. Without comparing the full BMD-based analyses there's less certainty about the most sensitive endpoint.

There are a set of recommendations. The studies shown for setting the HED at 9 milligrams per kilogram are appropriate, and the 2Gen study of the Sprague Dawley rats is most rigorous for demonstrating developmental effects. Points raised in the other sections regarding loss of body weight for dams and pups should be

mentioned here as additional outcomes, albeit separate from the Frank toxicity tests -- effects, rather.

The conclusion that no endocrine disruption is incomplete without consideration of thyroid and adrenal axes test. Are any data available? The bases for extrapolation of oral exposure to dermal or inhalation roots of exposure is important and details in the appendix do help clarify the rationale. However, it is not clear how much exposure would be predicted.

Do these roots of exposure pose a significant hazard? It would seem so from other documents in that soil and surface water deposition would be primarily airborne. As such, how far from the source is a hazard?

One discussant commented, I do not agree with the Agency's proposal to use the data from the 2Gen reproduction study employing the same POD HED for all three durations of exposure. It is fine for the acute value because the hazard value is based on effects identified on postnatal

day 4. However, there is a general consensus across most, if not all, other regulatory bodies internationally that the liver is the most sensitive target tissue when assessing DIDP's longer-term effects and deriving hazard values for longer-term chronic exposures.

Thus, the Agency should look at candidate studies with a compatible exposure durations and timing of findings that evaluate liver effects. While they did, but did not use any of them for selecting the POD HED for risk characterization, most of the candidate studies were conducted using rats with two exceptions, one with mice and one with dogs. The result in the rat studies? In one case the NOAEL for liver effects was identified, and it's LOAEL was significantly lower than the NOAEL for reproductive developmental effects. It was identified in the 2Gen study, which is a LOAEL of 22 milligrams per kilogram per day versus a NOAEL of 33 milligrams per kilogram per day. That rat study would likely yield a NOAEL even lower if a

lower dose had been tested. However, the Agency expressed some uncertainty about this study and dismissed it as Canada.

On the other hand, as EPA points out, there is consensus across existing assessments of DIDP by U.S. CPSC and other citations that will be provided. That's based on increased liver weight, histopathological findings, and several of these other regulatory authorities have used the study in the derivation of their long-term chronic health value.

EPA seems to have dismissed this study for use in the derivation of hazard values because in its view this study is limited by a small sample size and the lack of statistical analysis.

A recommendation with regard to sample size: Both EPA's harmonized test guideline for daily oral toxicity in non-rodents is intended to meet the testing requirements of the FIFRA and the TSCA and the OECD test guideline for at least eight animals, four female, four male, to be used

in each dose level if no interim sacrifices are planned. While the Hazleton study utilized groups of only three male and three females, this should not be seen as a disqualifying factor in this case. Also, it would appear that these other agencies did at least one crude measure of testicular analyses as they did identify a NOAEL. Obviously, these other agencies were not deterred by either issue.

Recommendation is that the Hazleton lab study be used for both subchronic and chronic POD HED. No additional uncertainty factor to accommodate subchronic Taconic extrapolation should be needed because there is general agreement that the 90-day study is adequate for predicting chronic effects based on the observation that the same or similar OIELs and LOAELs are little different for a chemical when compared to 90-day and one- to two-year chronic studies.

In fact, the chronic study has been eliminated from most regulatory agencies premarket

testing schemes for pesticide based on the determination that the longer exposures seldom provided any added value, identified few new effects, and rarely yielded lower NOAELs or LOAELs.

As EPA's office OPP states, even for the small percentage where there are indications that a one-year dog toxicity study would potentially provide a lower LOAEL than a 13-week study for purposes of RFD determination, differences between the LOAELs and NOAELs between the two dog studies were small, less than four-fold or less. It is unclear to what extent these small differences in LOAELs are meaningful from a practical standpoint relative to the hundred-fold default uncertainty factor commonly used in calculating RFT. In no case did these small differences have regulatory impact on pesticide risk assessments.

As a result of their large retrospective analysis cited above, OPP eliminated

the routine requirement of the one-year dog study while retaining the 13-week dog study.

EFSA states that for the approval of plant protection products, the scientific rationale of using dogs as a second species in the regulatory process has been debated and culminated with the elimination of the one-year dog study, from data requirements in EU, U.S., Brazil, Canada, Australia and recently Japan, leaving the 90-day study as the only study available in the data set for hazard assessment in nonrodent species.

There is limited evidence besides a previous study by the same author supporting decreased F2 survival on postnatal day one and postnatal day four. While other studies suggesting developmental toxicity additional 2Gen data is lacking -- are lacking.

EPA is considering the 2Gen as acute exposure. Unclear if it is to take into account indirect exposure.

I believe I already read these in. I think these are repeats. Sorry about that.

Okay. There are a number of specific comments, and I will just provide that in writing to the EPA.

DR. GEORGE COBB: Thank you, Dr. Ottinger.

The specific comments, those are editorial or suggested formatting kind of things?

DR. MARY OTTINGER: They are.

DR. GEORGE COBB: Okay. Great. Excellent.

DR. MARY OTTINGER: Well, there's one.

Clarify the point in this sentence: Are you stating that the EPA in the lines 2771 to 2775? Are you stating the EPA considers the study to support a developmental toxicity NOAEL of 40 milligrams per kilogram per day? If so, then consider removing the a.m. before the phrase.

DR. GEORGE COBB: Yeah. I think those are -- yeah. I think those are all clarifications.

DR. MARY OTTINGER: That's -- yeah. Okay.

DR. GEORGE COBB: Excellent. Thank you.

Let's move to our associates now. Let's see, we are at Dr. Heiger-Bernays.

DR. WENDY HEIGER-BERNAYS: I have no additional comments. Thank you, Dr. Ottinger. That was everything -- everything.

DR. GEORGE COBB: Ms. Jenkins?

MS. ALLISON JENKINS: No other comments. Thank you.

DR. GEORGE COBB: Dr. Przybyla?

DR. JENNIFER PRZYBYLA: All my comments were captured. Thank you.

DR. GEORGE COBB: Dr. Howdeshell.

DR. KEMBRA HOWDESHELL: All of my comments were included.

DR. GEORGE COBB: Thank you.

At this point, we're close to the --

DR. ALAA KAMEL: Are you going to ask the rest of the Committee?

DR. GEORGE COBB: Oh, yes. I'm sorry. Thank you, Alaa. I was so happy we had gotten to this point that I was about to skip the rest of the Committee.

Let's hear from the rest of the Committee. Are there any comments from others on the Committee?

Dr. Wolf.

DR. DOUG WOLF: Since I won't be here tomorrow when you're talking about DINP, they make a case for using a common point of departure to protect against all effects, and I think DIDP could be the same approach. I think it would behoove the Agency to look at that and make that case within the report outs that using a common point of departure protects against all acidities, including chronic toxicity and the potential for carcinogenicity as the case they make for the DINP.

DR. GEORGE COBB: Great. Thank you for that comment.

Other committee members?

I should point out when I say committee members, I also mean ad hoc committee members as well.

Well, seeing none, we are at the end of Charge Question 3. I think this is probably the end of what we're going to do today. But I want to turn it back over to EPA for a minute to see if there are any clarifying questions from what we've gone over in this last segment or any part of today.

DR. ANTHONY LUZ: Thanks, Dr. Cobb.

This is Tony Luz with EPA. There's no questions for clarifications on Charge Question 3.a.

Just want to thank all of the Committee members for their really thoughtful and really thorough and helpful discussions throughout the day on all the charge questions that we've gotten through thus far. Thank you.

DR. GEORGE COBB: Okay. Great.

Let's circle back to the other Committee members. Are there comments about any of the topics that we've talked about today that we need to have additional discussion about?

All right. If not, I think we should adjourn for the day, and then we can pick up with 2.b tomorrow. We will probably circle back to a couple of risk-related concepts that have partially been captured in some charge questions and may not be. Those of you who said you were interested in that, we'll circle back to that, or we'll get to that right after we do 2.b tomorrow morning.

We're nearly a full day -- perhaps a full day ahead of schedule -- so I commend everyone on that.

Also, I think there are a couple of questions we're waiting to hear back from EPA. We'll try to get through those early in the morning.

With that, I'm going to turn this over to Dr. Kamel for closure.

DR. ALAA KAMEL: Thank you, George.

Well, I'd also thank all the SACC Committee members and the ad hoc reviewers and the EPA team for answering all the questions.

Thank you very much. We'll adjourn and join tomorrow.

Thank you.

[MEETING ADJOURNED FOR THE DAY]

OPENING OF MEETING DAY 3

DR. ALAA KAMEL: Good morning. My name is Alaa Kamel, and I am serving as the Designated Federal Official to the U.S. EPA's Science Advisory Committee on Chemicals, SACC, for this meeting. And in my role I will be opening the third day of the public meeting on EPA's Draft Risk Evaluation for Di-isodecyl Phthalate, DIDP,

and the Draft Hazard Assessment for Di-isononyl Phthalate, DINP.

I'd like to repeat that the SACC meetings are subject to all FACA requirements. These include open meetings, timely public notice of meetings, and document availability to the public. All documents are available to the public in the docket at regulations.gov. The link to the docket is present in the agenda. As a reminder, this meeting is being webcasted, transcribed, and recorded. A livestream of today's meeting is available on YouTube. See the link on the meeting agenda too and on the meeting website, which also has links to meetings that we had on July the 30th and July the 31st. I'd like to thank the Chair, Dr. George Cobb, for chairing the sessions and for the Committee. And also thank the Committee members and ad hoc reviewers for responding to the charge questions. And now I hand it over to the Chair, Dr. Cobb.

DR. GEORGE COBB: Thank you Dr. Kamel. And welcome, everyone. And I'll echo my

thanks to all in attendance today. We do have a few things we need to perhaps revisit from yesterday with some responses to charge questions and some clarifications from EPA. But before we do that, I'd like to go through and take a roll to make sure we know who's here for the record. So, Dr. Apte.

DR. UDAYAN APTE: I'm here.

DR. GEORGE COBB: Dr. Baker.

DR. MARISSA BAKER: Here.

DR. GEORGE COBB: Dr. Chaisson.

DR. CHRISTINE CHAISSON: Present.

DR. GEORGE COBB: Dr. Eick.

DR. STEPHANIE EICK: Here. Good morning.

DR. GEORGE COBB: You're early up there. Dr. Gentry.

DR. ROBINAN GENTRY: Here.

DR. GEORGE COBB: Dr. Graham.

DR. CYNTHIA GRAHAM: I'm here.

DR. GEORGE COBB: Dr. Heiger-Bernays.

DR. WENDY HEIGER-BERNAYS: Here.

DR. GEORGE COBB: Ms. Jenkins.

MS. ALLISON JENKINS: I'm here.

DR. GEORGE COBB: Dr. Li. Dr. Merced-Nieves.

DR. FRANCHESKA MERCED-NIEVES: Good morning. Present.

DR. GEORGE COBB: Dr. Ottinger.

DR. MARY OTTINGER: Here.

DR. GEORGE COBB: Dr. Przybyla.

DR. JENNIFER PRZYBYLA: Present.

DR. GEORGE COBB: Dr. Reif.

DR. DAVID REIF: Here.

DR. GEORGE COBB: Dr. David.

DR. RAYMOND DAVID: Present.

DR. GEORGE COBB: Dr. Fanning. Dr. Fenner-Crisp.

DR. PENELOPE FENNER-CRISP: Here.

DR. GEORGE COBB: Dr. Howdeshell.

DR. KEMBRA HOWDESHELL: Present.

DR. GEORGE COBB: Dr. Martinez. Dr. Shuman-Goodier.

DR. JEANELLE MARTINEZ: (Audio distorted Inaudible).

DR. ALAA KAMEL: Dr. Martinez was there, but she was on mute.

DR. GEORGE COBB: Yes, you're correct. Dr. Shuman-Goodier.

DR. MOLLY SHUMAN-GOODIER: Present.

DR. GEORGE COBB: Thank you. Dr. Spade.

DR. DANIEL SPADE: Present.

DR. GEORGE COBB: And I believe Dr. Wolf is on travel today. So, let's go back to a couple that we missed. Dr. Li. And Dr. Fanning. All right, we do have a quorum, so we can proceed.

PANEL MEMBERS: FOLLOW-UP ON PREVIOUS DAY

DR. GEORGE COBB: The first thing I'd like to do today is there was a public comment that EPA received related to the manufacturer's request and placing that in the context of TSCA review process or the language, and it was

language I used about that. So, I think EPA has maybe someone to clarify or respond to that public comment that they received. And I believe that was Dr. Morris.

DR. JEFF MORRIS: Good morning, everyone. This is Jeff Morris at EPA. It's a pleasure to meet with you this morning. I can clarify the comment regarding the distinction between the risk evaluations that the EPA itself prioritizes and those that we evaluate per manufacturer's request for evaluation.

So, these evaluations are done under Section 6 of TSCA, and Section 6 provides two opportunities for -- or possibilities, pathways, for the EPA to evaluate existing chemical substances. One is through our own prioritization process where we identify a chemical substance that we would like to propose for a high priority for risk evaluation. And ultimately if after a 9- to 12-month process we designate that chemical as a high priority for risk evaluation, and it moves into our three- to three-and-a-half-month process

for conducting that evaluation, which includes public comment and peer review.

Section 6 also provides an opportunity for chemical manufacturers to request that the EPA conduct an evaluation. We will review that request. And if we believe there are adequate data to evaluate the chemical substance, we'll grant that request, open up a docket, and provide a -- or public comment to review the proposed evaluation and the conditions of use under which EPA would evaluate it. So, we could take comments on whether for example members of the public believe that additional conditions of use should be included in that risk evaluation.

And that process has taken various amounts of time. I wouldn't characterize it at all as necessarily expedited. It's just two paths under TSCA for getting a chemical into the risk evaluation process. But once the chemicals are in the process via through our own initiated Section 6 process or through the manufacturer request, the evaluations are conducted under the same

scientific standards under Section 26 of TSCA and undergo the same public comment for draft evaluations and peer review.

So, I hope that clarifies that distinction between the process for initiating evaluations under Section 6 of TSCA and recognizing that, once again, once they're in the process we conduct evaluations under the same scientific standards. So, I hope that clarified, but I'm happy to follow up or provide additional explanation if anyone wishes.

DR. GEORGE COBB: It certainly does. And I do appreciate that. This is George Cobb speaking. And I will say that I used the term expedited. I was intending that to imply that there was a request that this be put in the docket separate from EPA's initial screening process. So, that was the intent and not that the process once it started was in any way expedited. So, we can have questions about that if the Committee prefers, or we can hear from Dr. Luz, who has some responses to our questions. But let's see if

there's questions from the Committee. Dr. Heiger-Bernays.

DR. WENDY HEIGER-BERNAYS: Yeah, I -- yes. Thank you, Dr. Cobb. I do have a question from EPA with regard to -- it's great to have the explanation of how Section 6 works. The question I think that was asked by the Committee as well was access to data. Access to data that the organizations that request the risk evaluation may have and whether EPA is able to make the same data requests under both situations under Section 6 for initiating the risk evaluation. Thank you.

DR. JEFF MORRIS: Thank you. Yes, it would be the same under either case. We'll evaluate the chemicals whether it comes in through our process prioritized or through a manufacturer request, looking at all reasonably available information. And we would expect parties who have data relevant to the evaluation to have that available, recognizing that with all assessments we have to ensure that we safeguard any confidential business information. But we do a

systematic review of the literature, and so we -- or in either case. And so, we evaluate the databases of chemicals whether they're manufacturer requests or prioritized in the same manner.

DR. GEORGE COBB: Yeah, thank you. So, I think the question truly was, does the Agency have the ability to request additional information to fill data gaps in the manufacturer-requested review as opposed to the other reviews? And my understanding yesterday was -- or earlier in the week -- I shouldn't say what day -- was that after the review starts -- you can consider that before the review is granted, but after it starts, you can't request additional data to fill data (audio skip).

DR. JEFF MORRIS: Yeah. Okay, that helps a lot. So, when we grant a request, the term we use is it's facially complete. We believe that the request is complete and that we have adequate information to do the risk evaluation. Under Section 4 of TSCA we have the ability to

require the generation of data if we believe those data are needed under Section 6 to conduct an evaluation.

I will say that from a timeliness perspective, once we do grant the risk evaluation, it's under the same clock as the prioritized evaluations, which means we have three years to get the evaluation done, which means we have somewhere around a year to 18 months to get the analysis completed and get a draft ready for public comment and peer review. So, the time between grant and issuing of draft risk evaluation is not a long time to require -- or acquire additional information. So, that's why we aim with manufacturer requests since we're not going through the 9- to 12-month year prioritization process to make the determination that the request is facially complete and therefore is ready to go in terms of having the information necessary to conduct an evaluation, which again, I'll just reiterate, doesn't preclude the statutory authorities we have under Section 4 of TSCA to

require the generation of data we believe is needed for risk evaluation.

DR. GEORGE COBB: Excellent. Thank you for that clarification. And I am sensitive to the -- and I think the Committee is too -- the time constraints. And I think we comment on that pretty frequently. So, I appreciate that response. All right. Let's see. Dr. Chaisson.

DR. CHRISTINE CHAISSON: Yes. Can I ask EPA? Is there any perceived advantage to the Agency or to the public for taking requests for these particular reviews since you already have a caseload that's pretty amazing? And so, there must be some public interest in adding to that pile. Can you speak to that?

DR. JEFF MORRIS: Yes, I can. It's actually a statutory requirement. So, section -- oh, I should back up. First of all, Section 6 requires the Agency -- I'm speaking to caseload -- to have at least 20 prioritized risk evaluations in the program at any given time. So, that means when we complete one we need to bring one back in

so we have a caseload of 20 prioritized evaluation. The statute also requires us to have no less than 25 percent, but no more than 50 percent additional chemicals in as manufacturer requests if we get that many requests. So, with a caseload of 20 prioritized, that would mean between five and ten extra as manufacturer requests. So, the ability of manufacturers to request and our requirement to accept those requests if they fill requirements is actually a part of the statutory requirements under TSCA.

DR. CHRISTINE CHAISSON: Thank you very much. That's very helpful. I appreciate that.

