CHEMICAL SAFETY ADVISORY COMMITTEE (CSAC)

OPEN MEETING

PEER REVIEW of the DRAFT RISK ASSESSMENT for TSCA WORK PLAN CHEMICAL 1-BROMOPROPANE (CASRN-106-94-5)

DOCKET NUMBER: EPA-HQ-OPPT-2015-0815

CSAC Website http://www.epa.gov/csac

Crystal City Marriott

1999 Jefferson Davis Highway

Arlington, Virginia 22202

(703) 413-5500

DAY 1

MR. STEVEN KNOTT: I would like to welcome you to the first peer-review meeting of the new EPA Chemical Safety Advisory Committee. My name is Steve Knott, and I will be serving as a Designate Federal Official for this meeting.

I want to begin by thanking Dr. Kenneth Portier for serving as the chair of the CSAC, and I'd also like to thank both the members of the committee and the public for participating in this meeting. In addition, I'd like to thank the EPA Office of Pollution Prevention and Toxics and my colleagues on the CSAC staff for all the work in preparing for this important review of the Draft Risk Assessment for TSCA Work Plan Chemical, 1-bromopropane.

I want to provide a little background for the record for the meeting. The CSAC is a federal advisory committee that provides independent scientific peer review and advice to the EPA on the scientific basis for risk assessments, methodologies, and pollution prevention measures or approaches. The CSAC only provides advice and recommendations to the Agency; decision-making and implementation authority remains with the Agency.

By charter, the CSAC consists of ten members. The expertise of the members is augmented through subcommittees. Subcommittee members serve as ad hoc temporary participants in CSAC activities, providing additional scientific expertise to assist in reviews conducted by the committee. As the designated federal official, or DFO, for this meeting, I serve as liaison between the committee and the Agency. I'm also responsible for ensuring provisions of the Federal Advisory Committee Act are met. The Federal Advisory Committee Act, or FACA, of 1972 established the system that governs the creation, operation, and termination of executive branch advisory committees.

CSAC meetings are subject to all of FACA's requirements. These include open public meetings, timely notice of meetings, and document availability, which is provided via the Office of Pollution Prevention and Toxics public docket, which is available on www.regulations.gov.

As the DFO 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 have received a briefing on provisions of federal conflict of interest laws. In addition, each participant has filed a standard government financial disclosure report.

I, along with our deputy ethics officer for the Office of Science Coordination and Policy, and in consultation with the Office of General Counsel, have reviewed these reports to ensure all ethics requirements are met. A sample copy of the financial disclosure form is available on the CSAC website, and the address for the website is noted on the meeting agenda.

The CSAC will review challenging scientific issues over the next two days. We have a very full agenda, so the meeting times are approximate. We may not keep to the exact times as noted due to the committee's discussions and the public comments. We want to ensure there is adequate time for the Agency presentations, public comments, and panel deliberations.

For presenters, panel members, and the public commenters, please identify yourselves and speak into the microphones that are provided for this meeting. This meeting is being webcasted and recorded, so it's important that you use the microphones and identify yourselves.

Copies of all the presentation materials and public comments are either currently available in the public docket, and materials submitted today will be available within the next few days.

For members of the public requesting time to make a public comment, please limit your comments to five minutes unless prior arrangements have been made. And those who have not pre-registered may notify either me or another member of the CSAC staff who are seated to my right.

As I mentioned previously, there is a public docket for this meeting. All of the background materials, questions posed to the committee by the Agency, and other documents related to this meeting are available in this docket. Some of these documents are also available on the CSAC website. And, again, the website and the docket number are provided on the meeting agenda.

At the conclusion of the meeting, the CSAC will prepare a report as a response to questions posed by the Agency, the background materials, the presentations, and the public comments. The report serves as the meeting minutes, and we anticipate that the meeting minutes will be completed within 90 days after the meeting.

So, again, I want to thank the committee for your participation. I'm looking forward to a challenging, interesting discussion over the next two days. And at this point I would like to turn the meeting over to our chair, Dr. Kenneth Portier.

DR. KENNETH PORTIER: Good morning, and welcome, all of you, to this first meeting of the Chemical Safety Advisory Committee, or CSAC. I'm sure all of us are going to know all these acronyms by the end of the day, but this is a new one for EPA, so that's good.

I'm Ken Portier, Biostatistician and Vice President of the Statistics and Evaluation Center at the American Cancer Society, and I'm honored to chair this first meeting.

At this point, we'll introduce the panel. Just so you'll know, the permanent panel is kind of sitting on this side, except that Dr. Thayer is also on the permanent panel, and then we have the ad hoc members. And we'll start with Dr. Davies.

Please introduce yourself.

DR. HOLLY DAVIES: There we go. Hi, I'm Dr. Holly Davies from the Washington State Department of Ecology.

DR. PANOS GEORGOPOULOS: I am Panos Georgopoulos, Professor of Environmental and Occupational Health at Rutgers University, New Jersey.

DR. KATHLEEN GILBERT: Hi, I'm Kathleen Gilbert. I'm an immunotoxicologist from the University of Arkansas for Medical Sciences.

DR. JOHN KISSEL: I'm John Kissel, Professor of Environmental and Occupational Health Sciences at the University of Washington in Seattle.

DR. JAYMIE MELIKER: Jaymie Meliker, Associate Professor from Program in Public Health in Department of Family Population and Preventive Medicine at Stony Brook University.

DR. DANIEL SCHLENK: Dan Schlenk, Professor, Environmental Toxicology, University of California, Riverside.

DR. LESLIAM QUIROS-ALCALA: Lesliam Quiros-Alcala from the Maryland Institute of Applied Environmental Health at the University of Maryland, College Park, Assistant Professor.

DR. MICHAEL PENNELL: Michael Pennell, Associate Professor of Biostatistics, College of Public Health, the Ohio State University.

DR. MELANIE MARTY: Melanie Marty, California Environmental Protection Agency, Office of Environmental Health Hazard Assessment.

DR. MUHAMMAD HOSSAIN: I am Muhammad Hossain from Northeast Ohio Medical University. I am an assistant professor.

DR. JAMES BLANDO: Jim Blando, an Associate Professor at Old Dominion University in Norfolk, Virginia, and I'm an industrial hygienist.

DR. KRISTINA THAYER: Kris Thayer, Deputy Director of Analysis at the National Toxicology Program, which is headquartered at NIEHS.

DR. KENNETH PORTIER: Thank you. And we've all passed the first test, which is to remember to turn off your mic after you speak, all right. And I'll be reminding you of that during the day because we'll be forgetting it.

At this point, we're going to move into the formal part of the meeting. We're going to have welcome and opening remarks by Dr. Stan Barone, who is the Acting Director, Office of Science Coordination and Policy, EPA, and Wendy Cleland Hamnett, Director, Office of Pollution Prevention and Toxics. I guess Dr. Barone.

DR. STAN BARONE: Yes, thank you, Dr. Portier. I am Stan Barone. I am a neurotoxicologist by training. I am in a new position now as the Acting Director of the Office of Science Coordination and Policy, and that is noted on the agenda.

I want to welcome all of you here, and I am looking forward to the robust discussion of this first peer review meeting of the CSAC FACA panel on 1-bromopropane. I can't really take credit for you being here. That's really -- I want to acknowledge the superlative efforts of our staff and the former director of the Office of Science Coordination and Policy, David Dix; Laura Bailey, the Executive Secretary of the Peer Review Panel Team; and Steve Knott is the DFO; and our peer review staff who are here in the room, who've put a lot of work into prepping for this meeting.

I also want to acknowledge OPPT and the staff at OPPT for their technical efforts in developing this Draft Risk Assessment and putting together a compendium of work for your review. And I really look forward to your discussions, your advice and recommendations, and hope that your recommendations are provided in actionable terms, not just what you don't like, but what you're recommending can be done by the Agency to make this assessment better.

And I want to thank you very much, and introduce Jeff Morris, to my left, who is here as our Deputy Office Director for OPPT, the Office of Pollution Prevention and Toxics.

DR. JEFF MORRIS: Thanks, Dan. Good morning, and on behalf of the Office of Pollution Prevention and Toxics, I welcome you and I thank you for this service to EPA and to the American public.

You know, the origins of this meeting really go back five years to when the EPA made the commitment to begin a program to assess existing chemicals that really the Agency has no requirement to evaluate, and yet we certainly had the mandate to do that. And beginning in 2012 we began our first risk assessments under what we call our Work Plan Chemical Assessment Program.

We issued the first five in 2014, and those underwent peer review. They underwent contractmanaged peer reviews by different panels for each one, and those were very good reviews, but it was clear to us that in order to have reviews that recognized the particular fit-for-purpose needs of these risk assessments to inform potential regulatory decisions under the Toxic Substance Control Act, or TSCA, we needed a standing panel that over time would gain an understanding of the Agency's work and the industrial chemical space and provide us with the type of context-rich technical advice on these assessments that would help us develop chemical evaluations that were not only scientifically sound, but also had the appropriate focus and quality that would be important for informing any potential decisions the Agency might take, whether under the current TSCA or any new TSCA that may come to us. And some of you know that there's activity on Capitol Hill to look at updating our statute.

Dr. Tala Henry, in a moment is going to talk about how we got here with 1-Bromopropane. I would just like to say that, while all of our TSCA Work Plan Assessments are important, the 1-Bromopropane assessment has its own special importance not only because of the particular role it plays in the economy in the nature of the hazard endpoints that are being evaluated here, and in the exposure scenarios that affect both consumers and workers, but also because 1-bromopropane is a potential substitute for some chemicals that we have already assessed, such as methylene, chloride, and trichloroethylene, but also other chemicals that are on our Work Plan, as well.

So this particular assessment will play an important role in the Agency's current and future work on this particular part of the chemical space. So we look forward to an excellent meeting. Again, I welcome you and thank you for your service on the Chemical Safety Advisory Committee.

DR. KENNETH PORTIER: Thank you. Does anyone on the panel have a question for Dr. Morris or Dr. Barone? Nope. You didn't know we were going to open it up to questions right up front. A new panel, we're never quite sure what people want to know. At this point, I invite Dr. Henry, who's the Director, Risk Assessment Division, OPPT, to introduce and talk about 1-bromopropane Risk Assessment. Dr. Henry.

DR. TALA HENRY: Thank you. I'll just reiterate the welcome and appreciation for all of you serving in this capacity to again review our approaches, our scientific analysis, and provide any recommendations, and advice, and ways forward, especially given, as Jeff pointed out, we have a few of these completed, but we have quite a number left to do. So I think I said last time during the orientation that we're learning by doing to a certain degree, and then that's where your input is most critical to really guide us through the early stages of this program because it doesn't look like it's going to be going away any time soon.

So just a couple of points to reiterate from the orientation. I'm assuming that the ad hoc panelists were able to view those materials. I did not prepare slides per se; I was just going to touch on a couple of key points from those and then get to how 1-bromopropane got on the Work Plan.

So, as I pointed out last time, you know, TSCA is a different thing. It deals with industrial chemicals or chemicals in commerce, but it specifically excludes pesticides, food, drugs, and so forth, so there is a very clear distinction as to our universe. So we don't touch certain things, but we nonetheless have the most chemicals in our purview.

I think I gave you some figures about there was a few thousand active ingredients under FIFRA, but we're in the tens of thousands as far as chemicals on the inventory. Those in commerce are quite a lot smaller, but still it's thousands, upwards of maybe tens of thousands.

So another point I want to remind you of is that under TSCA, there is no base set of data, whether that be hazard data, exposure information, or whatever. We must use that data which is available to us, and that's a whole other discussion on what is available.

But, again, I think you can see from this assessment we go to great lengths to find all available information, whether it be hazard data, exposure information, surveys that other agencies might've done, or the published literature, and so on. So, again, that can be a limitation, but it is about available data.

So then, also, as I walked through last time, there's this TSCA Work Plan that Jeff Morris spoke of. It was 2011 I think we developed the methodology by which we were going to take a large number of chemicals on the TSCA inventory and screen them in a very basic way to come up with those chemicals which should be the highest priority to EPA to assess under TSCA.

So the usual kinds of information were gathered for this screening. So there was a hazard component, and we particularly focused on any chemicals that might be potentially of concern for children's health, so those things that might have reproductive or developmental toxicity. Neurotoxic effects was an endpoint that came to be added to our hazard considerations based on our stakeholder input process and then, of course, probable or known carcinogens, so it's very similar to a lot of state and European-type things focused on what can be severe and lifelong effects for hazard.

As far as exposure, we wanted to look for things that were known or thought to be used in products that children may be exposed to, as well as consumer products. And then in that exposure realm, we also used data again on this available information vein, data that comes to us under TSCA under the Chemical Data Reporting rules so that any chemical produced over 25,000 pounds, every four years or so, the manufacturers and processors need to report to us what volumes are used and what they're used for. Some of that is -- can be claimed CBI, so again we filter through that and use it to the extent that we can without revealing any of the CBI.

And then also information from the Toxics Release Inventory; it's another program at EPA, but, again, facilities that have no chemicals need to report yearly in that case about how much they release the air, water, waste, and so forth.