DR. GEORGE COBB: Yes. Thank -- yes. I feel that. Thank you very much for those answers and for taking the questions kind of on the fly. We didn't anticipate that we were going to have this discussion this morning. So, thank you very much. Dr. Morris.

At this point Dr. -- sorry -- Dr. Luz has a response to some questions we had a day

or so ago, and most of them were by Dr. Chaisson, I believe, but perhaps by others. So, Dr. Luz, do you have that response?

DR. ANTHONY LUZ: Morning, Dr. Cobb. Yes, we have responses from EPA. And, again, these were in response to questions primarily from Dr. Chaisson that she kindly provided to us via email and writing, as we respond in writing. So, I'm going to do my best to paraphrase the questions, and I'll provide EPA's response and read the response verbatim into the record.

So, the first question pertained to the Consumer Exposure Model, or CEM, whether or not it had been peer reviewed. That question also was asking related to the Exposure Factors Handbook, whether or not that had been peer reviewed. And it had kind of sub-questions related to portions of size of fish consumption that the Agency used.

So, the Agency's response. "CEM went under peer review in 2016. Feedback from the peer review process was incorporated into CEM

before public release of Version 2.0 in 2017. Fish ingestion rates and factors are discussed and cited in Section 7 of the Environmental Media and General Population Technical Support document."

Do you want me to pause there to see if there's any responses from the Committee to that questions? Or do you just want me to continue on with --

DR. GEORGE COBB: You can proceed either way. It's fine with me either way.

DR. ANTHONY LUZ: Okay. Great. Thanks, Dr. Cobb.

Okay. The next question again pertained to EPA's use of CEM and it not being used actually for the dermal exposure assessment for consumers. This question's a little technical, so I'm just going to read the question verbatim. "Did it use degrading absorption and transfer coefficients with repeated exposure? Are the dynamics of leaching understood for the different plastics and other matrices such as cellulose from which the different phthalates can

escape under conditions of aging, structural stress, temperature, et cetera? Is that factored into the exposure scenario? Can you please summarize how that was represented in Draft Consumer Exposure Analysis?"

So, EPA's response. "EPA generally discussed DIDP formulation and potential leaching in the first paragraph of Section 2.2. Further considerations mentioned in the question are not included in the estimates. EPA welcomes SACC recommendations for references that can be used to qualitatively discus such complexities in the context already provided in Section 2.2."

Okay. So, the third question. "In Section 5" -- so Page 115, Lines 2052 through 2058 -- "pertaining to chemical rate was derived from surrogate data. Could you point to where the surrogate data are identified and extracted for use here?"

EPA's response. "Section 2.1.2.1, see chemical migration rate subsection, Line 806. This subsection contains references and

descriptions of the chemical migration rate selection." And that's a response to that question.

The next question, Question 4. "So, as migration proceeds over time, migration dynamics change function of integrity of the initial plastics, decreased concentration of a plasticizer, dynamics of use of the product. So, the distribution of values of migration rates can be frontloaded in relation to plasticizer concentration of the product, but also degradation of the product plastic in older items can affect the rate of release. How is this handled? What value was chosen for the deterministic value to be used? Was this discussed and surrogate chemical migration dynamics shown?"

So, EPA's response. "EPA recognized the sources of uncertainty from some of the mentioned considerations, specifically migration of DIDP from solid products to aqueous solutions in the dermal assessment and uncertainties due to chemical leaching for products. So, see first

paragraph in Section 2.2 and Section 5.1, chemical migration rate discussion. And concerns are available in Sections 2.1.2.1. That's the chemical migration rate subsection, as well as in Section 5.1. In article inhalation scenarios, DIDP is released into the gas phase. The article inhalation scenario tracks chemical transport between the source, air, airborne, and settled particles indoor sinks by accounting for emissions, mixing with the gas phase, transfer to particulates by partitioning, removal due to ventilation, removal due to cleaning of settled particulates, and dust to which DIDP has partitioned, and sorption or desorption to slash from interior surfaces. The emissions from the article were modeled with a single exponential decay model." That's our response to the Question 4 that posed.

And then Question 5 was asking for clarification for products under the domain of FDA for regulation. "Do the FDA risk assessments consider the exposure scenarios mandated by TSCA?"

Some of the examples given in this being pertaining to phthalates and food uses, PESS, phthalate uses in medical equipment.

So, EPA's response. "EPA OPPT is currently focused on assessing the exposure and hazard to DIDP and DINP under TSCA. To respond to these questions, EPA would need to coordinate with FDA."

The next question, so question number six. "Lines 987 through 988, EPA based confidence in weight fractions for different products on the number and age of data sources that were used, and the difference between moderate and low confidence was based on the age of the sources. Particularly given that DIDP is a replacement for DHP in some products, how does EPA define more current or less current? Is there a generalizable trend in the rate of DINP use across product categories that could be used to reduce uncertainty?"

So, EPA's response. "EPA recognizes that the terms more current and less current are

difficult to apply across products and articles and further description may be needed. Articles that remain place can be reformulated in the content of DIDP change. Having weight fractions that are reported in past CDR reporting cycles but not in current ones is considered less current, as this is our indicator of manufacturing and production practices and changes. Completed assessments and product testing reports published before CDR reporting changes are evident, are less current. Obtaining SDS for products such as adhesives that are contemporary with the products available to consumer the moment of assessment development are considered more current." And that's the response to that question.

And then the final question, so Question 7. "Are phthalates used in hydraulic fracturing for oil and gas? Where is this included?"

So, EPA's response. "EPA's COU table for DIDP and DINP do not include hydraulic fracturing for oil and gas. As EPA develops the

draft risk evaluations for other phthalates, EPA will consider hydraulic fracturing for oil and gas as appropriate." That brings us to the end of the EPA responses to the questions posed yesterday morning. So, I'll turn it back over to you, Dr. Cobb.

DR. GEORGE COBB: Thank you, Dr. Luz. That was a comprehensive response.

DR. CHRISTINE CHAISSON: Excuse, Dr. Cobb. I have follow-up question on the first question.

DR. GEORGE COBB: Well, I was getting to that.

DR. CHRISTINE CHAISSON: Sorry.

DR. GEORGE COBB: We'll now turn this over to the Committee for further question or comment regarding this. So, Dr. Chaisson, you had --

DR. CHRISTINE CHAISSON: Yeah. On the very first question -- thank you for that, by the way. That was very helpful. The very first question I asked if the peer reviews are publicly

available documents. Are they? And if so, how do we get one of those?

DR. LAURA KRNAVEK: Hi, this is Laura Krnavek. We're currently working on getting those, this specific goal, 2016 document, to see if it's publicly available. We do have it. Just not entirely sure it is publicly available.

DR. CHRISTINE CHAISSON: Will you be getting back to us about that?

DR. LAURA KRNAVEK: Absolutely. As soon as I know a path to get it across to you. Yeah.

DR. CHRISTINE CHAISSON: Just to comment, when I read something like that in a document generically, it seems to infer some kind of pedigree. And without the documents being publicly available, I'm not sure that that is fair, if you will. So, I think it's really important to have claims of peer review available to anybody to take a look and see what was discussed during the peer review and whether or

not the current versions of these models reflect what the peer review issues were. Thank you.

DR. GEORGE COBB: It's an important point. And perhaps we can capture in the meeting minutes. And thank you for that response. Okay. Are there other questions?

If not, now I would like to circle back to any comments that Committee members -- not believe, did not get covered yesterday. We went through a lot of material. We're nearly an entire day ahead of schedule. So, I'm sure there are a few things that got omitted. And if there's anybody that would like to enter information in from previous charge questions that we've already covered, I would entertain those now. Dr. Gentry.

DR. ROBINAN GENTRY: Thank you, Dr. Cobb. Can you hear me okay?

DR. GEORGE COBB: Yes, we can. Or at least I can.

DR. ROBINAN GENTRY: Okay. I think around our discussion -- and first I have to thank Dr. Chaisson. Like we said, she had a lot to deal

with yesterday, a lot of questions. And I think there were a few issues around Charge Question 1.b.i for DIDP that may have not been included yesterday. So, I wanted to make sure those were add. There were some issues in the comments around the sentinel exposures for the screening approach that suggested some food chain issues were overlooks, like consumption of fish and especially to PESS communities and subsistence communities. I think we'll need to clarify that or discuss that because tribal ingestion for the subsistence fisher was considered a sentinel exposure scenario in Section 7. It's also displayed in Figure 2-1 of the document.

Also, there was an issue raised around swimming or surface water consumption, and that is covered in Section 5 of the document, where swimming and incidental ingestion of water is part of swimming is included in the sentinel exposure. So, I'm not sure we discussed that or that was entered thoroughly yesterday, so I wanted to make sure that was added.

DR. GEORGE COBB: Yes. Thank you for entering that into the record because that's important, especially to get the comments right. If there's nuance behind any of that, it's really good to have that in the report. And I really appreciate you clarifying that. Unless there's more, I think the next respondent is Dr. Heiger-Bernays.

DR. WENDY HEIGER-BERNAYS: Thank you. Yes, this I think fits with yesterday's comments. And, again, thank you to Dr. Chaisson for that incredible summary and to Dr. Luz and EPA for responding too with some really important answer.

I want to recognize that this is with regard to the risk -- so the risk assessment. And for occupational exposures, central tendency in 95th percentile exposures were evaluated, but only the central tendency conditions were carried through to the risk characterization. EPA does justify why the pivot -- I think it's a pivot -- from the past practice. I will note that

benchmark was exceeded for some COUs using the 95th percentile exposure conditions. For the record, like EPA to provide justification for the use of the 50th percentile exposure estimates carried through the risk analysis. Thank you.

DR. GEORGE COBB: Thank you, Dr. Heiger-Bernays. And I will echo that comment because this is a topic that the SACC has brought to EPA repeatedly regarding protecting from higher exposure, especially for sensitive types of groups. So, thank you for that comment. Are there other comments from the Committee regarding things that we've covered in previous charge questions? Okay. Seeing none.

CHARGE QUESTIONS FOR DIDP RISK EVALUATION

2. ECOLOGICAL HAZARD

CHARGE QUESTION 2.b

DR. GEORGE COBB: I believe yesterday we skipped Charge Question 2.b, and we can resume our discussion today with Charge

Question 2.b. If Dr. Luz or someone from EPA can read that into the record for us.

DR. ANTHONY LUZ: Dr. Cobb, this is Tony Luz with EPA. I'll read DIDP Charge Question 2.b. "Fate and transport modeling analyses indicate that when DIDP is released to the environment it is expected to partition primarily to soils and sediments; therefore, these media are of high priority for environmental exposure analyses. As described in Section 4 of the Draft Environmental Hazard Assessment for DIDP, no hazard data were identified for DIDP for soil invertebrates. DINP was selected as an analog for read across of soil invertebrate hazard data as described in Appendix A of the Draft Environmental Hazard Assessment for DIDP. Please comment on the appropriateness of the methods used to identify DINP as an analog for DIDP."

DR. GEORGE COBB: Okay. Thank you. And our lead discussant is Dr. Reif. Dr. Reif, are you there? Is Dr. Reif there?

DR. ALAA KAMEL: Can anyone else from the discussants -- do they have their response?

DR. GEORGE COBB: Dr. Reif was there just when we started this.

DR. ALAA KAMEL: Yeah.

DR. GEORGE COBB: He disappeared.

DR. SHARLENE MATTEN: Maybe by phone. It is the 919 number. It may be a telephone, but he needs to unmute his telephone.

DR. GEORGE COBB: Dr. Reif, are you there?

DR. ALAA KAMEL: We can come back to him if he's not here. We can go to the discussions if you would like to and then come back to him.

DR. GEORGE COBB: Let's see. This is George Cobb here. Is there anybody in the group that is prepared to read the response into the record for this charge question.

DR. KEMBRA HOWDESHELL: This is Kembra Howdeshell. We didn't receive -- or I

didn't receive a compiled response from Dr. Reif. He may be having connectivity issues.

DR. GEORGE COBB: Looks like that's the case. There is a phone there that's muted.

DR. ALAA KAMEL: Yes, I see this 919 number that is muted. Right.

DR. GEORGE COBB: It's not like the online where we can mute and unmute people. Can't do that. So, okay. Well, if there's nobody that's prepared to -- let me ask it this way. Do individual associates in this topic have comments that they would like to offer at this time rather than a unified response? So, I don't see anyone who's ready to do that because we're trying to compile all of these together. So, I think we're going to have to move to the -- no, we're not going to move to the DINP yet.

Let's do this. Still try to get Dr. Reif back in communication. There were a number of folks who wanted to comment on how things from the exposure assessment and the risk assessment paradigms influenced the risk assessment document

-- the risk evaluation document. So, I think maybe we can move into that without leaving DIDP yet. So, this is primarily related to DIDP, but perhaps not. It was not a charge question, but there's some related issues from the hazard and the ecological exposure side and human exposure side that truly do cascade into the risk evaluation. So, there were a couple folks that indicated a desire to comment on this, and I'd like to open it up to those folks or anyone else to comment on the risk assessment aspect. Dr. Chaisson.

DR. CHRISTINE CHAISSON: Well, I'll start this conversation off. As part of the exposure assessment commentary, we're trying to expand the conversation, if you will, to touch on, if not include completely, the issues around how the risk assessment -- in other words, from the perspective of the exposure assessment review, it is the -- or the data and the methods or approaches in the models in the way the exposure assessment and the things that were included, if

you will, in the exposure assessment, is that appropriate to the needs of the hazard assessment? In other words, what's being done and how the data are used in models really must comport to the inferred questions that come out of the metrics of the hazard assessment. I mean, the most obvious for the kind of thing is you don't want an acute assessment to be used in place of a lifetime of chronic assessment. That's simplistic, but it just illustrates why something could be mathematically correct but not relevant to the hazard question. So, we're trying to structure, if you will, some of the conversation.

That gets particularly important or let's say invites commentary from us when we take a look at the entire spectrum of phthalates and the types of exposures that could occur. So, there is obviously an intent that EPA is headed toward doing some kind of cumulative assessment across the phthalates. So, once again, this very important issue of how the exposure assessment

meets the needs that come up across from the hazard assessment.

So, I just point that out to people to try to understand the structure for our comments and to invite particularly the people on SACC to lend their comments to us directly in Sections 1 -- in Charge Question 1.a.v - or, yeah, five in particular. And 1.a.i in particular. So, not to limit it to those, but those are clearly places where we will be beginning this kind of conversation. And so, anybody from the SACC or otherwise, we would invite their participation to lend us their thoughts on that. Thank you.

DR. GEORGE COBB: Thank you, Dr. Chaisson. I see Dr. Ottinger.

DR. MARY OTTINGER: Good morning. Thank you, Dr. Chaisson. You captured the essence very well. And I just want to drill into one of the areas that perhaps could make this a more concrete discussion, and that is that in terms of both hazard and risk there are sets of data that aren't there. And so, the question is, can one

conclude that if no data are available or, conversely, if there are data but there's a mismatch between measured and environmental levels and then lack of response -- we've seen it going several different directions there, but they didn't coincide -- is the conclusion that there's no hazard actually logical at that point? And I realize in saying that that the frustration is the lack of data for some of the specific species. So, that brings up the question of the model species, sentinel species, and going down that path, which is extremely useful, extremely important.

But circling back, is it appropriate to say there's no hazard in the situation where data aren't available to actually draw that conclusion? Are there models or literature out there that would give us more insights that then could be used to at least partially develop a more complete estimate, if you will, of both hazard and risk? And, sorry, that's probably a bit

confusing, but at least hopefully getting the discussion continued along those lines.

DR. GEORGE COBB: That helps a lot. Those are similar to my comments. And I had some follow-ups, but I see Dr. Fanning has been waiting. So, I'd like to go to her next.

DR. ELINOR FANNING: Thank you. And I'm going to continue a little bit in the same vein of the comments by Dr. Chaisson and Dr. Ottinger. I think our final comments will reflect some detailed input on the aggregate exposure assessment that was done and kind of how EPA does and in some places does not carry forward the concepts of aggregating exposures and therefore risks across articles within a COU, across COUs. And then as we get to other phthalates, the issues that Dr. Chaisson brought up, really making sure that we are capturing those highly-exposed consumers through these sort of cumulated and aggregated assessments.

And I wanted to add one other thing on that which has to do with the definition of

PESS in this assessment. I think that it's very important to recognized that PESS groups may be defined through biological susceptibility as has been done here. We have susceptible life stages for phthalates. But also through high-exposure scenarios. So, exposure PESS, if you will, is a piece that we will provide some more detailed comment on. And I think we did begin that discussion during the earlier discussion on Charge Question 1.a for DIDP. But we would like to make sure that this risk evaluation in the end really has captured those high-exposure PESS, and that might mean aggregating over the general population exposures and the indoor consumer dust for example.

So, I'm not going to give detailed comments on those recommendations yet because we need to work them out. I just want to say that we can expect some comment on that. So, thank you.

DR. GEORGE COBB: Thank you. That was an important comment about how these data aggregations should be considered. Appreciate

that. Are there other comments from the Committee? Back to Dr. Ottinger.

DR. MARY OTTINGER: Again, just to further muddy the waters so to speak, most not only PESS populations but most wildlife are exposed to multiple chemicals in mixtures. And clearly working with mixtures is a whole different issues. But as EPA looks at the high-priority other phthalates, it would be very, very helpful to be able to look at them individually but then look at them in combination if the locations are such that there's likelihood of multiple exposures or environmental movement of these chemicals.

So, I just want to raise that as something that perhaps is a little bit more outside the scope of what we're looking at right now but a reality that many populations, both wildlife and human, have to encounter.

DR. GEORGE COBB: Yeah, understood. Dr. Fanning, you're back.

DR. ELINOR FANNING: Yes. Dr. Ottinger's comment made me realize there was one

other piece I wanted to add to that earlier remark. And that is that our group has had some discussion, and the questions answered this morning were part of that, of the non-TSCA uses of phthalates. And while those will not be an explicit part perhaps of the risk evaluations -- at least they are not in the current document -- we do feel they are very important considerations for defining who the high-exposure PESS are. And the data and authoritative evaluations that have been carried out to date indicate that diet is the predominant route of exposure for the majority of the population, so food contact articles are very important in that regard. However, there can be some very highly exposed individuals. Again, this is a set of uses under FDA authority, but there are very highly exposed individuals receiving exposure through medical products. So, I just wanted to say that some of the non-TSCA uses may be relevant to help identify who are really the PESS groups of concern here. Thank you.