So that sort of fills out our screening areas for the potentials for exposure. And I say potentials because this is just information that's available, and it's helping us to prioritize. It's not the end-all per se.

And then finally we certainly wanted to take -- put some attention to any chemical that might be persistent and bioaccumulative simply for the fact that it's going to be around awhile, and what exactly happens when things bioaccumulate should be considered.

So those are the key components, and there is a whole methodology about -- with a little more in-depth about what specific data sources were used to gather the information for prioritization, what -- how each of those endpoints were scored, and then eventually what came down to be on the TSCA Work Plan.

So today we're not here to talk about the Work Plan itself or the methodology; that all went through a public process. But I will tell you that, as I mentioned at the beginning here, our first TSCA Work Plan which results from this process had 83 chemicals on it, and we did update it in 2014 to include the latest CDR and TRI data. And it now has -- some chemicals went off because they were in commerce or for other reasons. Some additional chemicals went on based on the scoring scheme, and so there are currently 90 chemicals on that TSCA Work Plan. And you heard from Jeff that we are completed with five, so hence my comment about your prolonged usefulness to us, as you can well imagine.

So based on that methodology, let me move into -- let me just mention one other thing because we get a lot of comments about this. Being on the Work Plan itself does not imply risk. It is a screening-level prioritization list; it's something we will look more closely at, the chemicals on this list. It in no way implies a finding in and of itself.

So, again, we go through this process and develop these in-depth risk assessments to sort all of that out. And, again, in this very screening-level list-making sometimes the data and information, they're not incorrect but they may -- there may be additional when we look further, deeper, that adjusts some of the findings there. So, again, that's what comes out during the problem formulation.

So, with regard to 1-bromopropane, however, the criteria or the findings from this screening level that got it on the list, the Work Plan, was its use both in consumer as well as industrial settings, the fact that many of these applications involve spraying, so it was a dispersive use. And, of course, given what we know about its volatility, it kind of gives it this ability to get around.

At the time was a possible human carcinogen. That certainly weighed in on the hazard side of things. And then, as far as exposure considerations, it was known to be in consumer products, present in multiple environmental media. And, again, as far as persistence in bioaccumulation for this chemical, that was very low, so that really didn't score heavily.

Nonetheless, an overall score anywhere from seven to nine put you on the TSCA Work Plan, and this one, due to its potentials for exposure as well as its hazards, scored high enough to go onto the list.

So as you all know I'm sure quite well at this point, we released our Draft Risk Assessment in March, and we focused on the occupational uses as a spray adhesive in the dry cleaning commercial world as well as in a variety of other degreasing operations. Then, moving into the consumer realm, it also may be used in those same types of applications, but the exposure scenarios will be different, as you'll learn. And then we also are focusing only here on human health toxicity, for reasons Kathy will explain during the conceptual model.

One thing I would just like to reiterate also, I showed you a busy colorful process diagram last time, and I took a lot of time to talk about problem formulation. So those first five chemicals that we started, 1-bromopropane was sort of in that first batch. It's the last one of the first batch, if you will, and we learned from that based on feedback and otherwise that we were going to have a specific and discreet problem formulation document moving forward.

So I'll just remind you this 1-bromopropane is the -- again, the last of the first batch. It does not have a stand-alone problem formulation document that was put out. It is fully incorporated into this draft risk assessment, so there's one difference there.

So, in the future, we've already begun our next chemicals, and they have a separate problem formulation step. But this one is, you know, right at that transition point, so that's just a little kind of logistical thing.

And then just one other final point, which I mentioned previously, gave multiple references, is that in conducting our risk assessments, we generally follow established EPA guidance, and that can be strictly technical scientific guidance, but also includes and incorporates certain science policy approaches. So, again, we pretty much stick with the guidance, but it is guidance. Each of these assessments are fit for purpose under TSCA, and so they will vary, and that's why we need all of you to examine the particulars of each of these assessments.

But when it comes to the overall approaches or some of those science policy decisions, we are generally following our established agency guidance. But certainly each of these has some unique features, and that's what we look forward to hearing from you about. So I think that's about all I have to say to you.

DR. KENNETH PORTIER: Thank you. One of the questions that came up this morning as the panel was doing its administrative work is -- and a question I ask as an evaluator -- I always think about, you know, what this panel is doing is evaluating your draft work, and we're going to provide recommendations back within 90 days. What does EPA plan to do with that?

One of the things I've learned as an evaluator is having an evaluation report that goes on the shelf has no impact, right? So I'm hoping this doesn't go on the shelf, but have you factored this in? I mean, it's a new committee; have you factored this into your Work Plan, and what is the short-term future of the BP Risk Assessment? The panel is always asked that question. You know, why am I here? Am I going to have an impact on the EPA?

DR. TALA HENRY: Absolutely. We craft the charge questions typically around the areas where we know there may be uncertainty, and we really do want the recommendations or advice from you. This available data thing is quite a dilemma sometimes, and maybe you all who are experts in a specific thing know of things we just don't know of or don't come up on searches and so forth, so we're always looking for anything else that you might have, certainly advice.

We do a lot of modeling, as you probably have ascertained here. So, again, there are approaches – but, bear in mind, if you have a -- one thing we really do ask is if you do have an idea about another approach or additional information needed we would greatly appreciate if you could show us where that is because we don't have the ability here to create data or require additional testing before we finish this.

But we take away very carefully what you say here now, but of course the final report is the final report. So we won't make any final decisions around changes or so forth until we see that, but I think we get a lot of useful feedback from these discussions, and we can go back and start thinking. We have all the public comments that we've received, so we'll be working on those while we're waiting for your final report.

But then we basically have to take some time there and look out the totality of the comments and, in particular, though, as a panel of experts, your input and recommendations, and then we decide if and how we can revise the assessment, and it will become then a final risk assessment.

So we have at least 90 days while you're working on your report, but we will be busily looking at some of the other things and contemplating what we hear here the next two days.

DR. STAN BARONE: Just to piggyback on Dr. Tala Henry's comments, you should also know that the OPPT website also lists the previous risk assessments, previous drafts, and the peer review comments, reports that we receive, and the response to comments documents. So that's a key aspect to the final peer review record is the response to comments document that goes along with the final assessment.

So you have -- you can also look to

that sort of record, and in response to your recommendations and peer review report there will be a response to comments document that includes response to public comments as well as the peer review comments.

DR. KENNETH PORTIER: Anyone else on the panel have a question? Dr. Thayer.

DR. KRISTINA THAYER: Sorry. There might not be much that you can say, but in terms of some of the language with the TSCA reform bill that's being floated, I imagine that this would sort of have impact on the way you might do business, and I was sort of wondering if there's anything you can speak to in terms of how it might impact some of the, you know, current proposed language, and then sort of what you might do if it, sort of actually pans out in the interim.

DR. JEFF MORRIS: So if Congress passes a bill and the president signs it, then one of the first things that we'll do this summer will be to take that bill and break it down and have discussions with everyone interested in all the issues that have been raised, whether it's prioritization, or safety standard, or review, etc.

So until we see something that's actually a law, I can't say specifically what we'll do; I'll just say that over this summer/fall, we'll begin that dialogue with everybody involved about how a new law will affect the assessment process and, you know, both the process for developing the assessments as well as their use in decision-making. That's about all I can say right now.

DR. KRISTINA THAYER: I have another question, but I can wait.

DR. KENNETH PORTIER: No, go ahead.

DR. KRISTINA THAYER: Okay. So the other one sort of gets at when you're sort of in the problem formulation and then you sort of see glaring data gaps. I was sort of wondering about sort of whether you've thought about how you might sort of leverage resources at the National Toxicology Program or, you know, research resources within the EPA to try to fill those data gaps when you're, you know, early on and they've been identified.

DR. TALA HENRY: We also have some authority under TSCA, as well, to gather data. It is at this time under the current TSCA a long arduous process, however. But if you looked around at all on our website you may have noticed in a group of flame retardants that we're assessing, there was one group in particular where when we sat down and really tried to break it down the right kind of information -- it was hazard information in particular -- just was not there. So, in that case, the result of the problem formulation was not so much an analysis plan for a risk assessment, but a data needs assessment.

And we are currently using our current TSCA authority to go after getting that data. Now, obviously, that will delay the risk assessment for some time.

With regard to NTP, we're in close contact with them. For example, they are doing some additional -- some of the more novel and newer approaches, not all the in life studies on one of the -- another of these flame retardants. And so we have a discussion -- I think it's next Wednesday, in fact -- to get an update on the status of that ongoing research. And, of course, anytime that would be available, we would very much appreciate using that.

And, again, I think bromopropane is an example where we worked across federal agencies, in particular with ATSDR as well as NIOSH, and I'm pretty sure you've seen that we did in fact harmonize quite a few things with NIOSH as far as some of the cancer dose-response modeling and so forth. So we're again trying to do the good federal collaboration-type thing.

And, of course, our own agency, the Office of Research and Development, can be very helpful to us, as well. And in several of the assessments, including this one, they were involved with us to help bolster not only some of our dose-response modeling, but were trying, I think I mentioned this last time, to adopt as much as possible or otherwise adapt some of the systematic review approaches that our IRIS Program has put in place, rather than reinventing the wheel.

But again there they also, like I mentioned, they have a PBPK modeling group of which some of our folks in my division are a part of, actually, across agency, so we do try to tap whatever resources within EPA or the federal family as much as we can. I would say in my career -- I would say we're more coordinated now than probably ever that I've seen.

DR. KENNETH PORTIER: Dr. Schlenk.

DR. DANIEL SCHLENK: Yeah, actually, Dr. Thayer asked the same question I was going to ask, but I just want to twist it a little bit more. So based upon the constraints that you have with the Work Plan, would it help you if we identify data gaps that aren't necessarily written into the Work Plan?

And I'm thinking more in terms on the eco side because, obviously, you're driven by what you can get data-wise, but also you're also limiting it to bioaccumulative and persistence in terms of that component. If we can identify data gaps that normally wouldn't be identified in problem formulation, would that be something you would be interested in, I guess?

DR. TALA HENRY: Always interested in more, you know, information or views. I guess if it was during problem formulation now that we have that step, it would be useful to -- the reason we put that step in place is so that we could identify potential gaps, or data needs, or whatever earlier in the process.

We learned from our first five that when you get to this point it's not the best time to find out that there might be a whole other use, or some other toxicity information, or whatever. So, again, those have a public process and so forth, so the earlier, the better, but sure, I mean, we're always trying to be -- and as I understand it, if we get new TSCA, there's potentially a broader scope of what we need to consider, so of course.

DR. KENNETH PORTIER: Okay. I think at this point we'll move on to the presentation. Oh, I'm sorry, didn't see the hand.

DR. HOLLY DAVIES: Hi, this is Dr. Davies. I wanted to ask you -- you mentioned kind of the short term, what EPA plans to do in the next 90 days, and if you could speak to longer term, for instance, in the introduction where it says EPA proposed a new rule to list 1-bromopropane as an unacceptable substitute in adhesives or aerosol solvents, but that rule hasn't been finalized yet. So if you could speak to like how this is going to be used in your TSCA authority to limit use …

DR. TALA HENRY: Okay. That rule in particular is an air -- under the Clean Air Act. The Agency also was petitioned to add bromopropane to the hazardous air pollutants, so again that's in another office.

However, we worked very closely with

them on this assessment, so they're familiar with it and we are familiar with them. So as far as that particular SNAP rule, as well as the HAP listing, the Office of Air is working on those.

But for the scenarios for which we found risks here under TSCA, you know, we need to finalize the risk assessment, but we're already thinking about what type of risk reduction activities should probably be taken around this chemical. And it would follow very much on the heels of -- right now we're developing rules under Section 6 of TSCA to limit, or prohibit, or -- there's a myriad of things you can do under Section 6 for a couple of the other chemicals that we found risks for, so TCE, and the MP, and methylene chloride, all for different uses.

We are pursuing regulatory action under TSCA now by way of rule-making, and that's a whole process in and of itself. So, again, here I envision that once this -- actually, the work will start before it's final, but we would take the same path and try to reduce risks where found.

DR. HOLLY DAVIES: And this also relates to the new TSCA, which you might not be able to comment on because there's very, you know, the two-year deadline for finalizing rules, and the deadlines are much shorter than has been. I don't know if you can comment on that.

DR. TALA HENRY: Only that then they're law.

DR. JEFF MORRIS: I think I would just add, I mean, current TSCA, new TSCA -- the TCE example is very instructive, and I think illustrative of the path we would take in that once we identified risks in the assessment the first thing we did was pull stakeholders together in a workshop to identify a path forward. And to the extent that we can get voluntary measures in place to reduce risk, that's the first step.

And in that particular case, there was one use that a manufacturer agreed to reformulate out of. And then what was left, and we didn't achieve voluntarily, we then moved forward with rulemaking. And so to get to your question, I think the notion is to the extent that from the time we do problem formulation up through issuance of final risk assessment and beyond, to the extent that we can begin the discussion about how we address the risks that are articulated in our documents, then that will help us achieve risk reduction in as timely a manner as possible.

MR. STAN BARONE: So one other additional point on coordination with other parts of the Agency and other programs with our toxics release inventory, we're also coordinating with them for many of the work plan chemicals that are not currently collecting TRI data. So again, we'll be looking at TRI collection of data. And 1-BP is one of those examples where it was not listed on TRI and will be listed in the not-too-distant future.

DR. KENNETH PORTIER: Any additional questions? If you raise your flag like that, turn it so I can see it. It was thin. I didn't -- all I saw was a line. I missed it. I apologize for that. That was Dr. Davis who led those questions.

I think at this point we'll move on to the presentation. Dr. Anitole and Dr. Macek will be presenting an overview of the draft for risk assessment. Dr. Anitole.

DR. KATHERINE ANITOLE: Okay. Thank you. So good morning, everyone. My name is Katherine Anitole. And I am the co-lead for the 1-BP Work Plan Chemical Risk assessment work group. And today I will be presenting -- Greg and I will be presenting a brief overview of the risk assessment for purposes of this peer review meeting.

So as was previously mentioned, in March of 2012 EPA identified a work plan of chemicals for further assessment under TSCA. And 1-BP was one of those original 83 work plan chemicals that was initially identified. And this was based on high human health hazard concerns due to its toxicity profile and exposure concerns due to its use profile and physical chemical properties.

So, next slide. I don't know if this is working. There we go. Okay, so again, this presentation will be an overview of the work plan risk assessment. And it's divided according to the peer review charge questions that outline the key science issues that we would like the panel to consider. For each slide, you'll be able to see which charge questions the information is linked to at the top of each slide. And then at the end of the presentation, we will entertain questions and points of clarification.

Next slide, please. So the next two slides refer to Charge Questions 1-1 and 1-2 relating to the background and scope of the assessment. Briefly, the physical-chemical properties of 1-BP; it is a colorless, volatile liquid with high vapor pressure and a low boiling point, low flammability, and no explosivity. It also has low environmental persistence with possible long-range transport via the atmosphere. It has moderate water solubility and high mobility in soil and can therefore migrate rapidly through soil to groundwater. Biotic and abiotic degradation rates range from days to months.

So these physical chemical properties are actually important considerations because they help to inform the scope of the assessment. And they provide a rationale for why our assessment doesn't include an assessment of ecological risk. And they were also input parameters that we used to inform the exposure modeling. We'll discuss this more on the next slide.

So this diagram is the conceptual model for 1-BP and depicts the process and approach we took for the risk assessment, illustrating the uses and pathways that may result in exposure. We'll briefly walk through the conceptual model. And then we'll spend some time going through each section in more detail on the technical approach, and the methods we used as we go forward in the presentation.

So during scoping and problem formulation, we considered all known TSCA uses for 1-BP. And we focused on those which involved products with high 1-BP content and those which are emissive and exhibit a high potential for worker and/or consumer exposure. The shaded areas, which aren't showing up very well on this, sorry, but they do in real life. The shaded areas on the conceptual model indicate the exposure pathways that were included in the risk assessment, and the unshaded areas are those that were not. So, I'll go through the unshaded areas first.

As explained on the previous slide, both the physical and chemical properties and environmental fate combined with a low ecological hazard profile, the ecological and environmental risks were not assessed. So you can see that on the top of the slide under the receptors. Also, exposures via the dermal and oral routes were not assessed. And for dermal exposures, we are aware that there's a potential for dermal exposure and dermal penetration. But dermal uptake is likely to be low because of the high volatility of 1-BP, and it will cause it to evaporate quickly if it comes into contact with the skin.

In addition, because there is limited toxicological data via the oral and dermal routes, and since there is no adequate PBPK model for route-to-route extrapolation, risks via these routes of exposures could not be assessed. And you can see that under the column headed exposure routes.

We also did not assess risks to the general population that may result from environmental releases of 1-BP. And this can be seen in the conceptual model where there are dash lines from the manufacturing box. This is because there is currently no reliable exposure data for calculating general population risks. At the time of the assessment, 1-BP was not on the TRA database, and it is not currently on the national emissions inventory or currently listed as a HAP. So therefore, we only focused our assessment on occupational and consumer settings via the inhalation route.

So for the occupational activities and uses, again, 1-BP is a high production volume chemical. It's used in numerous solvent applications in the occupational setting, which includes spray adhesive, dry cleaning, and degreasing uses. Exposures to 1-BP in the occupational settings were considered to be both chronic and acute in nature, and therefore we identified endpoints of concern used to evaluate chronic and acute exposures. And that can be found in the last column under effects.

For consumer uses, we identified 1-BP uses in those that involve aerosol spray adhesive spot removers, and cleaning and degreasing products, and many of these were identified to contain between 62 to 100 percent of 1-BP. Exposure in consumer settings were considered to be acute in nature, and we identified endpoints of concern to evaluate acute exposures. And those again can be found in the effects column and included reproductive and developmental toxicity following acute exposures.

So now that you are familiar with what is covered under the scope of our assessment, we will walk you through the technical approach for each one of the segments of the conceptual model for the remaining of our presentation. And Greg Macek will discuss the exposure assessment next.

MR. GREG MACEK: Thank you, Kathy.

Good morning; my name's Greg Macek. And just a quick clarification, Dr. Portier's introduction, I don't have a PhD, so. I am a chemical engineer. I work in the Risk Assessment Division of Office Pollution and Prevention Toxics. And I work on exposure assessments for the new and existing chemicals that EPA reviews under TSCA. And I've been the project manager for the occupational exposure component of the 1-BP work plan chemical risk assessment project.

Today I'll be presenting some of the details of the occupational exposures assessment, and I'll also be covering the consumer exposures assessment that we did. And then, Kathy will cover the remaining parts, the hazard and risk parts. I'd like to keep it at this slide which has the conceptual model. The Occupational Exposure Assessment is discussed in Sections 2.1, in Section 2.1 of the Risk Assessment, and it relates to the peer review charge questions 2-1 through 2-4. It's referring to the conceptual model.

There were six uses in our scope, as you can see depicted there. There's 1-BP used in spray adhesives, 1-BP used in dry cleaning. We covered both a scenario where the 1-BP is used in the spot cleaning as well as in the dry cleaning machine. And then we also covered separately standalone 1-BP just used in spot cleaning. And then we covered three types of degreasing operations, vapor degreasing, cold cleaning degreasing, and aerosol degreasing. Next slide, Kathy?

Oh, thank you. For the Occupational Exposure Assessment, we had three main objectives. The first was to estimate the number of workers exposed to 1-BP in those different uses that we assessed. The second, which is the objective that we spent the bulk of our time on the project was estimating inhalation exposure levels for workers at these facilities for each of those different uses.

As previously discussed, the risk associated with environmental and durable exposures were not part of the scope of our assessment, so we were focusing on the inhalation route, estimating levels of inhalation exposure.

And then the third objective, using the inhalation exposure levels that we had estimated, we calculated acute concentrations and then chronic concentrations, which the average daily concentration and lifetime average daily concentration because those were the values actually used in the risk assessment. So those were the three main objectives. I'd like to break out the second one in a little bit more detail because that was the one, by far, that we focused on the most.

And within that objective of estimating inhalation exposure levels for those six different uses, following EPA assessment exposure guidance, we wanted to present both a central tendency and a high end exposure. And for the purposes of this assessment, we defined essential tendency as 50th percentile and for the high end, 95th percentile. Second, we wanted to estimate exposures for workers, and we defined workers as those more directly involved in handling the 1-BP; for example, sprayers in the spray adhesive use who could manually spray apply the adhesive.

And then we also had a second category, which we called occupational nonusers, and those are other workers at the facility, you know, who have, you know, job activities but are not as directly linked to the 1-BP as the workers, and I'll describe how we did that analysis for each use. And then we also wanted to see if we could account for the presence of engineering controls by estimating exposures pre-EC, before engineering controls were implemented, and then post-EC, after engineering controls were implemented to reduce exposure just to see what the effect on exposure would be and then also in the risk calculations.

So I'll go over briefly what we did for the first objective, which was estimating number of workers. We used a top-down approach, basically three main steps in following this approach. The first is identifying the NAICS codes for the industry as standards. And NAICS stands for North American Industrial Classification System. And in doing this particular assessment, 1-BP, where we were following work that was done on TCE and within that TCE assessment, they had done a lot of work on identifying NAICS codes for vapor degreasing, for example.

So that was the starting point, getting a NAICS code, and the reason why we had to have the NAICS codes, because a lot of the worker data is organized by NAICS codes.

So we then went to data sources of employment, UFs from the US Census and Bureau of Labor Statistics. And that resulted kind of in a pretty large high estimate of number of workers because we were still at, like, total for that type of NAICS code for that use category. The third is probably the most important step was refining that estimate of total by applying a factor, you know, data we had gathered to estimate the market penetration of 1-BP within that use to refine that high estimate down to, you know, a 1-BP specific estimate of the number of workers.

For example, for dry cleaning, we had a market penetration estimate of 1.1 percent, which came from a survey that was conducted in 2012 that indicated that 1.1percent of respondents used Drysol, which is a formulation containing 1-BP. So there's more details on the approach and you know, the specific data sources we used in the actual risk assessment report. So applying that method produced those results that are depicted there on the slide.

For cold cleaning, we didn't really have sufficient data to develop that third step in the approach of the market penetration, so we don't really have an estimate for cold cleaning at this time.

Next slide. Okay, now I'd like to focus on the second objective, estimating inhalation levels in these workplaces associated with these uses.

And this was, again, where we spent the bulk of our time. The method involved first conducting a comprehensive literature search for monitoring data for each of the uses covered in the scope. In Appendix G of the risk assessment provides more details on the method we used to search for monitoring data, including the data acceptance criteria we applied.

Second, in addition to the monitoring, we did exposure modeling to augment and compare with the exposure monitoring data. And as part of the modeling approach, that also included a targeted literature search focusing on the key parameters in the model to see if we could find data to come up with an estimate of what the value for 1-BP specifically would be for that modeling parameter.

For example, the generation rate, you know, from the admission source, that was something that was a key parameter, probably the most important, and that was something, you know, we did try to find 1-BP specific data to develop an estimate to use in the modeling.

With that as background, I'm now going to go over five of the use, five of the six. I'll just present some of the details associated with the use, how it's used, the worker activities. I'll go over the monitoring data part of the assessment and then the modeling and modeling results. So I'll do that for five. For the purposes of this presentation, I admitted the spot cleaning only of dry cleaning use just to, you know, make a cut there, but that is described in detail as with the others in the risk assessment report.

Next slide? So the first use category I'll cover is the spray adhesive use. For spray adhesives, 1-BP is used in spray adhesives for foam cushion manufacturing, for example, in the furniture industry. During the foam cushion manufacturing process, spray guns are used to spray apply an adhesive onto flexible foam surfaces.

For this use category, there were three NIOSH health hazard evaluation reports which provided comprehensive information on worker exposure to 1-BP from spray adhesives in foam cushion manufacturing. And two of these three HHEs also compared exposure pre- and post-engineering controls. NIOSH did an initial assessment, monitored for a number of different job categories at the plant, made recommendations for engineering controls, and then came back later and did a follow-up assessment, and measured exposure. And you know, you see there's a way to compare the exposure levels pre- and post-engineering controls, and that was for two cases there.

So in our analysis of the monitoring data, again, relating back to our objectives where we wanted to estimate exposure to workers who more directly handle and then differentiate that from occupational nonusers. In this particular case, we had three categories that we categorized the data in. We provide a specific appendix that dealt with the spray adhesive monitoring data analysis, but for this assessment, you know, the sprayers were the ones manually spray apply the 1-BP adhesive.

The nonsprayers were workers who were not sprayers but either handled the 1-BP adhesive or spend the majority of their shift working in an area where spraying occurs. For example, in one of the NIOSH HHEs, one of their studies, it indicated spraying occurs in the assembly and covers departments. And so we, in our analysis of the NIOSH data, assume workers in these departments who do not perform spraying, we put them in the category of nonsprayers. We thought, you know, have a higher exposure potential than the occupational nonusers but not obviously in the sprayer category. So for this one, it's a little different because of the detail that was available in the NIOSH HHEs on what they were monitoring in the workers' categories. We were able to break out three categories.

And then the occupational nonusers, workers who did not regularly perform work in an area of the facility where spraying occurs. For example, in the same study I referenced for the nonsprayers, we assume the workers from this study in the saw and sew departments at the furniture manufacturing plant were categorized as occupational nonusers. So that's the way we analyzed the worker categories.

And then the next slide shows the results from the monitoring data collection. This slide presents a plot of the monitoring data. We used a box-and-whisker plot here in this slide. And these type of plots provide a method of graphically displaying data in a way that allows easy visualization of the overall range of data and key percentiles. So you'll see, you know, there's a plot for each of those three categories of workers, and then you can easily see there, you know, where the different percentiles are, the 50th and the 95th. And these are all pre-EC in the document itself, we have the post-EC results there. So just for the purpose of presentation, presenting one example plot from the analysis we did.