DR. GEORGE COBB: Thank you for that comments. I think that's important as well. I did want to circle back a little bit to some of the thing to -- to amplify on some of the things Dr. Ottinger was saying and perhaps repeat a thing or two that have been brought up before.

The risk assessment has no consideration, no evaluation of the toxicity data compared to the ecological exposure data. And so, that's a hole. And as we discussed yesterday, the document by Adams et al. clearly states they did not consider immobilization in their toxicity assessment. They observed it, and if it was too great, they repeated the study. So, that study did not consider entrapment; it considered immobilization as the endpoint. And so, the premise to disregard that study because it was entrapment is, in my estimation, erroneous. And that completely changes the assessment. So, that's the first thing.

The other aspect is there are mentions of high exposure scenarios in the

ecological exposure assessments that are not high exposures. They are mean exposures from municipal discharges or from watersheds that may or may not include industrial discharges, but nowhere are there evaluations of concentrations near industrial discharges in any of the publications that I saw. If you are to take a high sentinel value from either the wind study or from the trans study -- one was from, I believe, Taiwan. And the tran study was from, I believe, France. If you were to take high sentinel values from those, you end up with hazard quotients above one for measured toxicity values. And so, that really needs to be carefully revised to ensure that the data are being accurately represented.

I think that's all that I had. There were a couple things on the exposure side for humans, but I think those were captured in some of the other comments that came up today. Are there other members -- ah, I see Dr. Fenner-Crisp.

DR. PENELOPE FENNER-CRISP: Yes. I wanted to make a comment on Dr. Fanning's comments about what all would be in the exposure assessment, and she was highlighting the non-TSCA uses for these seven chemicals. One might need to think about additional scenarios. There are other chemicals in this subclass that aren't being analyzed at the moment. Many, if not all of those, are also on the TSCA inventory and therefore do have TSCA uses and might well have non-TSCA uses. How will exposure to those be accommodated in these assessments and in the CRA once they get around to be doing that?

DR. GEORGE COBB: So, Dr. Fenner-Crisp, is that something you're the Agency now or something you think should be addressed as a question in the report?

DR. PENELOPE FENNER-CRISP: I'm suggesting that the extension of Dr. Fanning's comments may include this particular issue.

DR. GEORGE COBB: Correct. Yeah, I understand. And I appreciate that.

DR. PENELOPE FENNER-CRISP: That is a separate question.

DR. GEORGE COBB: Yeah. We will make sure that those --

DR. PENELOPE FENNER-CRISP: How might you fold that into the discussions of the aggregate slash cumulative exposure.

DR. GEORGE COBB: Right, TSCA, non-TSCA uses. Yes.

DR. ELINOR FANNING: Yeah, thank you for that. And I think that just goes to -- Dr. Chaisson opened kind of this conversation by saying our group would welcome any input and comment from you and others as we try to put together our comments on these issues. So, very helpful and please do share with Dr. Chaisson what input you have on that.

DR. PENELOPE FENNER-CRISP: Yeah, I'll write a little note and send it off to her and put on paper what I've just said.

DR. GEORGE COBB: Thank you. Okay. So, I think we're -- Dr. Li. Dr. Li, you're still on mute. There you go.

DR. LI LI: Oh, can you hear me all right?

DR. GEORGE COBB: Yes.

DR. LI LI: Okay. So, I just want to read this into record. So, because I just saw lot of discussion when talking about risk assessment, a lot of discussion, a lot of attention just being put on the toxicity or toxicological side, I just want to mention this from another angle, which is exposure angle.

So, my point is like, if we do want to pursue a risk assessment, maybe we have to consider the multidimensionality in exposure so that aggregate exposure can be evaluated by considering, number one, multiple exposure pathways, number two, multiple environmental media or multiple scales of the environment, and, number three, emissions from multiple stages in the lifecycle.

So, for example, at this moment the exposure assessment is done for one source at a time, and they consider different aspects of the environment, different aspects of exposure pathways, and different aspects of the human and the population characteristics and the behaviors. And so, in this case, the estimated exposure cannot be compared or cannot be added, cannot be aggregated, into the totality. So, this is why the report keeps concluding that there's no risk for this, there's no risk for that. But if you add everything together, maybe the risk can be higher than the acceptable level. For example, at this moment, the indoor environment or the consumer environment is something separated from the outdoor environment or the natural environment. Which means, if you used DIDP-containing products or containing articles in a certain COU in the indoor environment, the chemical will be confined within that indoor environment, or the residential environment. So, in reality, if you do use the chemical in your

home and when you open the window, when you open the doors, the chemical can be ventilated out, or the chemical can move from the home to the natural environment, which also cause the contamination in the environment nearby.

And we have to consider the contamination from one scale of environment to the other scale of environment. And that example is at this moment the emission into different settings of environment has been considered separately. One thing is the emission -- we consider the industrial emission to the natural environment, but we consider the consumer emissions from products into the indoor environment. And when we do the assessment, we just do the people separately. We focus on someone who is living very close to the industrial sites and the consumer who is isolated from that industrial site, but actually, we can imagine some worst case. That is, there is a person who is living very close to the industrial sites who is in a fence-like community. And same time, this

person also use the products and the articles, so they also have the chance to be exposed to DIDP through the daily behavior. At the same time, this guy is also swimming in a water body which receives the DIDP from the release from the industrial discharge. At this moment, the report just consider these three things as separate things. But if you add them together, maybe the situation would be totally different. So, that would be some point I want to make.

DR. GEORGE COBB: Thank you. And those are important parts of this kind of consideration. So, thank you very much for that comment. Did I see Dr. Fanning had her hand up? It seems to have disappeared.

DR. ELINOR FANNING: No, I'm fine. Thank you, Dr. Cobb.

DR. GEORGE COBB: Okay. So, I think we're done with that. I do not believe Dr. Reif has joined us. He had a connectivity issue that he's having to try to get to another computer, which may be a ways away. At the risk of getting

off track, perhaps we can take a ten-minute break now and try to give Dr. Reif a chance to return. If he has not returned, perhaps we need to have the other discussants read their comments in as best they can.

DR. ALAA KAMEL: Dr. Cobb.

DR. GEORGE COBB: And I see Dr. Lowit. I see Dr. Lowit is there, and I kind of got -- again, got off track with our connectivity problems with Dr. Reif. Dr. Lowit.

DR. ANNA LOWIT: Yeah. You didn't ask us for clarification before you transitioned to what you're doing next. So, I just was wonder --

DR. GEORGE COBB: Yeah. Yeah, please ask for questions or clarifications.

DR. ANNA LOWIT: Just one sort of point of clarification. I really enjoyed that whole conversation, and I really appreciate the points made by several of the commenters about the importance of what I like to call the connectivity of the hazard and exposure and to make sure that

they match on a temporal and spatial basis, ensuring that the connection between hazard and exposure is vitally important. And particularly, as we think about the cumulative assessment and more and more potent compounds that go through the program, we're going to need to be doing more and more very spatially-explicit, temporally-explicit, life stage-specific, very refined assessments.

But I'd like to just remind the panel that the program is moving towards a -- in a way to use our resources efficiently that we're step-by-step starting to build, for lack of a better word, a tiered process where we start with a tier-one screening kind of thing and move incrementally to more and more refined assessments that look like what I described that are temporally-, spatially-, life stage-specific and get more and more refined in that sense. And so, as the panel thinks about asking us to add up more and more things, we would have to move away from those tier-one screening level assessments to more and more refined because you're not going to add

up the highest of the high, to the highest of the high, to the highest of the high in part because those things just don't kind of make sense. But as we think about the hazard for most of the phthalates that are going to be these shorter term durations related to either the development of through the PPAR alpha, through non-cancer liver effects, or through the changes in testosterone, all of which are relative short periods. And so, it becomes very complex when we think about adding up scenarios in that temporal situation.

So, I would just ask the panel as you think about writing up the things that we just talked about building -- our goal is to build a tiered process starting with a screening level. In most cases, if it passes at the screening level, we're not going to invest resources to get uber refined. We're going to refine to the extent that first we have the data to do. And right now, as many of you have acknowledged, the data in not only the phthalate space but the industrial chemical space on some of these very refined

behavioral parameters, monitoring data, et cetera, just don't exist. So, we can help us move our approach to get better and better, recognizing that there is a lot of data and methodology that needs to be advanced, and some of that lack of data and methodology will become apparent in the cumulative assessment.

So, I just wanted to sort of make sure that we're not setting up unrealistic expectations and maybe to add information to that conversation about how to help us do better, recognizing where the science is. So, that was my sort of plea or request.

DR. GEORGE COBB: I understand. I hope the Committee does too. I will say that the solution to this is, when these reviews come up, where there're data gaps, require the manufacturers to produce the data. And that solves the solves the data availability problem. Otherwise, you're stuck with high sentinel -- if you don't have data to model, you're stuck with high sentinel estimates, and that's just how risk

assessment works. And the refinement is to gather the data. And so, I understand you're stuck with the data that you have, but there's also the opportunity to obtain more. And I know that's getting into policy, so I hesitate to have that kind of conversation. But scientifically, that's what's needed.

DR. ANNA LOWIT: And I wouldn't disagree with that. But as the program begins to work sooner and use the pre-prioritization pieces of the process more effectively and efficiently, we'll have better opportunities to get those data because we'll be talking about the needing for those data years in advance.

DR. GEORGE COBB: Exactly.

DR. ANNA LOWIT: Because monitoring data takes a long time. Developing models, it just takes a long time.

DR. GEORGE COBB: Exactly.

DR. ANNA LOWIT: And some of these risk evaluations we're doing now, like the phthalates for example, we're in this position

where we have to do assessments with the data that exists today. Whereas, the ones we're going to do in the future, we're getting smarter about doing that earlier.

DR. GEORGE COBB: Yeah.

DR. ANNA LOWIT: Just putting in --

DR. GEORGE COBB: Exactly. And all of the responsibility is not necessarily on EPA. The organization can voluntarily provide information without you having to request it. So, thank you for that. I do appreciate that. I see some other hands up. Dr. Ottinger.

DR. MARY OTTINGER: Dr. Lowit, I really appreciate what you just said. Personally, my intent is more along the lines of trying to take advantage of literature that's already out there that can provide some additional information and enhance the use of sentinel species. The other point I would make is that, as time goes on, more exposomics kinds of approach is getting utilized in wildlife and eco kinds of applications that should actually go from, if you will, step

one to step at least six or ten in providing us more reliable measures, measurement endpoints, that can be utilized for hazard and risk evaluations. So, I really do appreciate what you've just said. Thank you.

DR. GEORGE COBB: And Dr. Chaisson.

DR. CHRISTINE CHAISSON: Dr. Lowit, your comments are very, very helpful and as well as the EPA staff attitude about accepting or listening to our commentary. One of the aims is to increase the power of the information that you do have. And one way to do that is through, if you will, some more powerful use of statistics, not just distributional and probabilistic kinds of things, but also the Bayesian. I'm not sure if the scientists there have access to people who can readily and efficiently and in a timely manner deal with compounded datasets and things like that that are required. But is it useful for you, for the institutional you, for us to keep dwelling or making that kind of recommendation if not being

able to be utilized immediately for your future work?

DR. ANNA LOWIT: Yeah, I'll respond to that, and then maybe it is time to move on. So, I appreciate that question, Dr. Chaisson. And, yes, it is because having section of the SACC report -- and this is just my personal view -- having sections of the SACC report that talk about the importance of the intersection of hazard and exposure and the importance of having more refined information and more refined models and using things like omics and modern technologies is actually really important because then we can take that SACC report and use it as a dialogue and as a facilitation to our stakeholders who may have those data or have the capacity to collect some of that information. It helps us with that dialogue that we can talk about the value of that information and the extent to what the SACC impressed on us the importance of that.

So, yes, it is. I just would add to that the recognition that it may not be something

we can do tomorrow. If all of you have things that you think we can do better with what we have today, we love to hear that, but sometimes we're stuck with what we can do today today and what we can do tomorrow tomorrow. But next year, we may be able to do something different, as long as there is a recognition of that. So, I hope that helps.

DR. CHRISTINE CHAISSON: Very much so. And we'll try to put recognitions like that into context for you as well. Thank you.

DR. GEORGE COBB: Thank you for that excellent dialogue. So, now I'm still looking to see if anyone could help me if Dr. Reif has arrived.

All right. Again, at the risk of getting a little bit out of sequence, we're pretty far ahead of schedule. So, what I'd like to do now is take maybe a 15-minute break. Hopefully, Dr. Reif can get online. If not, maybe this time can be used for the evaluators -- or, excuse me, the associate discussants to prepare some comments

so we can get through Charge Question 2.b. So, Alaa, you're --

DR. ALAA KAMEL: Dr. Cobb, is it a suitable time? There was a further clarification from EPA regarding the comment that we were talking about earlier.

DR. GEORGE COBB: Oh, I thought that's what we were doing.

DR. ALAA KAMEL: Oh, okay.

DR. GEORGE COBB: If EPA has further comments, please. I see Dr. Morris is up.

DR. JEFF MORRIS: Yeah, Jeff Morris, EPA. Yeah, I just wanted to make sure that I interpreted one of the follow-on questions that I received this morning correctly. The question posed to me was, does EPA for these manufacturer requests have the ability to ask for additional information? And I replied, yes, there's nothing in the procedures for manufacturer requests that precludes us from using our data gathering authorities, which is perfectly correct under the rules we're now operating. So, any future

manufacturer requests, those authorities are compromised.

If the question though -- I don't think it was -- but if the question was for these two chemicals, could we use our authorities? Which I assume late in this process you're not suggesting that. But these two chemicals were brought in under old rules that we would interpret as not allowing us to actually ask for additional information through our authorities for these two chemicals. But I just wanted to clarify that because I wanted to make sure that I was answering the question in the spirit that the person asked me, which I think was going forward for the future of this program.

DR. GEORGE COBB: Yeah, that is an excellent clarification. And I understand perhaps rules changed a bit. And I understand that. But that's an excellent clarification about that dialogue.

DR. JEFF MORRIS: Yeah.

DR. GEORGE COBB: So, are there other clarifying question from EPA about the things we've talked about this morning? Okay. If now, I really think we should take a 15-minute break now until half past the hour and hopefully get Dr. Reif connected in that timeframe.

DR. ALAA KAMEL: Thank you.

[BREAK]

DR. GEORGE COBB: So, welcome back. This is George Cobb, Chair of the Science Advisory Committee for Chemicals. And we have Dr. Reif back. I'm sorry you had your connectivity issues. We've all experienced that, maybe not as acutely as you just did. So, thank you for getting back aligned. And now if EPA can read in Charge Question 2.b for the DIDP assessment.

DR. ANTHONY LUZ: You said 2.b? This is Tony with EPA. It looks like 2.a is on the screen right now.

DR. GEORGE COBB: Yes, it's 2.b. Yes, sir.

DR. ANTHONY LUZ: Okay. Thank you. Now I see 2.b. All right, so this is DIDP Charge Question 2.b. "Fate and transport modeling analyses indicate that when DIDP is released to the environment it is expected to partition primarily to soils and sediments; therefore, these media are of high priority for environmental exposure analyses. As described in Section 4 of the Draft Environmental Hazard Assessment for DIDP, no hazard data were identified for DIDP for soil invertebrates. DINP was selected as an analog for read across of soil invertebrate hazard data as described in Appendix A of the Draft Environmental Hazard Assessment for DIDP. Please comment on the appropriateness of the methods used to identify DINP as an analog for DIDP." Thank you.

DR. GEORGE COBB: Thank you for getting that into the record for us. And now

we'll turn it to Dr. Reif and then after that to the other discussants.

DR. DAVID REIF: Yes, thank you. So, my machine did this to me earlier this week when I turned my camera on Zoom. It just died. So, instead of fixing it, I just hoped everything would be great, which is not scientific. So, I apologize for the waste of the Committee's time on that. I will say, I'm going to read a document from a different computer, and I ask the associate discussants and Dr. Cobb to chime in because I had received input from everybody. And just in case this version that I'm reading hasn't synced all of the consolidated comments that were made, please, associate discussants, pipe up and add them in here. But I think it's mostly correct, mostly complete.

So, general comments for Question 2.b. The EPA appropriately selected DINP as a suitable analog for DIDP based on very similar structural chemical and physical characteristics between the two compounds and comparable

environmental fate and transport. The use of NAMs for comparison of structural and chemical characteristics identified a number of analogs. The further screening of analog candidates to those of physical properties of log KOW and log KOC that were within one log unit relative to DIDP refined the list of potential analogs, of which two were DINP, or approximately one-third of the possible choices. So, finally, DINP was selected as the appropriate analog largely based on the available data for DINP from previous literature identification, data extraction, and risk bias assessment from toxicity studies. This approach seems reasonable and is appropriate for protection of terrestrial invertebrate health given the DINP was a phthalate for which environmental hazard assessment was conducted, and risk assessment is ongoing. In my opinion, the EPA addressed the potential concern with using DINP as an analog where both are outside the domain of applicability of ecotoxicity predictions due to high octanol-water partition coefficients and by not

supplementing empirical hazard data with predicted data.

Since DINP was determined to be a good analog for DIDP, why were other read across data from DINP or other analogs not considered for other species in the environmental assessment that lacked empirical data such as avions or plants? In a couple detailed points on the Draft Hazard Assessment, both having to do with the confidence assessment, on Line 317 it stated that EPA has robust confidence that DIDP poses no hazards. But the screening level assessment was based only on one study from an analog chemical. So, questioning the sort of robust versus slight confidence for this assignment. And relatedly, on Line 399 in the hazard assessment for DIDP, the same confidence is then listed as moderate rather than robust. So, just wanted to point that out in case a continuity or editing error and actually was meant to reduce the original rating, or if that was a scientific assessment. And, yeah, that's the consolidated info that I have.

DR. GEORGE COBB: All right. So, thank you for that. And let's go to our associate discussants. And we'll begin with Dr. Shuman-Goodier.

DR. MOLLY SHUMAN-GOODIER: Thank you. My comments are in there. Thank you, Dr. Reif, for the comment.

DR. GEORGE COBB: Great. Thank you. Dr. David.

DR. RAYMOND DAVID: No further comments.