So for the sprayers, you can see the 50th percentile. It's actually 131, so you see that between the 100 and 150. And this is pre-EC sprayers. Ninety-fifth was up to two fifty-three parts per million. Now the post-EC, when NIOSH did the follow-up assessment, concentrations dropped six to eight times lower for the sprayers at the 50th and 95th, and, again, I'll refer you to the document where actually see the post-EC results. And then the nonsprayers there, the 50th, you can see it's, again, between that 100 and 150.

At 127, the 95th percentile was 211, and again, similar types of drops when NIOSH did the follow-up assessment; 6 to 8 times lower at the 50th and 95th. And then the third plot there is the occupational nonusers. The pre-EC results, the 50th percentile was 3 parts per million; 95th was 129. And then the post-EC dropped way down for the 95th percentile by a factor of 24 from that 129 value. And it was already a 3 for the 50th, so it did drop by half for the post-EC, the occupational nonusers. So that's for the spray adhesives and again, more of the details are in the document itself, including the post-EC.

The second use category on the next slide that I'd like to cover is dry cleaning. And as I mentioned, we covered both dry cleaning where it's used in all aspects at the site, and we also, kind of building initially from the TCE assessment, we assessed standalone where 1-BP is just used in spot cleaning. And from there, we built the assessment to cover this broader case where it could be used in the spot cleaning in the machine itself.

So it's a solvent used in dry cleaning machines and in spot cleaning. The workers are exposed, you know, during the spot cleaning step when adding solvent to machines, removing loads from the machines, and then in the finishing and pressing areas where there could still be some residual 1-BP on the garment. We had monitoring data available from a NIOSH health hazard evaluation of 1-BP use in four New

Jersey commercial dry cleaning facilities.

Again, our analysis of the data, you know, looking through the information there, we separated into the two categories in accord with our objectives. Workers were the operators of the dry cleaning machines. Occupational nonusers are workers who did not spot clean or operate the machine. And again, that's the advantage of a NIOSH HHE, which has a lot of detail that facilitates that kind of analysis.

Let's see. So next slide shows the results of our review of the monitoring data that we collected based on that data in the NIOSH HHE. Again, we used the box-and-whisker plots, two categories of workers there. These are the pre-EC results. There was no monitoring data that we could categorize as post-EC in this particular situation. For workers the pre-EC results, the 50th percentile was 29.4 ppm, so you can kind of see that on the first plot there. And then the 95th percentile was 50. and for the occupational nonusers, the pre-EC 50th percentile was 12.1; 95th percentile was about 21. And again, as I mentioned, we didn't have monitoring data for post-EC for the monitoring aspect of the dry cleaning assessment.

Now the next slide, in addition to monitoring data, we also did exposure modeling to estimate 1-BP inhalation exposures at dry cleaners. We used a multi-zone modeling approach to count for 1-BP vapor generation from multiple sources within the dry cleaning facility; in particular, three distinct locations. The first were the spot cleaning would take place. Second is at the dry cleaning machine itself.

And then third, in the finishing and pressing areas. And the multi-zone modeling approach was an expansion of the near-field, far-field modeling approach where there's a single emission source that we had used in TCE. So we kind of benefited from the work that was done in TCE, brought it into this assessment, and then built from there. And that was one thing we did in particular for this 1-BP is expand it to count for three different zones.

On the dry cleaning model we used, it's based on four mass balance equations. There's one equation for each of the near fields where the emission source is located. And then there's also an equation for the far field. But 1-BP vapors generated in each of those near fields, the spot cleaning dry cleaning machine and then finishing, and so that results in occupational exposure to workers who would be in those near-field zones. It then dissipates into the far field, and which is the facility space surrounding those near fields resulting in occupational nonuser exposures.

In developing our modeling approach, one of the keys was sort of constructing a worker's day in terms of estimating, you know, activity durations and how much time they might spend in a near zone, because they don't spend the entire shift in the near zone. So there's a portion of their shift that would be in the near zones to receive that concentration and then also into the far fields.

So we developed that for each of those areas, and that's something also described in the model. We had two separate appendices, J and K, which include details on the modeling approach that we used for all the scenarios as well as the parameters.

I think there's some good tables there that show you all the key parameters for the models, and what our estimates were, and what distributions we assumed, and what the basis for it is. So that can be something you can refer to in your review, hopefully, you know, we wanted to lay that out as clearly as we could.

The next slide depicts the modeling results. These are pre-EC. We used box plots here to present the modeling results. For the spot cleaning, that's a worker who would be in charge of the spot cleaning, so spends some time in that near field admission and then the rest of their shift in the far field. The results we got there, the mean, the 50th percentile was 1.8 parts per million, and the 95th percentile was 6.9.

The second category, we combined, so a worker who could be in the near-field zone where the machine is located and then also in the finishing area. So you see higher exposures estimated from the modeling there; 50th percentile is 7.4 ppm and 95th percentile, about 61 parts per million. And then the occupational nonusers, basically workers who would be in job categories where they'd spend their entire shift in the far field, and that was lower. It was the 50th percentile, about 0.9 parts per million; 95th percentile, 4.8.

And for modeling, what we did, just

made a, you know, an assumption that sort of a what if controls were applied with a 90percent reduction. So the post-EC levels would be a factor of 10 lower for each of those cases.

I'd like to cover the third category of the five I'll be describing, which is the vapor degreasing use. 1-BP is a potential replacement for chlorinated solvents in vapor degreasing. Vapor degreasing is an operation to remove dirt, grease, and surface contaminants in a variety of metal cleaning industries.

There are several types of vapor degreasing equipment. They include batch degreasers, in line degreasers, airless vacuum degreasers. We obtained exposure monitoring data from several sources, which include journal articles, NIOSH HHEs, OSHA IMIS database, data submitted to the EPA SNAP program. Most of the data that we did collect for monitoring data were for batch open top vapor degreasers.

And we were able to do some categorization here in accord with our objectives; categories of workers, what we define as workers who operate or perform maintenance tasks on the degreasers such as draining, cleaning, and charging, and then occupational nonusers who do not regularly handle the 1-BP or operate the degreasers.

So we were able to utilize the detail in some of those sources in our review to categorize into these two categories, and that is described in more detail in the risk assessment. And then there was also some detail available to also categorize some of the data as pre-EC and post-EC to give some indication to what levels might reduce to after engineering controls are implemented.

So the results of the monitoring data review for the vapor degreasing use are depicted in the next slide. Again, the box-and-whisker plots, pre-EC results here, two categories here, worker, occupational nonuser. And the 50th percentile for the worker, 8.2 parts per million; 95th percentile was about 48.

For the occupational nonusers, 50th was 0.44 and 95th was 4.9. Not depicted in this presentation slide but discussed in the risk assessment is the post-EC results. Post-EC was 5 to 6 times lower than pre-EC for workers at both the 50th and the 95th, and the post-EC was many times lower for the occupational nonuser, 20 to 200 times lower. So you'll see the tables in the risk assessment; Section 2.1 will have those values in there.

Now we also did modeling for this use category, vapor degreasing, the next slide. And this one, similar type of model but simpler where it's a near-field/far-field model based on two mass balance equations; one for the near field source and one for the far field. In this case, it's an easier case to model because there's just one single emission source, the emission coming from the vapor degreasing equipment itself as depicted there in the diagram.

You'll see there, you know, in the part that represents the degreaser. Coming up from that is G; that's the generation rate. And that was, as I'd mentioned previously, one of the key parameters for modeling. And so that was one as part of our data search objectives we tried to find 1-BP specific data to develop that estimate as part of the modeling. And again, I'll just refer you to Appendices J and K, which have more detail on the modeling approach and then also the parameters.

So again, as I mentioned, that importance of that vapor generation rate parameter, in this case, we did in our search of data found a source from the California Air Resources Board (CARB), and they had some emission factors that they had developed from survey of facilities. I believe it was 213 facilities, and it had a 1-BP emission factor. So I mean, that was very useful for us to use in our analysis as a starting point in developing the modeling approach.

And for post-EC, if you're familiar with the TCE assessment, as I mentioned, we did benefit from that work as we started our 1-BP work, so brought some of that in. And they had some data on efficiencies for both engineering controls where there was data on an LEV system that had been installed for an open top vapor degreaser and showed 90 percent reduction. So we used that as an assumption in our modeling of effectiveness of engineering controls.

And then there was also another source that estimated 98 percent reduction from equipment substitution where an enclosed vapor degreasing system was installed. So it showed 98 percent reduction before and after. So we just added those two cases, a 90percent and a 98 percentile to see with the model to estimate pre-EC without those assumptions and then post-EC with those assumptions. The whole range of values was provided for the risk assessment calculations.

And for the modeling, you know, for all the modeling we did, we did a Monte Carlo simulation to capture variability. And again, I refer you to those tables in the appendix, K, which has the values we assumed, including the ranges and the type of distribution we assumed for that parameter. So that was part of developing the Monte Carlo simulation for these, and that's described in more detail there.

So next slide shows the results of the modeling. Again, we had the box plots. And these are the pre-EC, the 50th percentile for workers, 1.8; 95th percentile, 25.6; occupational nonusers, the 50th percentile, 0.7; and 95th percentile was 9.4. And again, as I mentioned, with the 90 and 98 percent reduction assumptions, that would then result in 10 times to 50 times lower concentrations for the post-EC. And there's tables in the Section 2.1 that give those results.

Okay, the next use category, and this is the fourth of the five. Again, I just skipped the spot cleaning alone at a dry cleaner from the six. So cold cleaning degreasing, and cold cleaners is a non-boiling solvent degreasing unit. Types include batch loaded, maintenance cold cleaner, as well as where the dirty parts are cleaned manually by spraying and then soaking in the tank. After cleaning, the parts are suspended over the tank to drain. A dip tank design provides cleaning through immersion with an immersion tank equipped with agitation. Emission sources of 1-BP from this type of degreasing similar to vapor evaporation of the solvent, from the solvent to air interface, carryout of excess solvent on the clean parts and then evaporative losses of the solvent during filling and draining of the machine.

So again, followed the same approach as for the other use categories. First, what monitoring data can we find that we can associate with cold cleaning of 1-BP? The next slide, we did obtain OSHA IMIS data for two facilities. The first facility manufacturer's decorative and church lighting using 1-BP to clean parts in an immersion process, an area with general ventilation. The second facility manufactured parts for the aerospace industry, used 1-BP in a degreasing tank equipped with a spray nozzle. So those are data that we collected that we associated with cold cleaning based on the descriptions and the information that we had.

Next slide, again, similar to previous presenting the data with the box-and-whisker plot. For the worker and the occupational nonuser, and this is for the pre-EC. We had 50th percentile at 8.2; 95th, about 48 parts per million; and the occupational nonusers, the 50th percentile was 0.44 and the 95th was about 5. And we did have post-EC. Let's see. Oh, I'm sorry. I got my presentation mixed up.

Pre-EC 50th percentile was about 14 and the 95th percentile was 47. This is for cold cleaning monitoring data. Pre-EC, we just had one data point at 2.6 parts per million. We did not have post-EC for this use. So a little bit more limited monitoring data for the cold cleaning.

We also did modeling, next slide, for this use category. Again, similar to the near-field/far-field, just a single emission source for the near field and the model approach, input parameters for cold cleaning were similar to vapor. For the key modeling parameter of the vapor generation rate, we referenced EPA P-42, a compilation of air pollution emission factors, which contained emission factors and included emission factors for several solvent cleaning operations including cold cleaning and vapor degreasing. So that was, again, another helpful reference of 1-BP specific to the operation we were assessing to extract some data to develop an estimate for generation rate for the model.

The next slide shows the modeling results. Again, these are box plots. Plots are pre-EC results. For workers, the 50th, 0.44 parts per million and 95th percentile was 7.8; and for the occupational nonusers, the 50th was 0.17 and the 95th was 2.9. Again, those are pre-EC results. Post-EC, we did the same assumptions that we used for vapor degreasing; two cases, 90th percentile and the 98th percentile, which would then reduce the exposure levels by a factor of 10 and 50. And so those results are presented in the Section 2.1 and again, all were provided for risk assessment calculations.

And in the fifth category of the five that I want to present here was aerosol degreasing. And that's a use involves use of an aerosolized solvent spray typically applied from a pressurized can to remove residual contaminants from fabricated parts. The aerosol droplets collect on the part and then drip off, carrying away any contaminants and leaving behind a clean surface.

For this use category, we obtained monitoring data for two studies. Keep it -- yeah, thanks, Kathy. Now these were test scenarios where they were designed to simulate aerosol degreasing applications, so, you know, definitely yielded useful information for our review. One of the studies in particular tested an exposure scenario where the aerosol degreasing occurred first inside a non-vented booth and as a representative of pre-EC and then they also conducted post-EC using a vented booth.

And the next slide shows the results of the monitoring with the -- we just had data for the worker category, and these are pre-EC results. The 50th percentile was 16 parts per million, and then the 95th was at 31 parts per million. It's not depicted on this slide, but we had the one post-EC point, which was at 5.5 parts per million, so you can see how that's lower than the box depicted there for pre-EC conditions. And that was a reduction from the 95th percentile about 6 times.