DR. GEORGE COBB: Dr. Li.

DR. LI LI: No further comments. Thanks.

DR. GEORGE COBB: Yes. And, Dr. Li, I need to apologize to you. We were trying to align some stuff while we didn't know if Dr. Reif was going to be back, and I omitted your name. And I apologize, from those emails. Dr. Howdeshell.

DR. KEMBRA HOWDESHELL: No further comments.

DR. GEORGE COBB: That was pretty succinct, and I appreciate the comments. I did have a question, and perhaps this is just some of my naïveté. On the high octanol-water partition coefficient or high KOW, KD values, am I hearing correctly that when you get to a certain threshold that the read across types of data may not be appropriate? Is that what I'm hearing?

DR. DAVID REIF: This comment in particular was related to the use of ECOSAR.

DR. GEORGE COBB: Okay, ECOSAR.

DR. DAVID REIF: Which does fall outside the bounds. I don’t know the answer why the GenRA from EPA wasn't able to contribute in this case. That was cited in the document as well. But there are many, many reasons for that, and I'm not sure if it was the same root cause.

DR. GEORGE COBB: But that comment was related to ECOSAR not (inaudible).

DR. DAVID REIF: That comment was related to ECOSAR. And as they cited in the

report, they call out ECOSAR there in particular. But I can adjust that in my comments.

DR. GEORGE COBB: And, sorry, I misspoke. I was simply curious. But that is in essence saying that you really need empirical data rather than trying to read across from other tox values. Am I capturing that correctly?

DR. DAVID REIF: Well, I think in this case ECOSAR could've provided additional predictions. And instead of adding additional predictions that weren't empirically based, they used the read across empirical values instead, instead of augmenting them with additional predictions.

DR. GEORGE COBB: Thank you. I appreciate that. That's good explanation. So, back to the rest of the Committee then. Are there additional comments related to the fate and transport of DIDP? I see Dr. Chaisson. Are you - -

DR. CHRISTINE CHAISSON: Yeah, I'm trying to find a little hand. Thank you, Dr.

Cobb. As you well know, ecology is way outside my wheelhouse, but I just have a curiosity. I've looked at this -- when I ask this question, you'll see how far out of my wheelhouse I am. Just curious about why we don't see markers, if you will, or representative organisms that are avian. And I keep thinking back to like the DDT times, where you had effects on the eggs that was eggshell thinning. But since this is also so lipophilic, it would seem to me that that might be relevant. Can somebody just explain to me why if aquatic animals, terrestrial animals, but no avian species there considered?

DR. DAVID REIF: I see Dr. Ottinger's hand, and I hope that she has a better answer than I was going to offer for this.

DR. MARY OTTINGER: I don't know if it's better, but for what it's worth. The short answer, Dr. Chaisson, is that measuring endpoints in field birds is difficult. And there are some measures that have been used traditionally, but usually it's more like lethality. And that's why

I made the suggestion earlier that as exposomics get more refined and we have the molecular tools which we have not had for birds because there's species differences, as well as differences in a lot of the -- they're unique in a lot of ways, hollow bones, air sacs, migration. I can send you a review paper that goes through that. But they're very unique. And because of that, it makes it very difficult to align the data from some of the mammalian species to birds, even if they're terrestrial mammals because there're going to be differences in the age receptor responses and all sorts of other things. And the whole HPG access, although very similar to mammals, has different kinds of unique characteristics.

So, the bottom line is the lack of tools and then being able to accept, which is in the literature that I've been collecting to add to this report, the use of domestic species, primarily the chicken egg, domestic chicken egg, and Japanese quail that have been used to a great extent in laboratory studies. Which then,

although not directly transferrable to wild species, at least gives you an indication from a sentinel, if you will, kind of -- or a test species kind of perspective. Does that help?

DR. CHRISTINE CHAISSON: Yes, very much so. Up until your explanation, I assumed that there was some reason why it should be excluded, not that, you know, just too hard to include, I think is what you're saying.

DR. MARY OTTINGER: The issue is not to exclude it. The issue is more to have reliable datasets that at least give you an indication of what might be the hazard and then, consequently, the risk to birds. And some of that then circles back to multiple ongoing studies. There's a very large study in the Gulf of Mexico currently that is actually going to put real measurement endpoints together with management practices and all sorts of other things that are, again, beyond the scope of this review. But we're at the cusp of having data and information and capabilities to at least get some sentinel species assessments

that will give us confidence that, yes, we can translate from mammal or, no, we can't.

DR. CHRISTINE CHAISSON: Can I ask a follow-up on that same sort of theme? Are the chemical, physical properties of chemicals like the phthalates concordant with the properties that you've seen historically with other chemicals that did in fact have adverse effects on avian species or that would affect -- would sort of bioaccumulate in eggs or have any of those kinds of effects just sort of historical reference?

DR. MARY OTTINGER: Are you talking about phthalates, or are you talking --

DR. CHRISTINE CHAISSON: Yeah, phthalates.

DR. MARY OTTINGER: Phthalates.

DR. CHRISTINE CHAISSON: Yeah.

DR. MARY OTTINGER: I've been able to find a bunch of papers that have to do with various phthalates, but it's more DHEP, which then brings it into the endocrine disruptor arena. And that then brings up a whole different set of

questions about comparability and mechanisms of action and all that.

But back to the DDT example. The mechanisms involved interacting with the receptors and all that are going to be similar if not identical to that in mammals. The question is the output. What effect does it have? So, egg thinning with DDT versus perhaps uterine effects because the shell gland is equivalent to the uterus in mammals so to speak. So, we can drill down on this, and I'll send you a few review papers, Dr. Chaisson, if you want to.

DR. CHRISTINE CHAISSON: Yes, thank you.

DR. MARY OTTINGER: There are unique characteristics that need to be considered that make it very difficult to do a broad stroke kind of answer, and so that's why I was suggesting taking advantage of the available literature that's there, at least to get a bit of a hint as to what might be going on.

DR. CHRISTINE CHAISSON: Well, I won't take up any more time, and I appreciate this sort of one-on-one on this. But I might not be the only non-ecologist out there who is -- where this looks strange. So, maybe it would be good for an explanation to the public as to a brief explanation as to why that seem -- it just looks like a hole to me. So, maybe other people would appreciate having an explanation from EPA. So, maybe you can --

DR. DAVID REIF: I agree for the write-up. But I think the comment in there about why it didn't have avian data, I don't know that knowledge that Dr. Ottinger just offered there. So, I think that's something I need to include in the final write-up.

DR. MARY OTTINGER: Dr. Reif, I'm happy to provide a few sentences and some references.

DR. DAVID REIF: Yeah, thank you.

DR. MARY OTTINGER: And that'll fill in some of the gaps. It's a hole, but it's not a

hole that is anyone's fault. It's just the state of the art more than anything else.

DR. GEORGE COBB: Yeah. Thank you. Dr. David, we'll get to your comment in just a second. I wanted to follow up on the specific question Dr. Chaisson asked. The biodegradation of these phthalates, DIDP included and DINP, are much faster than the biodegradation of DDT. It turns out that the first couple transformation products of DDT are still relatively equally toxic for eggshell thinning, but once you do a hydrolysis or some oxidations of the phthalates, they're not nearly as toxic. So, there's a bioaccumulation factor, and there's also a residual toxicity factor that make these phthalates much less potent, in my estimation, than DDT would be. And saw that in the bioaccumulation factor data that the Agency brought up yesterday I believe it was. So, Dr. David, you had a comment.

DR. RAYMOND DAVID: Well, I just wanted to add to what Dr. Ottinger had said, and

this is from the perspective of the regulatory requirements for registration of a substance. The avian reproduction in which eggshell thinning is measured is typically applied -- that study is typically requested -- and Dr. Fenner-Crisp can correct me -- for pesticides but not necessarily for industrial chemicals in the U.S., unless there is a perceived potential for a problem. In Europe and of course with REACH, they have a different approach in which that test may be required for very high production volume substances regardless of their uses. As I recall -- and I was just trying to do a quick search through some of my files -- I think some of the phthalate esters were tested way back when, and so I'm talking about the '70s and '80s. And I don't recall any of them demonstrating a problem with regard to eggshell thinning. But I would have to go back and double check what at least I have in my files.

DR. GEORGE COBB: Thank you for that comment, Dr. David. Dr. Ottinger.

DR. MARY OTTINGER: I believe, Dr. David, you are absolutely correct. And, in fact, that's another one of those very far downstream kinds of measures. For something to affect eggshell thinning, you have to engage the estradiol receptors and everything else, as well as alter the lipid metabolism. So, for a significant effect on that, it's going to be very, very significantly affecting the animal.

I believe that as we get more targeted and sophisticated methods that allow us to actually ask specifically for a chemical mechanism of action that will enable us to directly ask what kinds of things are happening. Acetylcholinesterase has been used by wildlife biologists in the field for the POPs and that sort of measure just because they persist. And so, there're traditional measure that have been used for birds, but they're not particularly insightful in terms of actually giving us an idea of how much effect there may be on those populations and on those individuals. There's more and more

monitoring data coming out. And the study that I mentioned at the Gulf of Mexico will integrate together the toxics with measures that are used on field species.

So, I guess what I'm saying is we have to be a little patient and use the data that are available right now from egg injection studies and feeding studies in more laboratory kinds of settings. But I agree with what you're saying, and I'm sure there's studies like that. Thank you.

DR. GEORGE COBB: So, Dr. Fenner-Crisp.

DR. PENELOPE FENNER-CRISP: I just wanted to confirm that Dr. David was correct. Yes, the avian study is a fairly standard requirement in the pesticide regulatory process, part of Part 158. But my question would be, if there data existed in companies' files for non-pesticides, why haven't the sponsors submitted them to the Agency?

DR. GEORGE COBB: Maybe that's a question that we can visit with EPA in a second. And thank you for that comment and clarification -- or confirmation of Dr. David's comment. Dr. David, you have additional comment?

DR. RAYMOND DAVID: Well, just a follow-up to Penny's question. And the EPA certainly has access to the TSCA 8(e) submissions. So, had there been a study like that that was not relative to a pesticide submission because those data are confidential, but under TSCA anything that identified a hazard, ecological hazard or human hazard, would have to be submitted under Section 8(e). And so, it would be in the files. And I'm sure the Agency did a search of their own files for that.

DR. PENELOPE FENNER-CRISP: Well, the other thing you mentioned is REACH. That's another data source that one could look at. Because even though REACH data are CBI and the Agency can't get them without permission, they can

go into the REACH database and look at the data summaries that ECHA has.

DR. RAYMOND DAVID: That's correct. Those are publicly available. You're right.

DR. PENELOPE FENNER-CRISP: Those are publicly available.

DR. RAYMOND DAVID: Yes. The summaries, yes. Sorry.

DR. GEORGE COBB: Yeah. Okay. Good discussion. DR. Reif, do you feel like you have adequately captured this? And please do send any comments you have relative to this discussion too, Dr. Reif, for inclusion.

DR. DAVID REIF: Yes, I will. Thank you. And I have an email thread already started from Kembra et al.

DR. GEORGE COBB: Okay. Thank you. And thanks, everyone. So, now we'll turn it to the EPA to see if you have clarifying questions or comments.

DR. ANTHONY LUZ: This is Tony Luz with EPA. No clarifying questions or comments.

DR. GEORGE COBB: Okay. Well, thank you. And let's see. We did Charge Question 2.b, and we also did the discussion of our risk evaluations for DIDP. So, at this point, I would like to circle back to the Committee one final time for DIDP and see if there're any comments that have not been captured for DIDP. Like to get them all on the record before we go on to DINP.

DINP HAZARD ASSESSMENTS

1. ECOLOGICAL HAZARD

CHARGE QUESTION 1.a

DR. GEORGE COBB: Okay. So, we can now move into the DINP charge questions. We'll start with the hazard assessment in the ecological hazards with Charge Question 1.a. I guess it's Dr. Luz.

DR. ANTHONY LUZ: Thank you, Dr. Cobb. Tony Luz here with EPA. I will now read DINP Charge Question 1.a. So, "As described in Section 4 of the Draft Environmental Hazard

Assessment for DINP, EPA had limited empirical toxicity data available for terrestrial mammals and therefore relied on data from controlled laboratory animal studies using human health animal models to derive a toxicity reference value," or TRV, "to evaluate risk from chronic dietary exposure to DINP. Please comment on the strengths and weaknesses of the methodology and data used to derive a toxicity reference value," or TRV, "for DINP." Thank you.

DR. GEORGE COBB: All right. Thank you, Dr. Luz. And our lead discussant for this is Dr. Ottinger.

DR. MARY OTTINGER: First, I'd like to thank the associate discussants for excellent input. And I will read into the record our comments.

General comments. There were high and medium data quality assessed for 32 publications that include sediment, aquatic and terrestrial habitats. The TRV was 139 milligrams per kilogram body weight per day. That was

derived from exposure effects on a generalized terrestrial mammal, with one earthworm study used. No effects on organism survival and fitness were documented. However, there was an increase in the number of juveniles of the earth -- or in the earthworm study. Predicting wildlife toxicity using test results from an experimental model of mammalian toxicity that supports human health is a reasonable alternative if data are unavailable for species of wildlife. Species inbreeding, selective breeding for specific sensitivity, and non-representativeness of wild strains are the primary argument against using animals that are normally used for modelling human effects. Regardless, using them is better than having no data at all. If there are concerns that species are not representative with an uncertainty factor of three could be used as protective measure. The alternative is to perform the toxicity test with species or in vitro tests that are more representative of wildlife and that could fill the current data gap. And I would also add to that

from our discussion just preceding this that also adding in literature that is available.

The strengths are it appears appropriate to use the mammalian studies to develop the TRV, and arrival at the resulting value was explained well. And this is on Pages 23, 24, Lines 485 to 517. Additional strengths were that EPA utilized offspring bodyweight data from in utero DINP rodent studies and bodyweight growth data from adult animals to define TRVs for terrestrial mammals. Survival data were also evaluated, and the quality of the data used to assess these endpoints was significant. EPA identified seven reproduction bodyweight studies, eight studies of growth in adult bodyweight, and three survival studies. The reproduction studies range in exposure, duration, and age to include in utero, early postnatal, and one two-generation study. Table 4.1 in the Draft Environmental Hazard Assessment for DINP is much clearer than the similar table for the DIDP Environmental Hazard Assessment. As with DIDP, I believe EPA --

this Committee member believes that EPA's choice to use human health models, meaning rodents, is logical and justified given the lack of available data for ecological relevant terrestrial species. And as mentioned earlier, the rodent studies were high and medium quality, 12 studies, and used apical endpoints that were appropriate.

There are some weaknesses. No terrestrial plant studies were available to assess potential hazards in DINP. This would indicate that soils and sediments should be considered high priority for environmental exposure analyses and should be considered by the Agency. The Draft Fate Assessment for DINP indicates that there's an affinity for sorption to soil and its organic constituents. Given these properties, there's an indication, likelihood of strong sorption to organic carbon present in soil, and, therefore, DINP is expected to have low mobility in soil environments. However, because no terrestrial plant studies were available to assess the hazards from DINP exposure, that could not be concluded.

The question becomes, how can one be sure that earthworms are the most sensitive terrestrial species? And why inhibition of fetal testosterone production in rats presents it is not a definitive hazard? There are lower-effect doses for androgen insufficiency than for bodyweight and growth. Therefore, the TRV derived here is a higher dose than the human reference dose based on androgen insufficiency, and it's reasonable to assume that the endpoint is applicable to terrestrial mammals in general in addition to human health.

And I would note here that we may want to do some comparisons with Charge Question 2.a later on because there are some areas that are similar in terms of what we're considering.

The report does not specify why the confidence in terrestrial mammal hazard is only moderate. Also, the report doesn't specify which value was used to set the TRV. It appears to be the NOAEL for bodyweight in the two-gen study by Exxon Biomedical in 1996. However, five of the

studies considered had low NOAEL values. No exclusion criteria are listed, so it's unclear why the lowest NOAEL was not selected. Also, the value of 139 milligrams per kilogram per day does not match one of the tested doses listed in the table for the Exxon study.

There's a minor weakness with respect to the report in terms of formatting, and that pertains to the reproduction studies separately identified by term reproduction but not referred to in the same language under the mammals heading. And that's more of an editorial comment.

There is significant variability in the LOAEL and NOAEL values from the 12 high-, medium-rated rodent studies used to derive the TRV. This variability does not appear to be accounted for with the current derivation process. As such, EPA might consider calculating 95% CIs around the geometric mean of the NOAELs and using the lower 95% CI as the TRV, using generic assessment factors as would be done to derive COCs for the aquatic hazard assessments, or adding a

description of uncertainty that is not address in the TRV derivation process.

As for other recommendations, specific recommendations, we would recommend: discuss the distribution of DINP in the environment, likely exposure related to distance from point source in the half-life of DINP in the environment. Discuss the relevance in transferability of laboratory studies on rat or mouse on a TRV for wildlife, specifically small mammals for deriving TRV for DINP. Will the studies provide transferable information about other terrestrial wildlife such as birds and reptiles? Add discussion related to the effects of environmental conditions on the half-life of DINP. What is the likely scenario for exposures and likely spread, meaning through air, water, and sediment? Many of the studies demonstrate general as well as reproductive effects, including lower maternal and offspring postnatal bodyweights. Describe how this might translate into hazard and risk assessments for terrestrial wildlife,

including mammals and birds. And the study on earthworms demonstrate no effects on mortality in adults; however, there was an effect on the number of juveniles, as mentioned earlier. Discuss what this means for the population over shot and long term, bringing into focus potential effects on the food web. And, finally, generate plant toxicity data to determine that plants are not the most sensitive terrestrial species since no toxicity studies on avian or terrestrial plants species were identified.

There're a number of specific comments that I will provide to the EPA in writing. And we have a number of references that we will also be providing. Thank you.

DR. GEORGE COBB: Thank you, Dr. Ottinger for that excellent summary. So, now let's turn to the associate discussants. Dr. Shuman-Goodier.

DR. MOLLY SHUMAN-GOODIER: Thank you. No further comment.

DR. GEORGE COBB: Dr. Spade.

DR. DANIEL SPADE: I have no further comment. Thank you for the summary, Dr. Ottinger.

DR. GEORGE COBB: Dr. Graham.