And as with those other scenarios, we did modeling, which involved a similar approach, the near-field/far-field solving two mass balance equations, one for the near field, one for the far field. For this one, we had to look at it a little bit differently than the other sources. In this particular category, we assume 1-BP vapors enter the near field in bursts where each burst results in a sudden rise in the near field concentration of 1-BP, which would then decay over time. And we assumed that there would be seven applications in an eight-hour workday, so one for each hour. Each hour, there would be the burst, and then the decay. And that's described in more detail in the assessment itself. And we also did the Monte Carlo simulation to capture variability.

And results of the modeling are depicted in the next slide. And for these, for the worker category, the 50th percentile was 2.2 parts per million; 95th percentile was 6.8. And then the occupational nonusers, the 50th percentile was 1 parts per million; 95th, 3.4. These are pre-EC. The post-EC, we just did one case, assuming a 90 percent reduction and what would be the corresponding level of exposure and then subsequently for the risk. And that's not on this slide but again, as with the others, it's in the risk assessment.

So the next two slides present summaries of the data and results I've been discussing for each of the five uses. The first summary's presenting with the graph depicted there, and you'll see on the x-axis, there's a separate plot for each of the five uses that I've described in this presentation. We could've also easily added the sixth. So and then on the y-axis is the eight-hour TWA concentrations in parts per million. And then we present comparisons of the monitoring results and the modeling results.

Now, for 1-BP, we did not do modeling, and there's a couple reasons for that. One is attributed just to the detail that was in those NIOSH health hazard evaluations, which really provided sufficient data for all of our objectives where we wanted to estimate by worker category, you know, 50th and 95th percentile, pre- and post-EC. So that was part of it.

Also, the near field, we didn't have a modeling approach at the time developed that would cover the type of exposure that would occur in a spray adhesive where the 1-BP would be moving through the facility versus some kind of stationary area which lent itself more to the near-field/far-field. So it's a little more complex situation, so given that we already had that monitoring data, we didn't do it for this particular use, but we did it for all the other ones. And you'll see the comparison of results there.

The next slide presents also summary results, this time in table form. Going down the first column is those use scenarios, the five I covered in the presentation, and then the air concentration broken down into central tendency, and high end, and then within each, the worker and occupational nonuser. So you have that for the 50th percentile and then the 95th percentile. So those numbers there are the monitoring data, and these are pre-EC.

So these are the same numbers I read off when I did my use by use part of the presentation, but they're depicted there for easy visualization in a table form. Now that was the second objective of the exposure assessment for occupational; by far, what we focused the most on.

The third objective then was calculating the values that could then be used for the risk calculations. And the next slide shows the equation that we used for acute exposure concentrations. You see the equation there, along with the parameters, and the values we assumed for those parameters. We also did, for the consumer exposure, which I'll get to in a minute; we estimated acute exposure except in the case of the consumer.

We assumed a 24 averaging time based on the fact that a consumer could be in their home for 24 hours, potentially, whereas, the worker would be there at the facility assuming for eight hours, so that's the difference between the acute for workers and consumers.

And then we also calculated, shown in the next slide, values of ADC, which is the average daily concentration, and then the LADC, which is the lifetime average daily concentration. So I have the equations we used depicted on that slide, the parameters, and then the values that we assumed for each of those parameters.

The main difference between the average daily and the lifetime average daily is that the average daily exposure averaged out over the working lifetime of the worker. For this assessment, we assumed a value of 40 years in our calculations, and then the lifetime average daily concentration is the exposure averaged out over the total lifetime of the worker, which for this assessment we assumed 70 years for the calculations. So that was the endpoint of the exposure assessment, putting those exposure concentration and levels obtained from the monitoring and modeling, putting them into these values and then that was the inputs for the risk calculations.

Now I'd also like to cover the consumer exposure assessment we did, the next four slides. I'll briefly describe the work we did on the consumer exposure assessment, and these relate to Charge questions 3-1 to 3-2, and this portion of the presentation corresponds to Section 2.2 and Appendix L of the assessment.

So our objectives for the consumer, first, identify consumer uses of 1-BP and to do that, we did a search of available literature. We were able to identify three consumer uses, and that's 1-BP used in aerosol spray adhesives by a consumer, aerosol spot remover, aerosol cleaner and degreaser. Again, similar types of uses as we covered in occupational, but these would be in potentially in consumer products where a consumer could do it in their own home. And also, our second objective, estimate exposure levels for those consumer uses and again, following EPA exposure guidance to present a central tendency and a high end. And in this case, the 50th percentile was used for the central tendency; a little difference between occupational use, the 90th, and that was based on our best judgment of appropriate percentage based on the input data we have, and that is covered in a little bit more detail in the report.

One difference to highlight, as well, between the two assessments, occupational and consumer. For consumer, we didn't have monitoring data, so we used modeling approach to estimate exposure levels. We also didn't have sufficient data to develop estimates of the number of consumers, so that's a difference from the occupational. And again, as I'd mentioned previously, we calculated acute concentrations using a 24-hour TWA.

The next slide shows some more details on the model we used. We used EPA's E-FAST model, and that model's routinely used within our office, Office of Pollution Prevention and Toxic, for our risk assessment program. It has been peer-reviewed, and within E-FAST is a module specifically for consumer exposure, so that's one of the modules within E-FAST. And that uses similar type of model and concept to what we were using in the occupational two-zone model. Zone 1 is the area where the product is being used, and then Zone 2 would be the remainder of the house.

And we used default values where applicable. Additional inputs were informed by EPA's exposure factors handbooks, and also we had consumer behavior inputs from a 1987 household solvent product use survey which helped us construct the individual scenarios with data on, for example, the amount applied for a particular type of use.

And the next slide shows, in table form, the results of the consumer exposure modeling. Down the first column is the different types of consumer uses that we covered and then air concentrations, both central tendency and high end, and then within each, user and nonuser.

So the next slide makes some summary points on the consumer exposure assessment that we did. And we did the estimates based on modeling. We estimated exposures for all the identified use scenarios that we identified with potential for 1-BP consumer use. The highest exposure potential was identified for 1-BP use aerosol spray cleaners and degreasers, and probably the key parameter that contributed to the higher exposure levels for some uses versus other uses was data on, for example, the mass product for that given use. And the appendices will have details on how we constructed each individual use, the parameters, and the values we assumed and the basis for them.

And so I think I'd made the point previously about we didn't have information to estimate number of consumers. So I think that covers the exposure component of the risk assessment, both the occupational and consumer, which resulted in the values that then were used in the risk assessment. And Kathy will cover those two parts of the assessment in her presentation.

DR. KENNETH PORTIER: Thank you. At this time on our agenda, we're due for a break. I think we're all due for a break. I have 10:42, so we'll reconvene at 11. And what I'd like to do when we get back is entertain questions on the exposure part to Mr. Macek, and then we'll move onto the second presentation, so prep your questions. We'll be back at 11.

(Brief recess.)

DR. KENNETH PORTIER: I think we almost have a quorum. Oh, yeah. I see two more over there.

So before we continue, I mentioned that my objective this morning is to get through the second EPA presentation and then questions before we break for lunch. So we may run a little bit beyond the noon hour. But I'll guarantee you an hour off for lunch, and we'll start a little later after lunch. And we've just clarified that with our DFO that we could do this.

At this point, I'll kind of want to open it up to any questions on the exposure presentation of Mr. Macek this morning. Do we have any questions? Starting with --

DR. JAMES BLANDO: Jim.

DR. KENNETH PORTIER: And remember to identify yourself so that --

DR. JAMES BLANDO: Sure. Jim Blando. I just had two questions on the exposure assessment.

You mentioned that you used the CARB emissions factors in the AP-42 emissions factors. And I was just curious if they were specific for 1-

bromopropane or if they were kind of a general overall VOC emission factor.

MR. GREG MACEK: Okay. Yes. Shall I say my name? Greg Macek responding and from EPA.

Yes, in those two cases that you reference, we did have 1-BP-specific data from those sources for use in the vapor generation.

DR. JAMES BLANDO: Great. Thank you.

And I just had one additional question, if I may, and this is just sort of a point of clarification. Earlier, you mentioned that the dermal exposure pathway was not considered for the reasons that you cited. And I was just curious. If there were some occupational exposure scenarios that are under consideration in this risk assessment, I was curious of how difficult it would be under your data collection rules to generate that information for specific occupational scenarios where that might be important.

MR. GREG MACEK: Again, Greg Macek responding.

Would this be measurements of dermal --

DR. JAMES BLANDO: Yes.

MR. GREG MACEK: -- exposure?

DR. JAMES BLANDO: Yes, because that was cited as one of the limitations, I presume, in why that was not performed.

MR. GREG MACEK: I mean, that is something we look for. There's much less dermal monitoring out in the literature sources in general than inhalation. And I mean, we didn't target dermal. We didn't target dermal specifically. We do have models that we use day to day in our PMN program that are for liquids that we use in new chemical reviews. And those can be used to estimate mass on the skin.

However, for this chem, because it's so volatile, I think we could develop an estimate of the mass of contact either on the skin or protective glove material. It would volatilize very rapidly. So the contact time would be low. And so we could develop from those models both an estimate of the amount of contact and the contact time. But I think it would be very low. So whether it would be there long enough for absorption to occur I think is a question because of its volatility.

DR. JAMES BLANDO: So just -- Jim Blando again -- just one quick follow-up on that.

If there were occupational scenarios

that involve occluded exposures, thermal exposures, do you think it would be possible to develop estimates based on that type of exposure?

MR. GREG MACEK: Sure. Greg Macek.

Can you clarify the occluded aspect of that?

DR. JAMES BLANDO: Where it's on the skin but it may not be exposed to the ambient atmosphere, there might be something over -- like clothing, for example, over.

MR. GREG MACEK: So there could be -- so that would reduce --

DR. JAMES BLANDO: Maybe --

MR. GREG MACEK: -- obviously, the evaporation --

DR. JAMES BLANDO: Right.

MR. GREG MACEK: -- rate.

DR. JAMES BLANDO: Right. Yes.

MR. GREG MACEK: I mean, I think that's something we could construct. A scenario, you know, the starting point would be the liquid models that we have that estimate the amount of contact. And then I think we'd probably have to gather more information on the type of exposure so that we could develop appropriate assumptions to apply, I guess, to the estimate.

So I mean, I always like to feel, you know, it would be a new methodology for us. So we'd have to develop it. But it seems like there's potential that we could do that.

DR. KENNETH PORTIER: Dr. Marty? Oh, wait.

DR. KATHERINE ANITOLE: I'm sorry. I just wanted to add that, even if -- Katherine Anitole -- even if we did have that information in a modeling format, that we still have an absence of toxicity data by the dermal route, and we don't have a PBPK model currently to do a route-to-route extrapolation. So there would still be some limitations even if we were able to get some sense of exposure via the dermal route.

DR. KENNETH PORTIER: Dr. Marty?

DR. MELANIE MARTY: Yeah, did you guys consider using CARBs emissions to then figure out what the emissions from a facility were to the neighboring community? Because that's CARBS. That's what they do. So they don't do occupational.

MR. GREG MACEK: Greg Macek, EPA.

You know, it comes back to the scope of the assessment. You know, I think, you know, we define the scope as those used categories and then, within those used categories, inhalation as the route. So we didn't include assessing releases to the environment for a general population. So I think that goes back to scope of the assessment.

So the CARB data was very helpful for the occupational because it gave some indication of emissions into the workplace. So we could use that as a starting point for the exposure modeling. But to estimate then the emissions from the facility, certainly, that would be a source we'd look at for that type of analysis. But it wasn't within the scope of what we had defined in the project.

DR. KENNETH PORTIER: Identify yourself.

DR. EVA WONG: Thank you.

This is Eva Wong. I'm an exposure assessor in the Risk Assessment Division. We would do general population exposed, but what we would need is representative data in order to fully flush out a good general population exposure assessment. And that is something we're lacking. It is not on the TRI list.

So we would need more information.

If you have information that could inform that, we would certainly consider that for refinement.

DR. KENNETH PORTIER: Dr. Gilbert?

DR. KATHLEEN GILBERT: Hi. This is Kathleen Gilbert.

I really appreciate the work that must have gone in to doing all those risk or the exposure assessments and the fact that you did a pre and post EC. Is there information about how common use of environmental controls is in terms of use with 1-BP?

MR. GREG MACEK: Greg Macek, EPA.

I'm turning back to members of our team who provide excellent support in our objective here. I think it was very limited, that information. So I can't really say anything specifically at this time.

DR. KATHLEEN GILBERT: So it's not required use of EC would -- when you occupationally use 1-BP?

MR. GREG MACEK: That's --

DR. JAMES BLANDO: There's no requirement. So there's no --

MR. GREG MACEK: Yeah, there's no

requirements that I'm aware of.

DR. KENNETH PORTIER: Okay. That's good.

Dr. Georgopoulos?

DR. PANOS GEORGOPOULOS: Panos Georgopoulos. I suppose we can ask questions about the scope as well as the exposure. With respect to the scope, I first of all, I would like to say I appreciated the challenge and those who worked on these calculations for the exposure. Pulling all this information together should be commended. I mean, there is no doubt about it. And clearly, EPA is facing an issue. They are both knowledge gaps and data gaps that need to be filled eventually. But nevertheless, the risks that are calculated appear to be quite substantial.