DR. CYNTHIA GRAHAM: Okay.

DR. GEORGE COBB: You are mute --

DR. CYNTHIA GRAHAM: Yes. All of my comments were included. Thank you.

DR. GEORGE COBB: Thank you. Dr. Jenkins.

MS. ALLISON JENKINS: No further comments. Thank you.

DR. GEORGE COBB: Okay. So, we have 1.a out of the way. And now we can turn back to EPA.

DR. MARY OTTINGER: General --

DR. ALAA KAMEL: Do you want to ask the rest of the Committee also?

DR. GEORGE COBB: Oh, yes, yes, yes. I'm sorry. My computer was telling me to unmute myself and had my screen all messed up. Sorry about that. Thank you for the recalibration there Alaa. Let's hear from the rest of the Committee.

Are there comments from the rest of the Committee on this charge question? Okay. Have none. So, now we can turn to EPA to see if there are any clarifying questions.

DR. ANTHONY LUZ: This is Tony Luz with EPA. No clarifying questions at this time. Thank you.

2. HUMAN HEALTH HAZARD

CHARGE QUESTION 2.a

DR. GEORGE COBB: All right. So, now we can move to Charge Question 2.b.

DR. ANTHONY LUZ: This is Tony with EPA. Think it's 2.a. We're actually now switching gears --

DR. GEORGE COBB: Correct. Correct. My fault.

DR. ANTHONY LUZ: No problem, Dr. Cobb. Yeah. So, this is Charge Question 2.a for DINP, so we're switching gears from environmental hazard to human health hazard.

So, "In Sections 4.1.1 and 4.1.2 of the Draft Non-Cancer Human Health Hazard Assessment for DINP, EPA has preliminarily selected the HED of 12 milligrams per kilogram per day," so BMDL5 of 49 milligrams per kilogram per day, "based on decreased fetal testicular testosterone production for assessing risks from acute and intermediate duration exposure to DINP. EPA is using benchmark dose," or DMD, "estimates calculated by the National Academies of Sciences, Engineering and Medicine, NASEM, 2017. Please comment on the strengths and uncertainties in the selected acute slash intermediate HED, including its appropriateness for these durations." Thank you.

DR. GEORGE COBB: Thank you. So, let's move to our discussants. Our lead discussant here is Dr. Spade.

DR. DANIEL SPADE: Yeah. Thank you. And thanks to all the associate discussants who had a lot of comments on this charge question. So, I'll read our response. In the Draft Hazard

Assessment for DINP, EPA derived points of departure in corresponding human equivalent doses for DINP from the benchmark dose analysis conducted by NASEM in 2017. The discussants agreed with the scientific justification to use developmental toxicity studies, specifically fetal testicular testosterone production data to determine HED for both acute and intermediate duration points of departure, and also enumerated a number of sources of uncertainty.

The strengths of the approach include the use of DINP developmental toxicity studies to derive the acute POD and HED. The endpoint used in the Draft Hazard Assessment is inhibition of testosterone production in the fetal rat testis, which is a rapid response sensitive to reduction by single-dose phthalate exposure consistent with an acute mode of action. It is appropriate to use data from developmental toxicity studies when deriving toxicity values for acute exposure in accordance with EPA policies

described on Page 70 of the Draft Hazard Assessment.

Two recent publications from Earl Gray and colleagues from 2023 and 2024 -- and we will insert the references in our written report -- support the conclusion that reduction of fetal testosterone production by DINP can cause male reproductive tract malformations, which are the apical outcome associated with this mode of action, and that DINP exerts dose additive antiandrogenic action when combined with another antiandrogenic phthalate, which in the case of the 2024 publication was dibutyl phthalate. The discussants agreed that the selection of the same POD for short- and intermediate-term toxicity is reasonable given that fetal testicular testosterone production was the most sensitive endpoint over any duration in the studies that were included in the NASEM analysis.

Although the duration of exposure in days in the developmental studies is shorter than what might typically be considered intermediate

duration, it could be argued that the time period modeled by these exposures, so from gestation day six to parturition in rats, is equivalent to an intermediate exposure duration in comparison to human gestation time. In other words, for developmental endpoints, the duration of exposure in the animal should be scaled to the timing of development rather than an arbitrary duration of exposure such as 30 days. The discussants agreed that the intermediate duration POD was appropriately selected for DINP.

The reviewers largely agreed that the interspecies uncertainty factor of three is consistent with non-toxicokinetic similarity between rats and humans for phthalates while accounting for uncertainties about toxicodynamic similarity. However, the discussants request that EPA provide more detail in writing about the justifications for the selected uncertainty factors. Notably, there is uncertainty about toxicodynamic similarity across species based on phthalate experiments conducted in human fetal

tissues, xenograft, or culture models. Those experiments indicated that at least under certain circumstances human fetal testis tissue is less sensitive to the antiandrogenic effects of phthalates than rat fetal testis. And we will enter references into the written report.

This introduces uncertainty with respect to sensitivity of the human fetal testis to phthalate-induced testosterone reduction. Although, phthalates cause germ cell toxicity in all species that have been tested, we believe that this source of uncertainty was addressed by EPA in Section 3.1.4.1 on Pages 77 to 79 of the Draft Proposed Approach for Cumulative Risk Assessment of High-Priority Phthalates and a Manufacturer Requested Phthalate under TSCA in February 2023. However, we request that the EPA clarify that rationale for selection of the interspecies uncertainty factor A of three, which may account for a toxicokinetic similarity between species allometric scaling to determine human equivalent dose and/or knowledge of toxicodynamic differences

between species. In particular, the text note in Table 4-2 should be included in the text of the report on Page 72, Line 2446. Adequate justification is not provided in the text of this report for the selection of the uncertainty factors as it was provided in the assessment of DIDP.

There were several additional sources of uncertainty that were identified by the discussants. A first concern which was expressed by multiple discussants was that EPA relied on the 2017 NASEM benchmark dose analysis rather than conducting a new analysis. Adopting the NASEM analysis means that some decisions made by NASEM may introduce uncertainty, and those include -- there's sort of a long list here. But it is unclear whether EPA attempted to replicate the BMD modeling and whether the results were confirmed. There was no justification provided for the use of BMDL values instead of BMD values for determining human equivalent dose. And the rationale for the use of only BMDL5 and BMDL40 values that

correspond to a benchmark response of either 5 percent or 40 percent was unclear.

The 2012 EPA benchmark dose guidance document states that for quantile data an extra risk of ten percent is the BMDR for standard reporting. Further BMD5 is considered biologically relevant for nested data, which may be available for developmental endpoints such as reproductive tract malformations. The guidance also says that for continuous data the preferred approach is to define a BMR based on the level of change in the endpoint at which the effect the endpoint is considered to become biologically significant. There is limited discussion in this report as to why the BMDL5 was chosen over the BMDL40 despite a biological reasoning being provided for why the initial NASEM meta-regression conducted the analysis with a benchmark response of 40 percent. And that's in the legend of Table 4-1 but not in the text. The BMD guidance also does recommend that values other than BMD10 are used in the hazard assessment. The BMD10 numbers

for the selected endpoints should be given in the document for comparison.

A second concern identified by the discussants related to the inclusion or exclusion of data in the NASEM benchmark dose analysis because the inclusion and exclusion decisions are reproduced here by default. It is unclear if EPA conducted a literature search that resulted in identification of any relevant DINP studies other than acute developmental studies. And there's a lack of clarity about the justification of exclusion of studies. So, specifically, the 2017 NASEM analysis reports that four DINP studies were considered; however, only two -- Boberg et al., 2011, and Hanna et al., 2011 -- were included in the analysis. EPA states that they have high confidence the NASEM meta-analysis because it considers data from multiple sources, but it appears that only two studies were actually used in the meta-regression analysis. There's also a written discrepancy about which two studies were included, and we can detail that in a written

report. EPA also mentions one acceptable study, Clewell et al., 2013, that was not included in the NASEM 2017 study. There was discussion of the justification for excluding single-dose studies, which would be reasonable if each study was being considered in isolation to identify NOAEL or LOAEL values, but it seems that data points contained in the single-dose studies could strengthen modeling estimates if a new meta-analysis was performed. And, finally, there may be new studies available that would strengthen a new analysis, so the discussants noted that there were two recent publications from Earl Gray and colleagues, which have been mentioned, which could be included in a new analysis.

A third and related concern that was raised was the lack of consideration of human epidemiological studies in the DINP dose response assessment. So, this is listed separately here because there's potentially an entire category of studies not being evaluated, and we will cite available human epidemiology studies as we are

able in our written report. But not including available epidemiologic data in the analysis introduces uncertainty about the dose response analysis. So, to summarize those three related concerns, the discussants suggested that EPA may want to consider conducting a new benchmark dose modeling analysis which compares multiple endpoints, including variables for which nested data is available, and that EPA should clearly state its rationale for selection of the benchmark response and the use of BMD or BMDL to generate a point of departure, as both choices could lead to over or underestimation of risk.

A final concern that was raised by several of the discussants was that the report derives a human equivalent dose for DINP as a single chemical. As the report states, reduction of fetal testicular testosterone production in rat model following developmental exposure to phthalates is similar across phthalates with differing potency but similar mode of action. Because phthalates co-occur and inhibition of

androgen production is a mode of action that is relevant for many other phthalates as well, several discussants stated that deriving a human equivalent dose for a single chemical would not be consistent with recommendations of the SACC's review of the Draft Proposed Principles of Cumulative Risk Assessment Under TSCA and Draft Proposed Approach for Cumulative Risk Assessment of High-Priority Phthalates and a Manufacturer Requested Phthalate, 2023. Given efforts within EPA to conduct cumulative risk assessments for multiple phthalates, those discussants are concerned that reaching a conclusion on an HED without the cumulative assessment would be incomplete, and hence the lack of consideration of mixtures and/or interactions would lead to potential underestimation of risk. The reference submitted in public comment by Gray et al., 2024, supports the argument that DINP and DID -- or DBP, excuse me, have dose-additive effects on testosterone-driven endpoints, which would justify including DINP in the planned CRA. So, that

concludes our comments on DINP Charge Question 2.a. Thank you.

DR. GEORGE COBB: Thank you, Dr. Spade. Now we can go to our associate discussants. Dr. Heiger-Bernays.

DR. WENDY HEIGER-BERNAYS: I have no additional comments. Thank you, Dr. Spade. That was great.

DR. GEORGE COBB: Dr. Jenkins.

MS. ALLISON JENKINS: I don't have any additional comments. Great job. Thank you.

DR. GEORGE COBB: Dr. Merced-Nieves.

DR. FRANCHESKA MERCED-NIEVES: Thank you, Dr. Spade. You've included all of my comments.

DR. GEORGE COBB: Dr. Przybyla.

DR. JENNIFER PRZYBYLA: No additional comments in that great, comprehensive review. Thank you.

DR. GEORGE COBB: And thank you to Dr. Spade and to all of the discussants there. I know you worked hard to get that pulled together.

And appreciate it. Let's go to EPA -- excuse me, let's go to the other Committee members to see if there are additional comments. Dr. Fenner-Crisp.

DR. PENELOPE FENNER-CRISP: I have comments on two of the areas that were discussed here. I'll start with the one about the cumulative assessments being considered when you're deriving an HED.

First of all, I would say one cannot do a cumulative risk assessment without having HEDs. But I believe it is premature to consider cumulative assessment at this point in the review process. Individual risk evaluations for each of the chemicals which will characterize risk from their respective conditions of use must be done first. In order to be most useful in cumulative assessment process, those risk evaluations must be, quote-unquote, clean, in my view. That is, focused only on a single chemical that's the subject of an individual risk evaluation. This is necessary so that the chemical-specific relative potency factors can be derived in each chemical's

proportional contribution to a cumulative assessment, of which there will probably be many, can be determined so that the Agency can identify appropriate risk management measures that may need to be taken to ensure that the group as a whole does not pose an unreasonable risk. Mixing cumulative factors into the derivation of a POD or HED will make these actions difficult, if not impossible, and inappropriately skewed.

I also have a comment to make. Didn't come up so much here, but was in some of the earlier discussions about the three-X uncertainty factor that remind after applying the bodyweight calculation to the original dataset. One can't not know for sure whether or not the remaining three-X, or even the one that was set aside, results in an over or underestimate of risk in the actual species differences. So, I'm offering the suggestion that the Agency may wish to consider refining that value by making use of a recently developed DINP-PBK model. And I've got the -- that's Campbell, 2020. In the pregnant rat

and human, that may help to refine that three-X that was substituted for with the three-quarter bodyweight thing. And I have some more quotes in here, citations in here that would show that it would be consistent with one of the other EPA policy documents on the data-derived adjustment factors. I have the citation for that as well. Those are my comments.

DR. GEORGE COBB: Thank you, Dr. Fenner-Crisp, and please send those comments to Dr. Spade. That'd be very helpful. Are there other comments from the Committee? Dr. Eick.

DR. STEPHANIE EICK: Hi, I just wanted to quickly add on the issue of cumulative effects that I just really wanted to underscore the point that the lead discussant made that I really think that in this situation it's critical that we consider cumulative effects considering that there's a lot of epi studies, including studies in NHANES that show that exposure to DINP co-occurs with DEHP and DIDP and, also, again, studies in NHANES that are representative of the

U.S. that show that DINP is associated with a reduction in testosterone.

So, I would just like to add that I'll send those references over so that they're included in the response and just really underscore the point that's been made the cumulative effects are critical. Thanks.

DR. GEORGE COBB: I agree with the critical nature of those cumulative effects. I think in this case the Agency may be constrained by what is being evaluated in this assessment. But the cumulative effects are being evaluated separately, if you will, and maybe the EPA can explain that a bit more once we get through our comments.

Let's see. Are there other comments from the Committee? If not, let's go back to EPA and see if they're comments or a clarifying question.

DR. ANNA LOWIT: Tony, I'll take this one. I'll get it started, and you can add in if you want. So, to respond to the question that

you just -- oh, Anna Lowit, Senior Science Advisor -- that you just posed, Dr. Cobb. Penny -- Dr. Fenner-Crisp's explanation of the step-wise process to develop a cumulative assessment is accurate. That the way that we are doing this and what's necessary for the risk management process is to do each one first individually and then -- step-wise to do each one and then do the cumulative using relative potency factors, and take those relative potency factors and do potency factor-adjusted exposures looking at co-occurrence. So, her explanation of the step-wise process is the way that we are working through it. And so, this panel will continue to see a few more individual assessments that looks at each one by itself, both the hazard and the exposure. And then the cumulative will be its own entity.

DR. GEORGE COBB: Excellent explanation. Thank you. Are there other questions or comments from the Agency?

DR. ANTHONY LUZ: This Tony Luz. This is Tony Luz with EPA. Thank, Dr. Lowit for

that explanation. I don't have anything to add on to that.

DR. GEORGE COBB: All right. Well, I want ask a question of Dr. Heiger-Bernays. Do you think we can get through the next charge question before the top of the hour?

DR. WENDY HEIGER-BERNAYS: I think we can, but there may be additional comments that we haven't heard. So, let's try.

DR. GEORGE COBB: Okay.

DR. WENDY HEIGER-BERNAYS: If we don't, we take a break.

DR. GEORGE COBB: Okay. Well, I think we can.

CHARGE QUESTION 2.b

DR. GEORGE COBB: So, Dr. Lowit, if you can read in Charge Question 2 --

DR. WENDY HEIGER-BERNAYS: B.

DR. GEORGE COBB: -- B. There's a page break here that has your name at the top of

what I'm reading. So, it looked like it was 2.a for me. Thank you.

DR. ANTHONY LUZ: This is Tony with EPA. I'm reading in Charge Question 2.b for DINP. "In Section 4.1.3 of the Draft Non-Cancer Human Health Hazard Assessment for DINP, EPA has preliminarily selected the HED of 3.5 milligram per kilogram per day," so NOAEL of 15 milligrams per kilogram per day, "based on a spectrum of liver effects, including incidence of spongiosis hepatis, increased liver weight, and serum chemistry for assessing risks from chronic duration exposure to DINP. This NOAEL has been selected by other regulatory agencies, e.g., U.S. CPSC, Health Canada, EFSA, ECHA, to characterize non-cancer risks associated with exposure to DINP. Please comment on the strengths and uncertainties in the selected chronic HED, including its appropriateness for this duration." Thank you.

DR. WENDY HEIGER-BERNAYS: Thank you very much. So, for this question, we first summarized the EPA approach to determine the

chronic duration non-cancer POD based on a NOAEL of 15 mgs per kg per day with the critical effect of the liver toxicity; in other words, increased relative liver weight, increased serum chemistry, AST, ALT, ALP, histopathologic findings, focal necrosis, spongiosis hepatis in F34 rats following two years of dietary exposure to DINP. No data were available for the dermal or inhalation routes that were suitable for deriving route-specific PODs. Therefore, EPA used the acute-intermediate slash intermediate-and-chronic oral PODs to evaluate risks from dermal exposure to DINP. For the inhalation route, EPA extrapolated the oral HED to an inhalation human equivalent concentration using a human bodyweight and breathing rate relevant to a continuous exposure of an individual at rest.

Adverse non-cancer effects on the liver were primarily observed in rats and mice of both sexes. Although, there was also evidence of hepatotoxicity from one study in beagles. Two studies in nonhuman primates with dose ranges

comparable to those in the rodent and beagle studies did not provide evidence of non-cancer or preneoplastic effects on the liver following a 14- and 90-day oral exposure to DINP. EPA states, "In general, short-term, 9 of the 12 studies, and sub-chronic-duration studies, nine of nine, consistently reported increases in absolute and/or relatively liver weight, sometimes in parallel with exposure-related histopathological effects on the liver, as mentioned earlier." EPA states that no human epidemiologic studies evaluating hepatic effects were identified in its review of existing assessments, primarily Health Canada, 2018A.

So, the strengths of the selected chronic exposure HED of 3.5 mgs per kg per day of DINP with a NOAEL of 15 mgs per kg per day are that, one, there were several adverse liver outcomes in a high-quality two-year dietary study. Two, many additional chronic exposure studies observed similar adverse liver effects; although, they had higher NOAELS. And, three, several authoritative and regulatory agencies in the U.S.

and around the world selected the same point of departure of 15 mgs per day, the NOAEL, based on liver outcomes in experimental rodent models. EPA reviewed 12 studies to determine the chronic POD and determine an HED for a spectrum of liver effects. Furthermore, the acute exposure HED of 12 mgs per kg per day of DINP based on the NOAEL for decreases in fetal testicular testosterone production occurred at slightly higher doses than that HED for adverse liver effects, and it reinforced the ability of DINP to induce adverse health outcomes in mammals, the experimental rat model. The chronic exposure duration is an appropriate exposure to consider because it demonstrated consistency with the acute exposure duration of 12 mgs per kg per day for decreased fetal testicular testosterone production.

Uncertainties. EPA considered new studies published since Health Canada's assessment. However, no studies were identified that fall within this date range, 2018 -- fall within this date range and evaluated liver injury

for DINP and/or its metabolites. The lack of human relevance of the spongiosis hepatis is a concern, but concomitant change in liver injury markers somewhat reduces that uncertainty. The use of liver endpoints for this purpose is also substantiated using sufficient data. Of note, the study in beagles also showed some liver toxicity but have a slightly higher NOAEL. The Agency did not use several studies in dog and rats due to either limited sample size or lack of GLP while performing the studies, which seems appropriate. EPA chose the Lington et al. developmental toxicity study NOAEL as the POD because it was more sensitive, lower than all over candidate NOAELs and LOAELs, as shown in Table 4, but neglects to determine benchmark doses for all the candidate studies, allowing the identification of endpoints and doses. This is particularly important for developmental effects for which inference about potential modes of action cannot be gleaned from the two-gen GLP studies conducted

before understanding of endocrine disrupting and potential effects on developing systems.

The rodent studies that form the basis for the selected NOAEL base POD are, one, insensitive compared with more recent in vivo studies, or even the use of NAMs where endocrine systems are targets, and, two, lack concordance with the epidemiologic studies regarding endpoints, including PPR-alpha-mediated induction of human relevant pathways. Health Canada stated, "However, the relevance of the hepatic effects of phthalates observed in rodents is difficult to establish due to the species-specific differences in the PPAR response, rodents being significantly more sensitive than human, at least for the PPAR-mediated induction of peroxisome proliferation." EPA did not give an explanation as to why the toxicokinetics would be similar via oral inhalation and dermal routes and if this extrapolation is appropriate. EPA states that differences in absorption will be accounted for in dermal exposure studies -- dermal exposure

estimates in the Draft Risk Evaluation for DINP; however, specifics are not provided.

Several recent human epidemiology studies of DINP non-cancer effects, including developmental effects, were excluded from the dose response assessment. These studies were excluded because of uncertainty about exposure. However, the studies focused on measurement of urinary biomarkers of phthalates, including metabolites of DINP. While there are technical issues when using urinary biomarkers for determination of exposure, this is a common approach, and it is the gold standard for phthalates to understand the association between the chemicals and outcomes relevant in people.

EPA individually assessed the merits of 53 epidemiology studies of DINP published from 2018 to 2021, applying a prespecified set of study quality domains and metrics that closely mirrors the approach used by EPA's IRIS, which has been favorably reviewed by NASEM. EPA's overall quality determination was medium or high for 46 of

these epidemiology studies. Each study was individually assessed for its exposure measurement methods and treatment of potential confounding. In another comment, EPA has not released the systematic review protocol used for DINP, and so the SACC is unable to review its approach or findings.

Our summary's recommendations. Overall, the available data support the Agency's selection of NOAEL and HED. The fact that several other regulatory studies have similar chronic PODs is reassuring to some respondents. Respondents agree that EPA should consider the fetal testicular testosterone production as the most sensitive effects based on the evidence from the animal studies; however, EPA should use all available dose range studies from which BMD-based points of departure should be developed, compared with each other in order to select the lowest BMD-based POD as the basis for the derivation of the human equivalent dose. EPA should provide an explanation as to why the toxicokinetics would be

similar by oral inhalation and dermal routes, and if this extrapolation is appropriate. EPA should provide documentation of its approach used for route-to-route extrapolation in the absence of dermal and inhalation data and should release the systematic review protocol for DINP. EPA has disqualified epidemiology studies in a manner inconsistent with its own prespecified procedures, and EPA's own overall quality determinations indicate that these studies are suitable for use. EPA should include these studies in its justification of studies potentially suitable for informing the POD. Alternatively, EPA could justify why these studies are not relevant. And, lastly, EPA should apply benchmark dose modeling to derive chronic non-cancer points of departure and select the one that is most sensitive lowest. And I have a series of editorial comments that I will provide in writing. That's what I got.

DR. GEORGE COBB: Thank you. Thank you for that thorough summary. And now we can turn to the associate discussants. And Dr.

Shuman-Goodier. Is Dr. Shuman-Goodier there? If not, Dr. David.

DR. WENDY HEIGER-BERNAYS: I wonder if that's the right --

DR. CYNTHIA GRAHAM: I think you have the --

DR. WENDY HEIGER-BERNAYS: -- list of discussants.

DR. CYNTHIA GRAHAM: Yeah.

DR. WENDY HEIGER-BERNAYS: It's Dr. Howdeshell and Dr. Graham. Dr. Apte.

DR. GEORGE COBB: Oh, you know what, I'm sorry. I'm sorry. I'm on --

DR. ALAA KAMEL: Yeah. The discussants are below the question, Dr. Cobb.

DR. GEORGE COBB: I know. We got multiple 2.a's and 2.b's.

DR. WENDY HEIGER-BERNAYS: It's okay.

DR. GEORGE COBB: Okay. Let's try again. So, I think Dr. Apte is the first person.

DR. UDAYAN APTE: Right. No, my comments were all captured in there. Thank you so much.

DR. GEORGE COBB: And Dr. Baker.

DR. MARISSA BAKER: No further comments.

DR. GEORGE COBB: Dr. Graham.

DR. CYNTHIA GRAHAM: Thank you, Dr. Heiger-Bernays. You have included all of my comments.

DR. GEORGE COBB: And Dr. Howdeshell.

DR. KEMBRA HOWDESHELL: Thank you. No further comments.

DR. GEORGE COBB: Right. Well, let's go to the rest of the Committee then. Are there comments from others on the Committee? If not, we can go to EPA for any clarifying questions, comments.

DR. ANTHONY LUZ: Hey, this is Tony Luz with EPA. No clarifying questions or comments from us.

DR. GEORGE COBB: All right. Well, at this point, I think it is about time for a lunch break. Perhaps we can take a one-hour lunch break and then reconvene. And at that point, we'll revisit and see if there's any further comments from the Committee on the things we've discussed today. And then we'll move into Charge Question 2.c, which will be led by Dr. Apte. So, we will hopefully see everyone back in an hour.

[LUNCH BREAK]

DR. GEORGE COBB: Welcome back. And this is George Cobb and we're in the Science Advisory Committee for Chemicals. Somebody's not on mute. Somebody's not on mute. Thank you. And I'd like to see if there's anything from our DFO, Dr. Kamel, before we proceed.

DR. ALAA KAMEL: Everything is fine. You can proceed. Thank you.

DR. GEORGE COBB: All right. Thank you very much. So, at this point as we do after

every lunch break and every break for the end of the day, I'd like to circle back and see if there are comments from committee members based on what we went over in the morning.

I know we know we had a couple times to do that but just procedurally it's better to get this stuff out of the way now than later. So, I think a couple people mentioned things that they wanted to get aligned from the morning's discussion, so open it up for that.

DR. ALAA KAMEL: Also, take the roll if you would like.

DR. GEORGE COBB: Okay. I'll do that first. I'm going to take the roll but get your questions/additional comments ready. Thank you, Alaa. Juggling too many things over here today. So, I should've known when Dr. Apte's image came up that that was my queue to take the roll but you're the next lead as well, so I got confused.

DR. ALAA KAMEL: Good coincidence.

DR. UDAYAN APTE: Yeah, I have always been the first on the roll whole life so, I'm just being Apte -- A -- that's how it works.

DR. GEORGE COBB: So, I don't have to call your name now. Dr. Baker.

DR. MARISSA BAKER: Here.

DR. GEORGE COBB: Dr. Chaisson.

DR. CHRISTINE CHAISSON: Here.

DR. GEORGE COBB: Dr. Eick.

DR. STEPHANIE EICK: Here.

DR. GEORGE COBB: Dr. Gentry

DR. ROBINAN GENTRY: Here.

DR. GEORGE COBB: Dr. Graham.

DR. CYNTHIA GRAHAM: I'm here.

DR. GEORGE COBB: Dr. Heiger-Bernays.

DR. WENDY HEIGER-BERNAYS: Here.

DR. GEORGE COBB: I think I left out Ms. Jenkins.

MS. ALLISON JENKINS: I'm here, thank you.

DR. GEORGE COBB: Yeah. I'm going too fast through the roll now. Dr. Li? Okay. Dr. Merced-Nieves.

DR. FRANCHESKA MERCED-NIEVES: Here.

DR. GEORGE COBB: Dr. Ottinger.

DR. MARY OTTINGER: Here.

DR. GEORGE COBB: Dr. Przybyla.

DR. JENNIFER PRZYBYLA: Here.

DR. GEORGE COBB: Dr. Reif. Okay. Dr. David.

DR. RAYMOND DAVID: Here.

DR. GEORGE COBB: Dr. Fanning.

DR. ELINOR FANNING: Here.

DR. GEORGE COBB: Dr. Fenner-Crisp.

DR. PENELOPE FENNER-CRISP: Here.

DR. GEORGE COBB: Dr. Howdeshell

DR. KEMBRA HOWDESHELL: Here.

DR. GEORGE COBB: Dr. Martinez.

DR. JEANELLE MARTINEZ: I'm here.

DR. GEORGE COBB: Thank you. Dr. Shumen-Goodier.

DR. MOLLY SHUMEN-GOODIER: Here.

DR. GEORGE COBB: Dr. Spade.

DR. DANIEL SPADE: Here.

DR. GEORGE COBB: And Dr. Wolf's not here today. Okay, so thank you for that. And Alaa, thank you for keeping me on track here. Let's go back to additional comments from this morning. I think there were a couple from 2B that I saw that needed to be clarified. So, let's see. Dr. Martinez?

DR. JEANELLE MARTINEZ: Hi. Yes, I had a couple of comments but one of them was covered previously. But my other comment was based on the HED of 3.5 based on the NOAEL of 15 and they did it based on the LinkedIn (phonetic) and Bio/Dynamics studies. But I'm wondering because there's also the other high-quality study of Covance labs.

So, since they're both high quality studies and they both have the same effects of the liver and kidney with the increased organ weights and the histopathology, should they maybe not

consider using the highest NOAEL that's below the lowest LOAEL.

And that's just a practice I use sometimes when they have the same type of effects and there's two studies. But along the same line, I'm wondering if there's -- I really like that flow chart that they had for the TRV and specifically identifying how they choose their endpoints and if there is any possible -- if they could put that into the Human Health Risk Assessment that would be really great. But that was my comment.

DR. GEORGE COBB: So, thank you for the comment, and please make sure that Dr. Reif gets those comments. I think he has them, but just make sure. And on the flow chart, you're not saying the same flow chart, you're meaning that's a similar flow chart that would give that kind of information for the human health?

DR. JEANELLE MARTINEZ: Yes, yes. A similar. That would be really helpful, I think,

for all of the endpoints that they use for the human health.

DR. GEORGE COBB: Okay. And Dr. -- go ahead.

DR. WENDY HEIGER-BERNAYS: It's Wendy Heiger-Bernays. Dr. Martinez, is that for 2B or for DINP-2B or for something else?

DR. JEANELLE MARTINEZ: Yes, it was for the DINP-2B.

DR. WENDY HEIGER-BERNAYS: Okay, thank you. And you've already sent that, I think, to me --

DR. JEANELLE MARTINEZ: I did. I sent you an email and I know it sent it a little bit late, but I did send it to you recently, okay.

DR. WENDY HEIGER-BERNAYS: Thank you.

DR. JEANELLE MARTINEZ: Thank you.

DR. GEORGE COBB: Now. Dr. Shuman-Goodier.

DR. MOLLY SHUMAN-GOODIER: Thank you, Dr. Cobb. Yes, we had some back and forth

during lunch about updating a comment from Charge Question 2B for DIDP. So, I'll just read into the public record the updates so that they're reflected. And this was the charge question related to the use of DIDP -- DINP as an analogue for DIDP with regard to the soil invertebrate study.

So, the comment is, did EPA consider read across data from DINP or other analogues to inform data gaps for the other species in the environmental assessment that lacked empirical data? While using DINP as an analogue for DIDP may not be justified for vertebrates based on the potential differences in mode of action that are well discussed in the DINP evaluation.

It could be useful for the agency to inform data gaps really to terrestrial plants, aquatic invertebrates, or algae for DIDP. Alternatively, if this has already been done EPA could consider adding a description of why the analogue data was not used to fill out those

hazard profiles for the additional species. Thank you.

DR. GEORGE COBB: Okay, thank you for that clarification. And was that all of the discussants there had put together? At least sent in.

DR. MOLLY SHUMAN-GOODIER: Yeah, thank you, Dr. Cobb. This was a specific comment that was stated by Dr. Reif into Charge Question 2B, and it reflects some updated language.

DR. GEORGE COBB: Okay. Thank you. And I see Dr. Howdeshell is there.

DR. KEMBRA HOWDESHELL: Yeah. I was just going to confirm -- this is Kembra Howdeshell -- that that is accurate.

DR. GEORGE COBB: All right, great. So, about this charge question after asking for comments over and over again, there was one of mine that got left out that -- there are actually two of mine that got left out.

The first one was -- the EPA acknowledges that one of the studies, that's

referenced as ExxonMobil, was done nominal concentrations. However, if you look at that document, there's no indication of any type of purity or how those nominal concentrations were measured. The quality of information that describes the dose in that experiment is woefully inadequate. And I've done those kinds of studies before.

I know the difficulties there but basically it says we did these at nominal concentrations and the purity of the compounds was reported by the producer and that's all you know. And so that's suspect for something that's deemed high quality.

And then the other option -- the other item, not option. The other item is with the bioaccumulation test, there are bioaccumulation data that could be used in evaluating some relative K_{OW}s. There's a wide range of K_{OW}s to maybe evaluate how those K_{OW}s -- those calculated K_{OW}s are truthful or

representative because we've got two and a half orders of magnitude of difference in some places.

So, I think that would be a way to ground truth that the K_{OW}s that are being used for bioaccumulation were correct. And other than that, I think Dr. Reif -- the discussants -- did a great job pulling that together.

So, circling back for final comments from the morning session. Dr. Howdeshell.

DR. MOLLY HOWDESHELL: Yeah, I'm not noticing that David Reif is here. I'm wondering if, George, if you'd be willing pass those comments along or perhaps you have already, and they weren't read in. Great. Thank you.

DR. GEORGE COBB: I may have gotten those to him too late to get incorporated. But anyway, those have been passed along.

CHARGE QUESTION 2.c

DR. GEORGE COBB: Okay, if there are no further comments let's move to our charge

questions and next Charge Question is 2C is where we are, and we'll turn it back over I believe Dr. Luz.

DR. ANTHONY LUZ: Hi, Dr. Cobb, this is Tony Luz with EPA. Before I read this charge question, I was wondering if I can ask a quick clarifying question?

DR. GEORGE COBB: Of course.

DR. ANTHONY LUZ: So, in your previous response, Dr. Cobb, you had referenced a ExxonMobil study. We're not sure what precise study you're talking about. Was it the earthworm study? Did you have hero ID?

DR. GEORGE COBB: It was the earthworm study and, yeah. That's exactly it. I've got the page numbers. It's on page 613 to 614 of the hazard -- environmental hazard.

DR. ANTHONY LUZ: Thank you.

DR. GEORGE COBB: I was trying not to read all that minutia into the record but if it helps you, we'll read it in.

DR. ANTHONY LUZ: Okay. I appreciate it.

DR. GEORGE COBB: Okay.

DR. ANTHONY LUZ: Okay, now I can read in DINP Charge Question 2C. In the Draft Cancer Human Health Hazard Assessment for DINP, EPA considered MNCL Section 3.2.2 kidney tumors, Section 3.2.3 in liver tumors, Section 4. EPA has preliminarily determined an α2u-globulin or (inaudible) α2u-globulin MOA for kidney tumors and that there is too much scientific uncertainty associated with the instances of MNCL observed in F344 rats to use quantitatively to estimate human risk for exposure to DINP.

Therefore, EPA focused its MOA analysis and dose response analysis on liver tumors. Please comment on the strengths and uncertainties of EPA's decision to focus its cancer assessment on liver tumors. Thank you.

DR. GEORGE COBB: Great. Thank you for reading that in, and now we can turn to our lead discussant, Dr. Apte.

DR. UDAYAN APTE: Thank you, Dr. Cobb. This Udayan Apte. I'm going to read into the responses I've gotten. I'm going to start with a summary of key points and then give some details. Overall, so the Agency's decision not to consider MNCL to drive quantitative risk assessment of cancer hazard is well supported by data. The Agency has provided substantial evidence that the kidney tumors produced by DINP are due to to α2u-globulin MOA and correctly classified them as not relevant to humans.

Overall, the Agency's decision to focus on liver tumors rather than other types of tumors for cancer risk evaluation is justified. The Agency did a good job in describing the data and effects on the tumors as the most appropriate endpoint for human decision. It is recommended that the data in Table 3.3 should be treated the same way as in Table 3.1 and 3.2 combining the neoplastic findings and comparing across those groups.

Thus, comparing males 4712-9 and females 1110-9, et cetera. It is appropriate to combine hepatocellular neoplasms as they are continuing from typical hypoplasia throughout adenoma and carcinoma. These are older studies, and the term neoplastic nodule is no longer used. A reference has been included to kind of justify that. Wolf and Mann (inaudible) TAB 2004/'05.

Changes in the terminology and interpretation can have an impact on a series of lesions such as the pathology of liver tumors. Non-malignant masses that arise from proliferating initiated at para sites have been variously called neoplastic nodules. Benign hepatic tumors, hepatomas, paracellular adenomas, and nodular hypoplasias. And so, a common nomenclature has been preferred in this paper.