Nevertheless, the main issue that is a problem is linking those exposures to biomarker data, the before with the after to make sure that this is really happening. And the first question that I have for EPA, we looked at from the entire life cycle approach, and I believe that is chemical safety in all the research work that we are doing right now, we are looking at life cycle from manufacturing to transport all the way to disposal. And this, you had the nice graph up there, but you focused on a specific slide that involves occupational uses and specific consumer uses.

So this is a selection that seems reasonable to work with except that some of the information on the biomarker data in both NHANES and the national children study so that it lists the metabolite that's associated with bromopropane appears to be ubiquitous. I mean, and again, I understand there are issues whether it is specific to bromopropane or the other sources in the environment that are associated due to this metabolite.

But the question that I have, basically, have there been any thought or any work to try to interpret this data because when we see this -- and I think both in the public comments. I was happy because some of the same references that I was planning to bring up were pointed out by many people. Did you try to look at all, you know, what would be potential other sources for the metabolite?

Let's say NHANES is identifying as bromopropane metabolite. And we see it is so ubiquitous because, given the short life, in some, they have to be ambient exposure at least that exposure that is added to this, that maybe it's due to the emissions from manufacturing from all the dry cleaners and so on.

That's the general question regarding the scope, I mean, whether any attempt to integrate information for human biomarker data with this assessment was taken or, you know, you plan to take this. And then I have a couple of simpler, more specific questions regarding exposure.

DR. KENNETH PORTIER: Identify yourself.

MS. ANDREA PFAHLES-HUTCHENS: I am Andrea Pfahles-Hutchens, EPA. And --

DR. KENNETH PORTIER: You're going to have to get closer. Sorry.

MS. ANDREA PFAHLES-HUTCHENS: Thank you.

DR. KENNETH PORTIER: I'm getting old. I can't hear as good even with the microphone.

THE REPORTER: You want to go closer.

MS. ANDREA PFAHLES-HUTCHENS: Can you hear me?

THE REPORTER: There.

MS. ANDREA PFAHLES-HUTCHENS: Yeah. So some of the new biomarker data that came out recently was not incorporated in the assessment, as you noted. And that's something that we'll have to take into consideration in our next iteration.

But again, as you noted, that 1-BP made -- so the biomarker itself that was measured in NHANES in that smaller sample of smokers was done specifically for smoking, first of all, for a specific smoke -- for smokers. And so we'll have to determine, first of all, the adequacy of using that biomarker because it could be also a biomarker for other things as well.

So that's going to take a lot of -- you know, we're still going to have to check into it more and find out what's available, what -- if there's anything else available in the literature that'll help inform us on that.

But according to the NHANES data that came out, it does look like you're right, that it is more ubiquitous, I think, than anyone would have expected. And they're expecting that it's not probably from smoking but from some other source.

DR. PANOS GEORGOPOULOS: It's

definitely not from smoking. But some -- a couple of similar questions -- and again, you -- that was very diligent work that was done with the exposure modeling.

One question regarding the occupational exposures -- did you consider -- you have data on professional carpet cleaners who actually go to homes and do the carpet cleaning or to institutions like churches and things like that because it appears that some of the products that they are using, at least the advertisements that are addressed to these people include products that use bromopropane. And the issue with this is if it happens in a residence, do you combine the occupational exposure with subsequent residential exposure that could involve children and so on.

MR. GREG MACEK: Greg Macek, EPA.

You know, that's a good point you raise. But within our scope, I guess it gets back to scope and the way we made decisions on scope -- which uses we were going to cover. So for the purpose of the assessment we've done, we had not picked that particular use category. So if we had, we would have followed the same approach of trying to gather as much monitoring data that's out there and then also modeling to come up with exposure. But we didn't do it because it wasn't in the scope we defined.

DR. PANOS GEORGOPOULOS: Okay. But that's something that you might consider if you find --

MR. GREG MACEK: Sure.

DR. PANOS GEORGOPOULOS: Okay. And one very quick question --

MR. GREG MACEK: Sure.

DR. PANOS GEORGOPOULOS: -- final question. If you go to the previous slide on -- I think it was Slide 34, they're -- the calculations here for the consumer exposure, you did not really do a distribution of all the basic calculation. The fact that you used for some parameters a median versus a conservative high-end value that exposed the 50th percentile of the parameter doesn't mean that you actually get the 50th percentile or the 90th percentile of the distribution of exposure.

So it's more a matter of semantics. I would feel a lot more comfortable if up just -- you said high end, the central tendency estimate rather than -- because when you put this 50th and 90th, it gives a quantitative character to this estimate that is not really there.

DR. EVA WONG: This is Eva Wong, EPA. Thank you for that comment.

You're correct in that -- in combining parameters for the 50th percentile. They are the 50th percentile for the human exposure factors as well as for the scenarios and likewise for the 90th percentile. The activity patterns are from the 90th percentile of the distribution, not an overall distribution.

And the reason we chose the 90th percentile is that, in our Westat survey, which we use for the activity patterns, it is a 1987 survey of these uses. So there is some uncertainty as to the higher end of the percentile range. But certainly, we appreciate the comment on the semantics of how we label in community --

DR. PANOS GEORGOPOULOS: Yeah, you use --

DR. EVA WONG: -- exposures.

DR. PANOS GEORGOPOULOS: You use percentiles, but you combined it. In some cases, there were default values. So it's a combination.

You did not use fully distribution. So calling it the high end versus reasonable, you'd be more appropriate. It's not really a 90th percentile because you did not use all the distributions and compiled it. I just don't feel comfortable. That's all.

DR. KENNETH PORTIER: Thank you.

I just remind the panel we're asking questions right now. And save your good comments for when the panel discusses -- Dr. Thayer, you had yours up, and it went down.

DR. KRISTINA THAYER: It came up.

DR. KENNETH PORTIER: Okay.

Dr. Hossain?

DR. MUHAMMAD HOSSAIN: Muhammad Hossain, North Ohio Medical University.

I have one clarification for the near-field and far-field monitoring. So here, maybe the distance could be the factor. So how far you consider for far-field monitoring?

MR. GREG MACEK: Greg Macek, EPA.

You know, when we did the modeling for each of those uses where we used the near-field, far-field, we had to construct, basically, the modeling approach, which identified the near-field zone, the far-field zone. And we had to put dimensions around it and make assumptions.

So I think if you're asking specifically what those were, they are in the appendix. So where we present in Appendix K, I think there's some good tables there that -- I got -- excuse me -- we got some tables there that lay out the parameters and the assumptions we made for those different zones.

Is that responsive to your question? Yeah, I don't have the specifics, but --

DR. MUHAMMAD HOSSAIN: Just I am wondering about for the far-field distance, how it --

MR. GREG MACEK: Yeah.

DR. MUHAMMAD HOSSAIN: -- area from the source is considered.

MR. GREG MACEK: Do you have --

MR. NHAN NGUYEN: Yeah, for the near-field, for the purpose of this assessment, we assume a 6-by-6-by-10-dimension box for the near-field. And the far-field varies -- depends on the setting. And we have data that -- a document in assessment for a different use --

DR. KENNETH PORTIER: Identify

yourself, please.

MR. NHAN NGUYEN: Yeah, this is Nhan Nguyen with the EPA.

DR. KENNETH PORTIER: Okay. Kind of conferring. Anything else? Okay.

Dr. Blando?

DR. JAMES BLANDO: Jim Blando here.

Just one point of clarification -- the biomarker you were referring to from the NHANES survey, can you just tell us what that biomarker was?

DR. KENNETH PORTIER: Conferring.

DR. JAMES BLANDO: I guess I'm just wondering if it's the same one NIOSH has been using.

DR. KENNETH PORTIER: They're looking it up --

DR. JAMES BLANDO: Oh, okay.

DR. KENNETH PORTIER: -- in the assessment right now.

MS. LESLIAM QUIROS-ALCALA: I have it here. Sorry. Yeah. I have the data here. I'm in the panel, and I also cited that because it also --

DR. KENNETH PORTIER: Say your name.

MS. LESLIAM QUIROS-ALCALA: Sorry. Lesliam Quiros-Alcala, University of Maryland. I'm in the panel.

So the biomarker that they used was N-acetyl-S-(n-propyl)-l-cysteine. And I'd just like to reiterate how ubiquitous it is. It was detected in 99 percent of pregnant women from NHANES data. And in children from a national -- sorry. It was data from a national children's study in which it was detected in 99 percent of pregnant women. And using NHANES data from children 6 to 11 years of age in the general U.S. population, it was detected in 60.8 percent.

DR. KENNETH PORTIER: Dr. Kissel?

DR. JOHN KISSEL: Yeah, I'd like to go back to the exposure assessment. Now I'm confused after Panos' questions.

The term "Monte Carlo Analysis" is used many, many times in this report. And if all you've done is multiply 95th percentiles together, that's not a Monte Carlo analysis. There is in the back -- there's discussion of distributions of individual variables, which do appear to be assumed distributions. So could you just clarify what was done?

And I will add that, given the uncertainty in the various parameters, I'm looking at the results. And the difference between the 95th and 50th percentiles ranges between a factor of 4 and a factor of 8, which implies a geometric standard deviation somewhere between 2 and-a-half and 3 and-a-half, which sounds kind of reasonable if you actually had data. But if you're just kind of filling in data where you've got it and if huge uncertainty, it strikes me as very low.

And I would really like to see a distribution of the results to get a sense of what's actually going on here because I don't know on the basis of the presentation.

DR. EVA WONG: Eva Wong, EPA.

So for the consumer exposure modeling, that was, in fact, deterministic. So we don't describe the consumer exposure modeling as Monte Carlo analysis. That was described in the occupational exposure. Is that --

DR. JOHN KISSEL: Okay. So that's one point.

DR. EVA WONG: Yes. Did you want --

MR. GREG MACEK: Hi. Greg Macek, EPA.

Yes, for the occupational, we did do the Monte Carlo for the modeling scenario. So as part of those modeling scenarios, we had the different parameters, and we did assume ranges for each of those values. And there's assumptions we made on the distribution type. And we did do Monte Carlo where we did, you know, million iterations for the near-field and far-field to generate the 50th and 95th percentile estimates. And we can, you know, provide more details on that -- on the distribution that you requested.

DR. JOHN KISSEL: Okay. Well, I think, ultimately, in putting things into the risk assessment, I think that would be useful. And I think putting your Slide 28 into the document would be really useful. That's the comparison of the biomarker --

MR. GREG MACEK: Yeah.

DR. JOHN KISSEL: -- to the -- it's not in the actual document.

MR. GREG MACEK: Good comment.

DR. JOHN KISSEL: And so if you're actually trying to do Monte Carlo analysis, that's a giant step forward for EPA because you've been doing that. Take the 50ths, which aren't really 50ths. Well, they're just kind of numbers, which don't seem really high. And we'll call that a 50th percentile and then report it as a 50th percentile, which is not a particularly good idea -- and similarly with the 95th percentiles.

But so my question then would be why not do a 2D Monte Carlo here. If you're moving to Monte Carlo, why stop at a one-dimensional Monte Carlo? Why not try to do it right?

DR. KENNETH PORTIER: Yeah, John, hold those comments for the report, too. So you're going to have to resay that again later today.

MR. GREG MACEK: Well, Greg Macek. Thanks for that comment.

I think -- I don't have an answer right now. But I think that's something we can --

DR. KENNETH PORTIER: I'm not sure it was a question to scope.

MR. GREG MACEK: Sorry. Well, the point of 2D, I guess.

DR. KENNETH PORTIER: This is Ken Portier. I have a couple of quick clarifying questions.

On the estimated number of workers, you have a pretty wide range -- you know, one of them 1,200 to 25,000. So does that represent uncertainty in the parameters from the underlying survey that was done? Is that -- I mean, is it that uncertain how many workers --

MR. GREG MACEK: Yeah. That's related to the third step in the approach where we tried to estimate the market penetration of 1-BP in those specifics. So generally, that resulted in a range, you know, just looking at sources. Some sources maybe could have been a little more conservative or maybe dated. And so some may be more recent.

So there is uncertainty, and it's reflected by the range of percentages, which then when you multiply by the other data results in a range for the estimate of workers.

DR. KENNETH PORTIER: So another comment -- in Appendix G, you gave us the methodology for the literature review, but you didn't really show us the results of the literature review itself. You didn't show us which articles you actually reviewed and rejected.

MR. GREG MACEK: Hmm.

DR. KENNETH PORTIER: Now, is that standard? Or is that something you guys are considering adding? I mean, this came up in the TCE

IRIS Assessment as well because the public likes to see what you threw out --

MR. GREG MACEK: Hmm.

DR. KENNETH PORTIER: -- as well as what you included. We see what you included here.

MR. GREG MACEK: Sure.

DR. KENNETH PORTIER: But we didn't see what you threw out.