About the mononuclear cell leukemia, also sometimes called as Fischer rat leukemia, is a finding in virtually hundred percent of Fischer 344 rats if they live long enough. Need to correlate with the lifespan of the rats unique to

that specific tumor, and so it is one of the reasons the Fischer 344 rats are no longer the primary rat species used by the NTP because of its confounder in the bioassay interpretation. The Agency's conclusion not to consider this rat-specific tumor for human risk assessment is scientifically correct decision.

About the kidney tumors, there seems to be sufficient evidence that these renal tumors are associated with excess α2u-globulin which is a well-characterized rat specific protein and associated tumors and renal toxicity due to its accumulation in the kidney are not relevant to human health risks.

There are some specific trends and uncertainties pointed out. Acceptance, not using MNCL is widely accepted by other international agencies, which is summarized on pages 17 of 48. The report provides a good overview on the problem of high spontaneous MNCL in controls. Notably, on the Fischer 344 rats, as stated before, were susceptible to MNCL.

MNCL in kidney findings lack concordance. Leukemia, MNCL, and kidney tumors are only found in one species and are one-sixth of one species where kidney tumors were only significantly induced in the male Fischer 344 rats. Plausibility, while biologically plausible, the hypothesized key event in the role in liver tumor MOA, which is PPARα is unlikely to induce such tumors in humans because of significant quantitative toxicodynamic and biological differences in the responses.

Thus, the rodent MOA is either not relevant or is unlikely to be relevant to humans as evidence provided here Corton et al 2013. Sensitivity. The most sensitive study endpoint to carry on to a dose response assessment is liver tumors recognizing that the hypothesized MOA for rodents is at least quantitatively different from humans. By using the most sensitive ethical endpoint it is assumed these doses will not cause toxicity to humans.

Cross species tumor site concurrence. Liver tumors are repeatable for DINP. They are found in both sexes and multiple strains and species. However, it is interesting that MNCL is also found in the liver. Some uncertainties that were pointed out for relevance. Relevance to humans is questionable. No human hematological evidence identified. Line 1137, page 42. In the U.S. EPA guidelines for carcinogen risk assessment tools on file, there is a lack of guidance for evaluating human relevance.

It has been pointed out that some immune related cancers are not addressed and the question we are asking is whether there was a specific search for them. This is because immune-related gene activation is seen in ToxCasts for DINP.

The inactivity of DINP in ToxCast data for nuclear receptors including CAR, HR, PPARα, and PPAR gamma, and other assays of PXR with positive responses found in other in vitro studies. A comparison of the doses and

experimental conditions used from other individual studies is warranted where the ToxCast data compared with these studies.

Dose response concurs PPARα MOA in rats. Males seem to be more sensitive to KE1, Key Event One, however, the species different should be included in Table 4.2, 4.5-3, since there are species differences in tumor doses. And then there are some specific comments that are editorial.

Further, other contributors to my charge question basically echo majority of the comments that I've said. The decision not to consider MNCL to derive quantitative estimates for cancer hazard is appropriate. While a statistically significant increase in incidents is noted, in once study of Fischer 344 rats in kidney tumors, this increase is very small, 4 out of 50 animals, after a very high dose of exposure, 1,000 PPMs, and thus the decision not to consider kidney tumors to derive quantitative risk assessment is appropriate.

The incidence of liver tumors was the only tumor type that was observed to be significant increase in multiple strains of rats, one strain of mice in both males and females following chronic exposure to high concentrations of DINP. To focus the mode of action and potential dose response analysis on these tumors is appropriate.

However, there is uncertainty in relying upon this endpoint to extrapolate to humans if EPA provides evidence from multiple studies to support that these liver tumors in rodents could occur through a PPARα mode of action. This suggests a mode of action in rodents that has been evaluated in multiple assessments beginning with (inaudible) Klonig et al in 2003 and then most recently by Corton et al in 2018 which is sited in the document.

While this mode of action for liver tumors in rodents is biologically plausible, it has been determined that in multiple assessments by multiple authoritative bodies sited by EPA

including NICNAS, USCPSC, ECHA, and Health Canada, they lack human relevance. In evaluations of DINP, no quantitative evaluation of these liver tumors were conducted plus the potential for carcinogenicity to humans.

EPA suggests that there is a reduced confidence in the proposed PPARα for mode of action for liver tumors because there is not enough evidence for every key event, however, evidence for every molecular event is not needed or not necessary to build a mode of action and described in the available evidence as strong. Therefore, to conclude that this mode of action for liver tumors lacks human relevance would be appropriate and consistent with the conclusions of multiple authoritative bodies cited by EPA. And we have several references included.

Further, EPA's determination that there's too much uncertainty associated with DINP -- α2u-globulin MOA for kidney tumors to estimate human risk for exposure to DINP is appropriate. There is uncertainty surrounding the MOA for

cancer for liver or concerning most notably conclusions from two panels (inaudible) Felter et al 2018 and Corton 2014, conclusions that PPARα is not human relevant.

Additionally, EPA manages that the POD from the non-cancer health hazard assessment is protective of concern given that this is lower than the suspected Key Event One in the MOA for liver cancer. However, no PPARα activation was observed in monkeys observed exposed to DINP at higher doses than some of the activation concentrations in rodent studies.

So, by doing so, EPA does not make a clear conclusion about the cancer-causing potential of DINP. So, it is not clear if non-cancer POD changes either through recommendations by the committee or other avenues and become higher than the Key Event One estimated activated concentrations. How the cancer assessment will proceed from this point onwards.

Further, there are other comments that are mostly editorial. There are a few

citations that we are providing including that is a workshop that was conducted by NTP to demonstrate that Fischer 344 rats and B6CTF1 mice are probably not a good species and that has been provided.

And overall, we think that the Agency's decision to focus on liver tumors rather than other types of tumors for cancer risk evaluation justified. Thank you.

DR. GEORGE COBB: Excellent. Thank you for getting the comments compiled and together for the discussants and so now we can now turn to our associate discussants, and we'll start with Dr. Przybyla.

DR. JENNIFER PRZYBYLA: No further comments, thank you.

DR. GEORGE COBB: Thank you. Dr. Gentry.

DR. ROBINAN GENTRY: No further comments, thank you.

DR. GEORGE COBB: Dr. Martinez.

DR. JEANELLE MARTINEZ: Hi. No further comments from me, either.

DR. GEORGE COBB: And Dr. Wolf is not with us today. Let's see about comments from other committee members. I see Dr. Graham's hand is up.

DR. CYNTHIA GRAHAM: Yes. I just want to comment, and I find it interesting that the Committee agrees that it was good that EPA focused on the liver tumors when most of their comments were explaining how it's not relevant to humans.

So, I don't know. I question that. If it's not relevant to humans, why would that be appropriate to use as the MOA?

DR. GEORGE COBB: That's a good question and I have to turn it to Dr. Apte and the discussants.

DR. UDAYAN APTE: So, the question is that what they've done is based on the data they had available and looking at that, the kidney tumors MNCL, they clearly are not related. I

mean, those were not relevant as well. The only data I think that this process was driven by was the clear connection between liver tumors and the dose. And the MOA happens to be PPARα which most people consider to be not relevant.

However, there are agencies other than us that still are not completely convinced. So, with the given amount of data and availability we thought most of the members seem to think it is what they could do as good as they could get is my interpretation of what they're saying. Does that make sense?

DR. CYNTHIA GRAHAM: Okay. Yes, but if we have a committee vote, I would vote against that. So. I know I wasn't in the group, though. So, thank you for your explanation.

DR. UDAYAN APTE: Would you provide a specific recommendation?

DR. CYNTHIA GRAHAM: I'm sorry?

DR. UDAYAN APTE: Would you provide a specific recommendation?

DR. CYNTHIA GRAHAM: I may, and I'll send it to you.

DR. UDAYAN APTE: Okay.

DR. GEORGE COBB: Great. Thank you, Dr. Graham. That's a good point and I had a similar thought, but this is not right in my expertise, so I didn't want to jump in. So, thank you for asking that question. Dr. Fenner-Crisp.

DR. PENELOPE FENNER-CRISP: I think I might be able to clarify why they did go forward and suggest that they needed to do the MOA analysis to actually determine if that might be the -- since there's some uncertainty and there might've been uncertainty about whether or not this was the mode of action for DINP. They had to go through the analysis to show whether or not it fit this paradigm or whether or not there was an alternative explanation for it.

So, whether or not it turned out to be relevant is irrelevant in the sense that they had to go through -- rope it (inaudible) to go

through the exercise to reach and confirm a conclusion of possible.

DR. GEORGE COBB: Thank you. That makes total sense. So other comments from the Committee? Dr. Gentry?

DR. ROBINAN GENTRY: I think I would just add to what Dr. Fenner-Crisp just said is we agreed to move down that path -- that EPA should go down that path like they did -- but I think part of the conclusions of the Committee, too, was also that once they went down that path we agreed that no quantitative evaluation should be conducted because of the lack of human relevance. So that was part of the conclusions as well.

DR. PENELOPE FENNER-CRISP: Right.

DR. UDAYAN APTE: That's well put.

DR. GEORGE COBB: And that may help answer Dr. Graham's question.

DR. CYNTHIA GRAHAM: Yes, thank you.

DR. PENELOPE FENNER-CRISP: And I think our discussions of the next two questions may also provide some perspective for her and

encourage her to weigh in as we talk about the two.

DR. GEORGE COBB: Great. This is good conversation. I'm glad we're having this. So, are there other comments from the Committee? If not, we'll go to the Agency to see if you have questions about our response. I see two people. I see Dr. Luz and Dr. Lowit.

DR. ANTHONY LUZ: Anna. Do you want to start, Anna?

DR. ANNA LOWIT: Did you have a question?

DR. ANTHONY LUZ: No, I didn't. I was going to say I didn't have any questions. I'll let you jump in.

DR. ANNA LOWIT: Well, first if there are dissenting views, like if Dr. Graham has a dissenting view and she just agrees it would be important to make sure that gets on the record if her comment is more of clarification, that's different.

But I was actually wondering if the confusion -- because I was also a little bit confused -- comes in that maybe some of the human relevance belongs in 2E that our questions have attempted to be step-wise -- that the first step in the analysis as Dr. Fenner-Crisp explains is just to look at those tumors and decide which ones to do more analysis on and that's the intent of the one that we just went through and that maybe some of the other sort of belongs somewhere else, it might help with the confusion.

But it's not my report, you do what you want. It's just I think it might help.

DR. FENNER-CRISP: Well, obviously the human relevance will be discussed in the other two questions.

DR. UDAYAN APTE: I've been in communication with Dr. Fenner-Crisp about that, so we'll have some more response.

DR. CYNTHIA GRAHAM: No, that's fine. I think you answered my questions. I'm

sorry, I wasn't involved in those and so therefore my question. Thank you.

DR. GEORGE COBB: So, A, don't apologize for getting things clarified. This is the time to do it, so that --

DR. FENNER-CRISP: Just hang onto it for a minute.

DR. GEORGE COBB: Yeah. That's what we're all supposed to do. Okay, so now I guess we can turn it back over to EPA for our next charge --

CHARGE QUESTION 2.d

DR. ANTHONY LUZ: This is Tony Luz with EPA, and I'll read the DINP Charge Question 2D. In the draft Cancer Assessment for Human Health Hazard Assessment for DINP, EPA preliminarily concluded that the weight of scientific evidence supports a peroxisome proliferated activator receptor alpha, or PPARα MOA for liver tumors in rats and mice in Section

4.1. Please comment on the strengths and uncertainties of EPA's preliminary conclusion.

In your response, please include discussion of the strengths and uncertainties of available data supporting key events in the PPARα MOA and the scientific rationale for threshold approach for cancer dose response. Thank you.

DR. GEORGE COBB: Thank you for that, Dr. Luz. Our lead discussant for this is Dr. Fenner-Crisp, and we'll turn it over to her now.

DR. PENELOPE FENNER-CRISP: Okay, thank you, Dr. Cobb. As an introduction I'd like to say that I hope I've captured the salient comments that the associates have provided in the past and if not, I would hope they would make comment on it following the presentation. And if there are any, would they please forward them to me in writing so I can add them to our report, thanks. For both questions.

Okay, let's answer this first one. Section 4 is a well-written section, clear and

straightforward in a manner consistent with the principles articulated in the WHOIPCS mode of action human relevance framework. Got a citation for that. And EPA's guidelines for carcinogen risk assessment. It is an exceptional example of how this type of analysis should be conducted by the Agency. It is very well done.

Nonetheless, of course, it could be strengthened by referencing the extensive database on examining the ability of PPARα agonists to produce liver tumors in rodents and other species in a specific predictable way rather than depending only upon DINP specific information. Extensive literature on this mode of action pursuant to other chemicals that bind to and activate PPARα including other closely related phthalates would be very useful in filling some of the data gaps or some of the key events that are less or no DINP-specific data at this time.

On that latter point, if you recall one of the public commenters provided a number of references claiming that they could provide --

DR. GEORGE COBB: Well, it looks like Dr. Fenner-Crisp has frozen. Is there anything on the technical side that we can do?

DR. PENELOPE FENNER-CRISP: Am I still frozen?

DR. GEORGE COBB: You're not frozen now.

DR. PENELOPE FENNER-CRISP: Okay. Where did I get frozen?

DR. GEORGE COBB: I would say, 30 seconds ago. I don't remember the exact words you were saying.

DR. ELINOR FANNING: You were saying a public commenter provided a number of references dot, dot, dot.

DR. FENNER-CRISP: Okay. I'll start there. Okay. On the latter point, one of the public commenters provided a number of references claiming that they could provide information that would fill in those data gaps. Hopefully that will be the case, and the Agency can resolve any remaining uncertainties they may have about

whether or not DINP produces the liver tumors by this mode of action.

In any case, the existing extensive body of literature collectively describes and integrates postulated key events into a well-characterized downstream outcome binding to the PPARα receptor resulting in liver tumors in rodents.

Carton et al 2018 does a particularly nice job of summarizing the current knowledge about this MOA including figures which incorporate confirmation of the key events and modulating factors involved. The order in which key events -- the order in which they occur supported by data in chemicals representing more than one class included below of the figure from the publication which visually presents the occurrence of key events in the PPAR mode of action.

If you'd put up the slide, please. Let me know when it's up. It's up, okay. One will notice that collectively the entire mode of

action pathway is filled in. If the table were updated today, more chemicals would be added. Just for example, permethrin and possibly some other phthalates and probably some other PFAS. The figure does include data from some phthalates other than DINP and as the remaining five phthalate risk evaluations are drafted, additional phthalate chemicals may be added to this figure.

Other phthalates not on the TSCA priority list at this time may also meet the criteria for inclusion in the MOA analysis -- if an MOA analysis were conducted for these observed to induce rodent liver tumors. In the meantime, to address lingering uncertainties that the Agency may have now about DINP acting via this pathway, it is incumbent upon it to exercise its historical practices of employing the tools used in the new chemicals program such as SAR/QSAR and read across to fill in the DINP key event gaps currently devoid of adequate empirical data.

For example, the figure shows that there are relevant data related to KE2 for two

other phthalates DEP and DBD. Additional candidates for read across include the other examples in the figure as well as the other five TSCA priority phthalates for which the risk assessments evaluations are being drafted currently.

Along with those that are on the list in the NAS 2008 phthalate report and the NASM 2017 report there are eight or nine more added that don't include the seven priority ones that are being evaluated now. Even though these phthalates were evaluated in those two reports with a focus on their effects on male reproduction, these chemicals do have other adverse effects associated with their toxicity profiles which may include the liver tumors.

Applying read across information from other PPAR agonists is relevant to KE4, clonal expansion as well. Furthermore, KE4 is obligatory in the pathogenesis of liver tumor genesis in rodents no matter the mode of action. The population model as described in Wolff et al

2019 illustrates how this occurs from the initial burst of mitogenesis to a new larger population of hepatocytes resulting in a greater population at risk of developing a neoplastic response.

With regard to the strengths and weaknesses related to the Agency's preliminary conclusion that DINP induces liver tumors via this mode of action, there's little doubt that this mode of action is the operative one based upon the DINP specific data and those were related in other chemicals as summarized in Corton et al 2018.

Did I freeze again?

DR. GEORGE COBB: No, you're fine.

DR. PENELOPE FENNER-CRISP: Okay, I got a message on the screen that suggested I was. This conclusion will only be strengthened further when the Agency more carefully reviews the Corton et al's 2018 study and performs a read across exercise.

As for the potential uncertainties articulated by EPA and this DINP cancer hazard assessment, more will be resolved after doing the

aforementioned work. EPA states on page 29 lines 817 to 20 quote/unquote. Quote, overall, there is some evidences for dose response concordance for KE1, KE3, and the adverse outcome. However, no DINP-specific data are available for KE2 or 4 or apoptosis at the moment in the rat hepatocytes which prevents a complete analysis of the dose response concordance across all KEs in the postulated mode of action, unquote.

We believe this is an unsupportable statement in the first instance because it is not necessary to illustrate all key events in a well-established mode of action so long as the molecular initiating event -- in this case, the receptor activation -- in some of them are qualitatively and quantitatively addressed which they are in this case. Using data from similar compounds that have the same biological effects also supports this mode of action conclusion for the reasons presented in the paragraphs above.

Some additional work on the Agency's part as recommended will hopefully resolve this

concern to their satisfaction. On page 32, lines 888 to 890, I think it is, the Agency states quote, in contrast other studies have demonstrated that PPARα activation Key Event One in cellular proliferation, KE3, occur at lower doses in male mice compared with females -- cite is in here. This apparent inconsistency cannot be explained, close quote.

This discrepancy is identified by EPA as an area of uncertainty. Quite frankly, we believe this is not a very valid area of uncertainty in this context. It is, in fact, irrelevant. This does not impact the characterization of the mode of action. Any dose response characterization or determination of the appropriate descriptor for prediction of human cancer potential.

In the latter case, gender discrepancy would matter only if one sex experienced a significant increase in incidence of a specific tumor and the other one did not. The scientific rationale that the PPAR activation MOA

is a threshold phenomenon is supported by available science. Section two summarizes a series of 20 studies that evaluated genotoxicity potential in a variety of systems. All of the studies were carried out in in vitro systems except the in vivo micronucleus studies in mice.

The only positive result was observed in one of nine available in vitro transformation assays in (inaudible) L3TC31-31 mouse cells in the absence of metabolic activation. I've got the citation for that. The Agency concluded that the weight of scientific evidence indicates that DINP is not likely to be genotoxic or mutagenic. The conclusion with which we agree.

This conclusion coupled with the observation that other nuclear receptor mediated modes of action like CAR, PXR, and et cetera, are generally observed to be threshold phenomena supports the conclusion that this mode of action is also. On page 32 the Agency states, quote, in

contrast, other studies have demonstrated that activation -- oh, I'm sorry, that's a repeat.

I guess that's it. About to repeat something that I've already said. So that's it for now.

DR. GEORGE COBB: All right, thank you for that comprehensive --

DR. PENELOPE FENNER-CRISP: Oh, no, I do have so more. Sorry, I do have some more if I may?

DR. GEORGE COBB: Okay. Please.

DR. PENELOPE FENNER-CRISP: As you might know I have a little trouble seeing, so I'm a little slow to pick up on stuff.

We have some recommendations. Section 4 would benefit from a more substantial discussion of species differences, structurally and functional in the PPARα nuclear receptor itself. Activation of it in rodents may lead to liver tumors via the described mode of action. Activations in humans does not, based upon the available epidemiology studies, which explore the

relationship between exposure of these agonists and cancer outcomes. The reference I have here.

While the lag in receptor binding kinetics are well documented for some chemicals including phthalates, there is no robust discussion of work that shows species specific differences in potency and efficacy of activation of the receptor that mice respond differently.

If the mice express mouse PPARα versus human which shows that mice expressing human PPAR that background levels have had carcinogenesis are higher in the mice expressing the mouse PPARα.

Additionally, a high affinity lag does not induce carcinogenesis in mice expressing human PPARα. The results demonstrate species differences in that mouse PPARα required in this carcinogenesis in response to the lag in exposure in the rodents. So, using human relevant rodent models continues to raise questions about how the evidence is used to conclude and justify a mode of action. I'm going to skip the rest of this.

The second recommendation is that Section 3.2 would benefit from the inclusion of additional human epidemiology studies which examine the relationship between exposure to any PPARα agonists and cancer. Refer back to the (inaudible) Bonobos et al reference and I have another one that I'll add to it. That's it. Now I am finished.

DR. GEORGE COBB: All right. Thank you and that was an important question, and a lot of associates there, so thank you for pulling that together. Let's hear from the other discussants. The first one is Dr. Eick.

DR. STEPHANIE EICK: Thanks for that great summary. I just had a few quick things to add. I would also recommend that in Section 4, EPA consider the key characteristics of cancer, and I'll provide a reference for some of that which really outlines -- I would think how some of the epidemiologic evidence could be integrated in some of this.

And I would also suggest that EPA review some of the well-designed epi studies that look at DINP alone and in combination with other phthalates in relation to biologic pathways such as oxidative stress and inflammation that are related to PPARα that could also inform some of this dose response. And, again, just highlighting the cumulative effects which I don't need to get into because that's been mentioned. Thank you.

DR. PENELOPE FENNER-CRISP: I should mention that both oxidative stress and others were considered and are integrated into the MOE as modulating factors. So, they haven't been ignored.

DR. GEORGE COBB: Right. Thank you, Dr. Eick. Dr. Heiger-Bernays.

DR. WENDY HEIGER-BERNAYS: Thank you, Dr. Fenner-Crisp, for capturing everything. There's one -- I think the very end about the human relevant models should be part of the battery and I'm not sure how it was stated, but I'll make sure in the written summary that it's

important to use human relevant animal models for analysis.

DR. PENELOPE FENNER-CRISP: That was one of your comments that I took as-is. So, I would appreciate it if you would expand on it because when we talked about it yesterday and you weren't able to join us, we were a little bit confused about what you had meant.

DR. WENDY HEIGER-BERNAYS: Yeah, other questions at the same time (inaudible) a long time. But yes, so using human relevant models is absolutely critical. Thank you.

DR. GEORGE COBB: Dr. Przybyla.

DR. JENNIFER PRZYBYLA: No further comments from me, thank you.

DR. GEORGE COBB: Thank you. I saw Dr. Apte pop on the screen. Was there a comment?

DR. UDAYAN APTE: No. I was just following up the discussion between Wendy and Dr. Fenner-Crisp because we had some discussion back and forth about the (inaudible) so, yeah, it's been documented.

DR. GEORGE COBB: All right. Thank you very much. All right, to the rest of the Committee, are there comments from others on the committee? Dr. David?

DR. RAYMOND DAVID: Just a comment about in the presentations there seemed to be an emphasis on making sure that all of the key events for DINP were somehow supported by data and I think in -- that may be important in looking at downstream events. But quite honestly, I think that just demonstrating activation of the PPARα receptor may be sufficient to show that the -- everything else should then fall in place and the Agency cites a study by Bility back in 2004 where they did look at binding to the PPARα receptor from a mouse and from a human.

And they show that DINP was pretty good at activating the receptor. Now the reason I point this out is because they looked at a variety of phthalates. One of them was butyl benzyl phthalate which has also been tested for

carcinogenesis and the NTP found that it was not carcinogenic in Fischer 344 and B6 mice.

So, the fact that you have a link between activation of the receptor, a powerful activation in the case of DEHP and DINP versus something like butyl benzyl phthalate, and tumors or the absence of tumors may be sufficient to make the link in terms of that mode of action.

DR. PENELOPE FENNER-CRISP: Well, in my summary and our discussion we did point out -- and the Agency has pointed out -- they do have data to fill some of the gaps with respect to the key events -- two of them -- and are missing either all or inadequate support for the other two.

That's why we're suggesting to use other chemicals in the read across that might fill in, and if, in fact, as the commenter offered the other day, we're bringing you newer studies that will fill in the data gaps that can satisfy that and it was pointed out by Dr. Apte and again here that not -- yesterday when they talk about DIDP,

it's not necessary to have every key event filled in to get from the beginning to the end.

DR. RAYMOND DAVID: Right.

DR. PENELOPE FENNER-CRISP: If you have a well-characterized mode of action standardized, which I think is pretty firm in this case.

DR. GEORGE COBB: All right, thank you for that discussion. Other comments from the Committee? Right, if not, we can go to EPA for any clarifying comments. I don't know if that's Dr. Luz or others.

DR. ANTHONY LUZ: Anthony Luz here, EPA. I don't have any questions or clarifications at this time. Thank you.

DR. GEORGE COBB: Well, we can read in our final charge question. Charge Question 2E.

CHARGE QUESTION 2.e

DR. ANTHONY LUZ: Okay. Charge Question 2E for DINP. As described in Section 4.8

of the draft Cancer Human Health Hazards Assessment for DINP, EPA has preliminarily concluded that DINP is not likely to be carcinogenic to humans at the doses below levels that do not result in PPARα activation, and that the non-cancer chronic POD based on liver toxicity will adequately account for all chronic toxicity including carcinogenicity. Please comment on the strengths and uncertainties of this preliminary conclusion. Thank you.

DR. GEORGE COBB: Thank you for getting that into the record for us and Dr. Fenner-Crisp is our lead discussant again.

DR. PENELOPE FENNER-CRISP: Okay. Our current response is that EPA's 2005 guidelines for cancer risk assessment include a discussion of the weight of evidence narrative that is to be included in all cancer hazard assessments. In the March 2024 draft Cancer Human Health Hazard Assessment for DINP the relevant text can be found in Section 4.8, Weight of Scientific Evidence,

Cancer Classification and in Section 4.9, Human Relevancy.

The weight of evidence narrative is to be a short summary of the detailed analysis conducted for the agent under evaluation. That explains the agent human carcinogenic potential and the conditions that characterize its expression.

The guidelines go on to say, quote, the weight of the evidence should be presented as a narrative laying out the complexity of information that is essential to understanding the hazard and its dependence on the quality, quantity, and types of information available as well as the circumstances of exposure or the traits of the exposed population that may be required for expression of cancer, unquote.

The weight of evidence narrative also is to include a section on a selection of a descriptor that sums up the agencies conclusions about the agent's human carcinogenic potential. In this DINP draft Human Cancer Assessment, EPA's

preliminary conclusion is that the descriptor should be, quote, not likely to be carcinogenic at doses below levels that do not result in PPARα activation, unquote.

The Section 4.8 Weight of Scientific Evidence -- that's a classification narrative -- captures the relevant facts well. We agree with the portion of the Agency's preliminary determination that the descriptor should be, quote, not likely to be carcinogenic to humans, but disagree with the inclusion of the phrase at doses below levels that do not result in PPAR activation.

This infers the DINP is likely to be carcinogenic to humans at doses above the levels that do result in activation. This disagreement is based upon, in good measure, on the preponderance of the evidence that PPARα activation in humans does not trigger the obligatory key events that would lead to the liver tumors as developed in rodents.

In the EPA cancer guideline section that expands upon this discussion of the not likely descriptor, it states that the descriptor is appropriate for agents for which there are, quote, convincing and extensive experimental evidence showing that the carcinogenic effects observed in animals are not relevant to humans, unquote.

We believe that this applies to DINP because, one, the rat kidney tumors could be explained as occurring in accordance with the male rat specific α2u-globulin MOA and thus are irrelevant to humans. The Fischer rat MNCL tumors were determined to be inappropriate for predicting human cancer potential. See discussion under DIDP Charge Question 2B and in DINP Charge Question 2C. And three, the liver tumors seen in rodents are not likely to be or are not relevant to humans for the reasons described above.

Beginning with Klaunig et al in 2003 which proposed a mode of action for PPAR activation in rodents resulting in liver tumors as

the case study using the mode of action human relevance framework for the first time followed by reviews, updates, and refinements by foreign assistants. (inaudible) Peters et al 2012 -- got (inaudible) the reference. Corton et al 2014, Felter et al 2018, and Corton et al 2018.

There is a body of convincing and extensive experimental and epidemiological evidence that the PPAR activation MOA for liver tumors in rodents is not operative in humans. Therefore, humans are not responsive to the carcinogenic effects of activation. Plus, the observation in rodent liver tumors occurring following PPARα activation is not relevant when evaluating DINP's human carcinogenic potential.

The conclusion is further reinforced by the Bonavis (phonetic) et al 2012. I have the reference citation can be found in the DINP Charge Question 2D, which describes a meta-analysis of 17 randomized control trials involving nearly 45,000 participants treated with drugs in the chemical class of fibrates which are BP PPARα activators

that lower cholesterol and triglycerides and can help protect from heart disease, heart attack, and stroke.

The follow up period averaged 5.2 years, the authors observed that, quote, a quantitative synthesis of data revealed that the RCTs was not indicative of a fibrate effect on cancer incidence or cancer death. When the analysis was restricted to the major RCTs, the results did not substantially change. Similarly, we found no evidence of differential effects by length of follow up or type of fibrate, unquote.

The authors concluded that the fibrates have a neutral effect on cancer outcomes, which include those in the liver. Quote, in summary, fibrate drugs have been on the market since 1977 without an apparent increase in liver cancer in people taking them chronically, unquote.

In conclusion, we recommend that it would be more appropriate to say that DINP is not likely to be carcinogenic in humans given that there's no reason to conduct any dose response

assessments or any tumor related key events/endpoints as related to the rat kidney, MNCL, or liver. The POD/HED determined from the data representing the relevant non-cancer endpoints of concern is the one appropriate one to use going forward when calculating risk estimates and making unreasonable risk determinations.

As an aside, we would recommend that the Agency revive the risk assessment form and initiate a project to update the cancer guidelines. We're getting quite out of date on the post 2005 efforts to update the IPCS framework.

The abetting of the IPCS framework into the OECD adverse outcome pathway process and the efforts underway worldwide to make use of many in silico and in chemico predictive tools and models that are already available, are under development as our test systems that generate empirical data but do so more quickly, less expensively, and without wholesale dependency upon traditional whole animal models.

The pressure is on EPA to follow this path as it is consistent with a 2016 TSCA mandate on invertebrate animal testing. The Agency's new assessment method strategy in the widely hailed three R's philosophy of Replacement, Reduction, and Refinement. Thank you.

DR. GEORGE COBB: Thank you for getting the assessment pulled together for the team. So now we can go to our other discussants and somehow, I've lost my list of charge questions. Here we are. Dr. Merced-Nieves.

DR. FRANCHESKA MERCED-NIEVES: So, maybe I missed it. I think a couple of respondents -- we had made another comment about cumulative assessments to be included here. But I just also want to expand upon that since we've been having the conversation all day. I think it is clear that the Agency has a tiered process to evaluate these chemicals and that it will be completed in the future.

However, I think it's still accurate that the assessment of a single chemical at a time

is not representative of true-life exposures. As many have acknowledged, their co-exposures with other phthalates ensure mechanisms which does leave space for uncertainty and potential underestimation making it a limitation of the current analysis. I, and maybe others -- but I will speak for myself -- have brought this up since we believe it's an important limitation just to acknowledge, not because we think it needs to be dealt with today. That's all, thank you.

DR. PENELOPE FENNER-CRISP: I forgot to mention that I was going to mention the top again and defer the discussion -- and refer to the discussion we had a few minutes ago on 2A because I think it -- rather than redo it twice. I think the discussion was covered but I'll put a sentence in there that refers people back to that. The 2A.

DR. GEORGE COBB: Yeah, a lot of times there's crosstalk between these questions.

DR. PENELOPE FENNER-CRISP: Yeah, exactly.

DR. FRANCHESKA MERCED-NIEVES: Yeah. I agree. Thank you.

DR. GEORGE COBB: Thank you for that comment. And then Dr. Eick.

DR. STEPHANIE EICK: Thanks for that summary. I just had a few additional comments. So, I would say that one of the same is that Dr. Fenner-Crisp just made that we recommend that it would be more appropriate to say that DINP is not likely to be carcinogenetic to humans and I would say that I don't think that that necessarily reflects the full opinion of the Committee.

Because myself, and at least some others, did think that we didn't really have the full information to make that sort of general conclusion in regards to some of the things we've already talked about today that we don't need to get into. And I would also, again, just add here that I felt that there were some epi studies that were missing, and I'll provide some references for those in the final report. Thank you.

DR. GEORGE COBB: Great.

DR. PENELOPE FENNER-CRISP: I hope you would write out your comments you've just made and appreciate the addition of other epi studies. I did make the point that others should be considered but I didn't have any at hand to plug in at the moment. So, this would be good.

DR. GEORGE COBB: Dr. Gentry.

DR. ROBINAN GENTRY: Thank you, Dr. Fenner-Crisp. I don't have any comments to add.

DR. GEORGE COBB: And Dr. Martinez.

DR. JEANELLE MARTINEZ: Hi. I think she covered everything and thank you very much. I'm good.

DR. GEORGE COBB: All right. Well, thank you and thank you to the whole team. Now, do we have comments from the remainder of the Committee? All right, seeing none do -- oh, Dr. Apte.

DR. UDAYAN APTE: Yeah. So, I think I just want to echo one of the comments made here. I think there is room for read across and cumulative assessment because of the true-life

exposure scenarios. And data gaps in one versus data availability in others and so I think that would be a solid recommendation for the agency I would say.

DR. PENELOPE FENNER-CRISP: I would also suggest that not be confined just to dealing with DINP but across the board as the phthalate evaluations proceed where appropriate. We don't have access to them so we don't know where specifically these tools might apply but they could be useful across the board.

DR. GEORGE COBB: Okay. We have some latitude in DIDP to, again, tie these concepts back to those questions that did deal specifically with broader concepts of cumulative risks.

DR. PENELOPE FENNER-CRISP: Right.

DR. GEORGE COBB: Other comments from the Committee? Okay, so let's go back to EPA to see if there are clarifying comments -- or clarifying questions, I should say. Dr. Lowit?

DR. ANNA LOWIT: Yeah, my mute wouldn't go off. Hi, everyone. Thanks for all that conversation. I do just want to -- if there's a dissenting view on the classification, make sure that that's represented but also give a sense of the extent of that dissent is the majority opinion the one as written -- as read by Dr. Fenner-Crisp and we have one or two or a small number of dissenters as opposed to the Committee as split. I think that's an important distinction to be made in the report if that's okay.

DR. FRANCHESKA MERCED-NIEVES: Yep, I'll make sure that's in there. Thank you.

CLOSING REMARKS AND MEETING ADJOURN

DR. GEORGE COBB: Great, thank you. Any other clarifying questions? If not we're at the end. I want to circle back one last time for any final comments that committee members have but we're nearing the end. Please, if you're on the committee, that means if I've been calling your

name for roll, these last few days, please do not leave the meeting until we have a couple of administrative items we need to take care of at the end about report writing.

So, let's go back to see if there are any final comments from the Committee related to topics that we've covered during this multi-day meeting. I'm not seeing any so perhaps we can begin to adjourn.

I do want to make the point that there were some email exchange that there would be clarification about some of the questions and responses in the conversation that Dr. Chaisson and David and Ottinger had. They'll be some references related to that and some clarifications of that conversation in the minutes.

So, with that, I'd like to thank everyone for participating, to the EPA for all the hard work you've done of preparing this assessment, preparing these questions. To everyone on the committee and all the public commenters, really want to express my gratitude.

And with that, I'll turn it back over to Dr. Kamel to close us out.

DR. ALAA KAMEL: Thank you, Dr. Cobb. So, in closing, I'd like to thank everyone who contributed to this meeting. I'd like to first thank the Peer Review and Ethics Branch in EPA for preparing for this meeting, including the branch chief, Steve Knott (phonetic), the executive secretary, Tamue Gibson, and the DFO's and assistant deputy ethics official, Dr. Sharlene Matten and William Wooge and also, the DFO Holly Munere (phonetic).

I would also like to thank Joyce Coates and Barbra Yule (phonetic) from the administrative staff and also thanks to the contractor EnDyna for their help in the Zoom meeting preparation and the YouTube webcasting. Thank you, Dr. Cobb, for leading the meeting and going through all the agenda items and for following FACA requirements. Thank you to the SACC committee members and the ad hoc reviewers for their input and participation in this meeting.

Thanks, are also due to the OPPT team for presenting the draft documents and responding to the Committee questions. Thank you to the public for listening or for presenting oral comments. We ask the committee members to stay, as Dr. Cobb indicated, in this meeting after everyone else leaves and the meeting is now adjourned. Thank you.

DR. GEORGE COBB: Thanks everyone.

[MEETING ADJOURNED]