MR. GREG MACEK: Yeah. I think -- I mean, there is some evolution in the report -- you know, in the risk assessment reports trying to keep improving it and how it's organized and what's included in, say, the body of the report and the appendices, what appendices to present. So I think the appendices in its current form is probably where we were at. But that's certainly a good consideration, I think, to expand it to provide -- I mean, that's the kind of feedback we want to understand from readers of the document what information's helpful.

DR. KENNETH PORTIER: In the spray adhesive exposure assessment, you indicated you used three studies. And one of the public comments kind of indicated that two of those three looked like they were problem cases rather than typical cases. And did you -- you know, I'm wondering to what extent is the distribution that we're talking about, the variability of distribution, based on typical versus worse case.

MR. GREG MACEK: Yeah, that's a good observation. I think that is something we have to, I think, consider and reflect. We did note that in the uncertainties discussion that, you know, this type of data -- you know, we didn't have complete distributions of data.

So the data we collected may not be representative be -- and that's an example of why, because in this case, yes, they were called in, I guess, on a corrective measure. So it -- you know, so there's limitations there --

DR. KENNETH PORTIER: Yeah.

MR. GREG MACEK: -- I think.

DR. KENNETH PORTIER: On -- you mentioned about engineering controls on 90 percent reduction. And I had noticed that you'd taken the -- you know, the pre-EC values multiplied by .1, and all of the sudden, you have the post-EC values.

So as an engineer, I wondered if you went back through the model to see, was a 10-fold reduction possible, for example? A lot of that reduction is airflow, right? I mean, you -- and part of your models are airflow.

MR. GREG MACEK: Yeah.

DR. KENNETH PORTIER: That's a key component. So did you look back and say how much airflow would I have to have to achieve that 10-fold reduction? I mean, would they be standing in a hurricane? I mean, I -- that was the -- and that wasn't addressed in the --

MR. GREG MACEK: Yeah. Well, thank you for that comment.

I think at this point it was an assumption. And so at this point, we haven't done that type of analysis that you were describing.

DR. KENNETH PORTIER: So another public comment in the code clean degreasing, you used a work year of 260 days. And yet somebody was pointing out that the standard EPA work year is 240 days. And I wondered what happened there. Is it that just we haven't quite gone through all the details yet? Or was there a decision to go with 260 because of some data or evidence?

MR. GREG MACEK: Yeah.

MR. NHAN NGUYEN: Yes. We at EPA have developed a series of what we call generic scenarios which are industry-specific documents that can be used to develop estimates to exposure. And as part of the process to develop these documents, we look at available literature information and so on. And 260 days is basically the data what we found and was included in the generic scenario document that we have specifically for --

DR. KENNETH PORTIER: Okay.

MR. NHAN NGUYEN: -- for the -- yeah.

DR. KENNETH PORTIER: That's my questions. Does anybody else have additional questions?

Yes, Dr. Gilbert?

DR. KATHLEEN GILBERT: Well, I was also struck by the NHANES data where they found that 99 percent of pregnant women had a metabolite of 1-BP. And in view of the relatively short half-life and the relatively limited number of consumer products that have 1-BP in it, how do you reconcile that data?

DR. KENNETH PORTIER: Identify yourself.

MS. ANDREA PFAHLES-HUTCHENS: Andrea

Pfahles-Hutchens, EPA.

We'll have to take it into consideration. So we haven't -- I mean, I -- I'm not sure. If you all have ideas on also what we need to do to use that data, then that would be helpful as well because they just became available fairly recently. And especially, the national children's study data wasn't published until the beginning of this year. So we'll still need to take all of that into consideration.

But again, it comes down to is it the appropriate biomarker, and can we trace it back to, you know, where it's coming from or what do we do with it.

DR. KENNETH PORTIER: Good answer.

Dr. Georgopoulos?

DR. PANOS GEORGOPOULOS: Yeah, I was not planning to go more. But since the issue of other consumer products came up, bromopropane was also ranked in the ExpoCast, using informational CPCat database. And when I went and looked at it for bromopropane, it actually ranks it very high because there is a whole group of products that are identified as cosmetics and fragrances, but I could not find information on those. I mean, they're in the ACTR system. They come out, and they actually -- they take the exposure ranking of bromopropane.

So I was wondering if you guys when you were looking at the consumer exposure -- of course, you limited this to the cleaning products, but did you look at the EPA CPCat database and the ExpoCast calculations?

DR. EVA WONG: So in our assessments, we use all available data. If we don't have data that would allow us to produce a reliable exposure assessment, then we may not include that in our scope.

And also, remember that in toxco we are looking at specific uses that are within our purview. And fragrances, for example, would not be. So you know, this may represent an underestimate, or it may account for some of the NHANES data. We don't know. Or I don't -- I'm not aware of that.

DR. KENNETH PORTIER: I think the problem is personal care products is a whole other area. And it's not excluded from toxco, right? So --

DR. PANOS GEORGOPOULOS: But that's a --

DR. KENNETH PORTIER: We could bring it back up --

DR. PANOS GEORGOPOULOS: -- EPA database.

DR. KENNETH PORTIER: -- discussion.

DR. PANOS GEORGOPOULOS: Yeah.

DR. KENNETH PORTIER: I think at this point I want to move forward with the next presentation so we can get to lunch.

You're between us and lunch, Dr. --

DR. KATHERINE ANITOLE: Sure. Thank you.

DR. KENNETH PORTIER: -- Anitole.

DR. KATHERINE ANITOLE: Okay. Thank you.

So we're going to get into the Hazard ID Dose-Response section of our risk assessment. And then we'll move into the risk characterization.

So this slide -- this figure depicts the process that we used to review and select animal toxicological and epidemiological studies that were used in our risk assessment. We reviewed authoritative assessments as well as primary peer-reviewed literature and secondary sources for both epidemiological, clinical and animal toxicity data that we identified through literature searches that we conducted through August of 2015 to help identify adverse health effects.

Some of the considerations we used to evaluate data quality employed general principles of systematic review. And we'll see those in the next couple of slides. Based on this review, we narrowed the focus to key endpoints following dose-response analysis that included cancer and five non-cancer organ systems, which consisted of liver, kidney, reproductive, developmental and neurotoxicity.

Specific endpoints were identified for each of these target organ systems with adequate information to perform dose-response analysis in select points of departures, or PODs. Benchmark dose modeling was applied to these endpoints. And when the model fit was adequate, a benchmark concentration lower confidence limit was used as the point of departures. And when model fit was not adequate, we used a NOAEC-LOAEC approach. The PODs were further adjusted to human equivalent concentrations, or HECs, for each of the health effect domains that we identified.

So on this slide, are examples of some

of the considerations that we used to evaluate data quality, employing the general principles of systematic review. I should note that not all of these may be relevant for the studies we reviewed for 1-BP. Studies that met these considerations were included in our hazard identification analysis, and all of the endpoints that we identified were evaluated for consistency, sensitivity and human relevance.

We also evaluated epidemiological studies and case reports for quality using these considerations. And again, I will note that not all of these may be relevant to the studies we reviewed for 1-BP. There were three epidemiological studies on 1-BP located in the literature, and several NIOSH hazard evaluations were also reviewed.

So now I'll describe the studies that we used to assess cancer hazard and dose response. The Report on Carcinogens states that 1-BP is "reasonably anticipated to be a human carcinogen," and this is based on NTP studies conducted in rats and mice via inhalation for two years.

The cancer findings included significant increase incidences of skin tumors in male rats, intestinal tumors in female rats and lung tumors in female mice. And while the mode of action of carcinogenesis is not known, we conducted a weight-of-evidence analysis for 1-BP carcinogenesis according to EPA cancer guidelines. And we evaluated multiple lines of evidence such as in vitro, in vivo and structure activity relationships that supported a probable mutagenic mode of action.

I should also mention that, according to the EPA cancer guidelines, EPA identified 1-bromopropane as a likely human carcinogen. And this identification is based on criteria including its presence in three tumor types in both genders and across two species. And I should also mention that our cancer assessment is consistent with the NIOSH assessment, which uses the same cancer endpoints.

So the data from the NTP study was used for the cancer dose response analysis. And the approach we used was harmonized with the NIOSH assessment. Benchmark dose modeling of this NTP cancer data was performed for all three increased tumor types. The data for the lung tumors in female mice generated the lowest benchmark concentration of .3 ppm, and this was used to derive the inhalation unit risk because it would be protective for the other tumor types. And the inhalation unit risk was calculated using the equations shown on this slide.

So this slide depicts the studies we use to assess the non-cancer hazard ID and dose-response assessment. As described earlier, we considered adverse effects for 1-BP across multiple organ systems. We have a comprehensive summary table of the full list of effects that were screened for this assessment, and these can be found in Appendix O of the Draft Risk Assessment.

As a result of this evaluation, we identified non-cancer hazards that included liver, kidney, reproductive, developmental and neurotoxicity. Reproductive and developmental toxicity were identified as health hazards based on a constellation of effects in animal studies on male and female reproductive parameters as well as effects on the developing fetus, which included decreases in body weight, brain weights and number of live births.

For neurotoxicity, the hazards that were observed in animal studies were further supported by human epidemiological data.

So for each of the target organ or organ system, we selected the endpoint that was amenable to quantitative analysis for dose-response assessment. The benchmark response levels were selected based on EPA guidance. Generally, one standard deviation or a 10 percent relative deviation was used. And the BMRs are shown for each endpoint in the figure.

I should note that, per EPA guidance, lower BMRs were used for developmental endpoints with 5 percent decreased litter size and pup body weight and 1 percent for brain weight to account for the increased severity of these endpoints. And this is because the variability in these endpoints is smaller, resulting in small benchmark response levels.

The points of departures were then adjusted to human equivalent concentrations, or HECs. And the exposure durations used in the animal studies were adjusted to the durations that were deemed relevant for each specific human exposure scenario that we were evaluating in the risk assessment.

So just in summary, on the hazard ID dose response, we employed the general principles of systematic review and identified non-cancer health effects, selected the most robust, sensitive and consistent endpoints in five organ systems. In each health effect domain, the HECs were selected to calculate risk. And these HECs occurred in a narrow range of low ALs, which provided further support that this range was the concentration level at which the adverse health effects occur in many organ systems.

We also identified health hazard for cancer, conducted dose-response analysis, identified lung tumors in female mice as the most sensitive and used those for the basis of the IUR. These points of departure and the IUR were then carried forward in the risk assessment to calculate risks.

So now the Risk Characterization section -- we calculated risks by bringing together all of the pieces that we've just described. The following exposure scenarios were assessed. For workers and occupational non-users, risks were evaluated for acute and chronic exposures. And for consumers, risks were evaluated for acute exposures. The different exposure durations were then compared with the different health points that we identified in order to calculate risk.

So for the acute exposures for both the occupational and consumer scenarios, developmental toxicity was selected as the most sensitive endpoint for evaluating risk, while cancer, developmental and neurotoxicity were selected as the most sensitive endpoints for evaluating risk associated with chronic occupational exposures.

I should note that we did not estimate added cancer risks for acute exposures because the relationship between cancer induction in humans and a single short-term exposure to 1-BP has not been firmly established in the literature.

So non-cancer risks were estimated for acute or chronic exposures using a margin of exposure approach where the hazard value, or the point of departure, is the selected HEC within each of the health effect domains, which is considered to be protective of all effects. And this is divided by the exposure estimates that were previously generated.

And this MOE is then compared to a benchmark MOE where the benchmark MOE is a product of endpoint and study-specific uncertainty factors based on standard agency guidance. And this resulted in benchmark MOEs of either 100 or 1,000. And these can be seen in Tables 3-1 and 304 in the Draft Risk Assessment.

So if the MOE is calculated to be less

than a benchmark MOE, then risks are likely for this particular exposure scenario. And if they're greater than the benchmark MOE, then risks are not likely for that particular exposure scenario.

So again, the MOEs were based on a hazard benchmark, or point of departure, that were relevant for both the acute and chronic exposure scenarios. And the point of departure we used to calculate risk for the acute occupational and consumer exposure scenarios was the same, and that was developmental toxicity.

But as you can see on the slide, the HECs differed because we adjusted the exposure durations based on either an 8-hour workday for the occupational scenario or a 24-hour exposure for the consumer scenario. And as a result, the HEC for the acute occupational scenario was 31, and that for the acute consumer was 10.

We used these two points of departure to calculate risk for the chronic occupational scenarios, and we adjusted the exposure durations based on an eight-hour workday, five days per week.

The HEC for the chronic occupational scenario is 43 ppm, and this is based on developmental toxicity. And it is 25 ppm based on neurotoxicity.

I should note that the non-cancer and cancer risk estimates for chronic exposures were only derived for the occupational scenarios because the consumer scenarios were not considered to be acute in nature -- excuse me -- chronic in nature.

So now we have the results. The non-cancer risk estimates were calculated for the entire range of health effects at both the 95th and 50th percentile for both acute and chronic inhalation exposures for all of the uses that we evaluated in the risk assessment. But the next series of slides will focus only on the 95th percentile, or the high-end exposures, without engineering controls for just three representative 1-BP uses -- that would be spray adhesive, dry cleaning and vapor degreasing -- using the most robust and sensitive points of departure that we had previously identified.

So from this table, we can see that the MOEs are one to two orders of magnitude below the benchmark MOE for the developmental endpoint and two to three orders of magnitude below the benchmark MOE for the neurotoxicity endpoint. And you can also see in the last column that the benchmark MOEs are different. And this is an example of where the endpoint and study-specific uncertainty factors would result in different benchmark MOEs.

So for the occupational inhalation exposures, with few exceptions, we found the similar findings for all of the non-cancer risk estimates that we calculated, including those for the 50th percentile. And those are shown in the Draft Risk Assessment.

So on this slide, the table shows the non-cancer risk estimates for the acute inhalation exposures in consumer scenarios. And this is based on modeling data for the high-end 90th percentile. We do not have any monitoring data to date available for consumer exposure scenarios. And as you can see, risk was identified for all of the consumer scenarios for both users and non-users. And in all cases where risk was identified, the MOE values were approximately one to two orders below the benchmark MOE of 100. And again, although not shown here, but in the risk assessment itself, similar findings were observed for the 50th percentile exposure estimates.

I should also mention that we evaluated consumer exposure in different age groups for both users and non-users. And for the acute exposure scenarios for consumer uses, we assumed that the users would be individuals greater than or equal to 16 years of age; both sexes, including women of child-bearing age. And non-users would be all categories from less than 1-year-old to older than 21 years of age.

So now moving on to the cancer risk estimation, as with the non-cancer risks, the cancer risks were calculated at both the 95th and the 50th percentile for all of the uses that we evaluated in our assessment. But for this presentation, we're just going to focus on the 95th percentile, or high-end exposures, without engineering controls, again, for just the three representative uses -- spray adhesive, dry cleaning and vapor degreasing. We will be using the inhalation unit risk that we described earlier in the cancer dose-response section. And this was based on lung tumors in female mice.

So the cancer risks were estimated using the equation shown on this slide. And the estimates for added cancer risks for repeated exposures should be interpreted as the incremental probability of an individual developing cancer over a lifetime as a result of exposure to a potential carcinogen. And that is referred to as either an incremental or added individual lifetime cancer risk. And those exposures, again, were adjusted to be lifetime average daily concentrations, as we described earlier.

So the occupational estimates for added cancer risks were compared to the benchmark levels of 1 times 10 to the minus 4 minus 5 and minus 6 incremental or added individual lifetime risk. These benchmark levels can also be expressed as number of cases per million. The cancer risks were then combined with the estimated worker populations to estimate increased incidence of cancer using the equation shown on the slide.

The worker populations used were the number of workers that would be expected to be exposed at the 95th percentile. And that would be 5 percent of the total worker population. And these workers were assumed to be exposed 8 hours per day, 260 days per year for 40 years.

I should note that our evaluation of cancer risk was harmonized with NIOSH, which used added cancer risks. And we calculated cancer risks as both excess and added risks, but only presented added risks in our assessment. But the difference would be insignificant.

So again, we calculated cancer risks for both the 95th and the 50th percentile for all of the uses we evaluated in the risk assessment. And these can be found in the supplemental files. But the next series of slides are just going to focus on the added cancer risks that were estimated for chronic exposures in workers following 1-BP use at the 95th percentile, or high-end exposure. And this would be using pre-engineering controls and monitoring data.

So this slide depicts the cancer risks estimated for use in the spray adhesives. And for all three groups, the added cancer risks are of the order 10 to the minus 1, which is several orders of magnitude from the highest benchmark level of 10 to the minus 4.

The number of workers, sprayers and non-sprayers, that were estimated to be exposed at the 95th percentile is roughly 100. And the number with possible increased cancer incidents would be 5 to 40 workers if we assume that the workers were exposed to 1-BP 8 hours per day, 260 days per year for 40 years.

This slide depicts cancer risk

estimates for 1-BP use in dry cleaning. For the workers and occupational non-users, added cancer risks are between 10 to the minus 2 and 10 to the minus 1, which is several orders of magnitude from the highest benchmark level of 10 to the minus 4. The number of workers estimated to be exposed at this 95th percentile is about 40. And the number with possible increased cancer incidents would be up to 40, assuming that, again, the workers were exposed to 1-BP 8 hours per day, 260 days per year for 40 years.

And this slide depicts the cancer risks estimate for 1-BP use in vapor degreasing. Again, added cancer risks for workers and occupational non-users were nearly 10 to the minus 1 and 10 to the minus 2, respectively, which is several orders of magnitude from the highest benchmark level of 10 to the minus 4.

The number of workers estimated to be exposed to 1-BP in this use activity is -- at the 95th percentile is, roughly, 500. And the number with possible increased cancer incidence would be up to 40 workers, again, with the assumption that workers were exposed 8 hours per day, 260 days per year for 40 years.

So the cancer inhalation exposures, the overall conclusions -- there are significant risks to developing cancer in workers if they are exposed to 1-BP for the assumed occupational duration for all of the uses that we evaluated. Occupational non-users also have significant increased risks to developing cancer if they are exposed for the same occupational duration at the estimated concentrations.

The cancer risk calculations are based on assumptions, and they have uncertainties, such as the exposure frequency of 260 days per year for 40 years of exposure over a 70-year lifespan. And therefore, we may have produced conservative cancer risk estimates.

However, if you look at the estimates, they are many orders of magnitude from the benchmarks of 10 to the minus 6 and minus 4, which supports the overall conclusion that workers and occupational non-users exposed to 1-BP in these use categories have increased cancer risks.

So in summary, the non-cancer and cancer risk estimates were identified for both worker acute and chronic exposure scenarios and consumer acute-only scenarios. Risks for most of the acute and consumer scenarios were one to two orders of magnitude below the benchmark MOE. Risks for chronic occupational exposures without engineering controls were two to three orders below the benchmark MOE.

And we should recall that while we have shown the most sensitive effects, which would be neurotoxicity and developmental toxicity, there are effects in five organ systems total, and they are all within a six-fold, less than one order of magnitude difference, which provides multiple lines of evidence that there are non-cancer risks for occupational exposures.

The non -- the cancer risk estimates for all occupational use scenarios that we evaluated for workers and occupational non-users was based on monitoring -- or modeling estimates, exceeded the benchmark cancer risk levels by multiple orders of magnitude. And we should keep in mind that these cancer risk estimates were exceeded with few exceptions, even after engineering controls were applied.

So while the strength of the evidence of our risk assessment provides confidence that there is a -- there are a number of assumptions and uncertainties. Some of these assumptions and uncertainties are part of every risk assessment and are essentially generic. For example, the exposure monitoring data for workers was not based on randomly selected sites. And so therefore, the reported data may not be representative. And for some of the uses, the number of data points were extremely small.

Exposure modeling approaches employ knowledge-based assumptions. And these are the best available data and professional judgment. However, they may not apply to all use scenarios.

The non-cancer risk estimates and cancer risk estimates are based on animal toxicity data, which depends on the assumption of relevancy of these effects observed in rodents for both cancer and non-cancer to humans. But I should note that, in the case of neurotoxicity, signs off neurotoxicity following 1-BP exposures have been observed in both human case study reports and in epidemiological studies, thereby supporting relevance of this effect to humans.

And the other assumption that we made that is essentially made in most risk assessments is that the developmental effect of decreased number of live births was assumed to have a window of susceptibility that is as short as one day. And this assumption is supported by the EPA's developmental and reproductive toxicity risk assessment guidelines.

There are a number of assumptions and uncertainties that are more specific to 1-BP. For example, the dermal exposure was not quantifiable and could not be aggregated with the inhalation exposure. And therefore, risk may be under-estimated.

However, although dermal exposures are possible, the physical chemical properties indicate that it will evaporate quickly when it comes into contact with the skin. And if we combine this with data indicating dermal uptake to be orders of magnitude lower than uptake by inhalation, the limited toxicological data that we have for this route of exposure and the fact that we have no toxicokinetic information to develop PBPK models for route-to-route extrapolations lessens our concern for the dermal route of exposure.

Another area of uncertainty involves the proposed mode of action for carcinogenesis. And a key factor in this uncertainty is due to the equivocal AIMS test results, which are confounded by the result of the high volatility of 1-BP. EPA determined a probable mutagenic mode of action based on a weight-of-evidence approach, which used multiple lines of evidence. And according to the EPA cancer guidelines, a linear low-dose extrapolation would be applied in the absence of conclusive information indicating a non-mutagenic mode of action. But in this instance, we have evidence of a mutagenic mode of action. So in either case, a linear low-dose extrapolation would be supported.

And this concludes our presentation.

DR. KENNETH PORTIER: Thank you. We'll open it up to any questions.

Dr. Marty?

DR. MELANIE MARTY: Melanie Marty.

So you guys -- I noticed you did a different way of estimating the IUR than is in your traditional cancer risk assessment guidelines. So, you know, we're all used to looking at the results of the multi-stage model with the benchmark response rate of 10 percent and extrapolation linearly. And I think I just heard you say that you guys did do that, but you didn't put the comparison in a document and that there wasn't very much difference in the IUR in the end. Is that --

DR. KATHERINE ANITOLE: Right. And -- I'm sorry. I'll ask Chris to step up. Chris Brinkerhoff is our modeler and did the dose-response analysis.

DR. CHRIS BRINKERHOFF: I'm Chris Brinkerhoff from EPA.

The first point, I think, to remember is that this assessment we communicated with NIOSH, who is also doing assessment. And we have harmonized what we were doing with what they were doing, agreed that it's different from EPA's cancer guidelines.

The different -- there is a small piece in the risk assessment in the Benchmark Dose Modeling Appendix that talks about -- we did -- I'm pretty sure we presented the multi-stage model results with a 10 percent BMR. And that may -- did -- we appreciate your comment, and I hear where you're coming from.

DR. JAYMIE MELIKER: Jaymie Meliker.

Can you just bring up Slide 40? And let's talk about this. I have questions on 40, 41 and 45.

So am I right in interpreting this .1 percent added risk is 1 out of 100? I guess .1

percent would be 1 additional cancer, tumor, per 1,000?

DR. CHRIS BRINKERHOFF: This is Chris. Correct.

DR. JAYMIE MELIKER: Correct. And you're saying that you get 1 additional tumor per 1,000 by increasing the ppm by .30. Is that right? That's what you're basing this on?

DR. CHRIS BRINKERHOFF: So the -- this is Chris again.

The .30 is the BMCL, so the 95 percent lower confidence limit on that estimate. Is that answering your question?

DR. JAYMIE MELIKER: Well, I guess. So -- but I mean, that's what you're using in the model, right, is that that's what gives you that one additional case per 1,000 is just that small of an increase of only .30 ppm.

DR. CHRIS BRINKERHOFF: Yes.

DR. JAYMIE MELIKER: All right. I mean, I don't know the literature. That seems tiny. Like, that seems unrealistic that you would see an increase. So that means, you know, per an additional 100 tumors, that would require 30 ppm increase. I mean, we have human studies, you know, in the level of around 25 or 30 ppm. And you're talking that would be a 10 percent incidence of tumors, you know, on top of background, right? I mean, that's what the model -- that's what you're modeling?

DR. CHRIS BRINKERHOFF: Right. So this is Chris Brinkerhoff from EPA again.

The modeling is based on the NTP study in mice. These are the numbers we have.

DR. JAYMIE MELIKER: Right. It just gives me some concern that those are the, you know, data we have and whether or not -- how much to base it on those data. So that's my first question for 41.

Then 42, let's just talk about the neurologic endpoint because, again, we have some human data with neurologic endpoints -- sorry, Slide 41.

So we have an HEC of 25 ppm, which I think is reasonable. I think, you know, that works. The question then is how do we take that, which we're getting from human data, and apply it in Slide 45. Or even -- yeah, I guess it's even -- Slide 44 is your equation, right? Your point of departure is going to be that 25 ppm, right? That's your point --

DR. CHRIS BRINKERHOFF: Yes.

DR. JAYMIE MELIKER: -- of departure. And we have a human exposure which is around there, right, I mean, from the model. It's around 25 ppm. And there's going to be some uncertainty there. But why is the uncertainty factor then 100? You know, we're comparing it with this benchmark dose when those are actually from human data, right? We're saying none of the HECs are from human data. They're all from animal data.

DR. CHRIS BRINKERHOFF: Correct. The neurotoxicity endpoint is based on animal data.

DR. JAYMIE MELIKER: Uh-huh. But we do have human data that would also suggest an HEC of somewhere around 25, right? Or no?

DR. CHRIS BRINKERHOFF: We did not quantify an HEC for the human data based on the epidemiological studies.

DR. JAYMIE MELIKER: Uh-huh. Is there a reason why not?

DR. SHARON OXENDINE: Hi. This is Sharon Oxendine --

DR. JAYMIE MELIKER: Hi.

DR. SHARON OXENDINE: -- EPA.

There were some problems with the human

studies that precluded their use in the risk assessment. We felt more comfortable leaning on the animal studies because the weight-of-evidence was fairly strong.

DR. JAYMIE MELIKER: All right. Okay.

DR. KENNETH PORTIER: I wasn't paying attention to who raised their what. So I'm going to switch from side to side.

Dr. Pennell?

DR. MICHAEL PENNELL: Oh. This is Michael Pennell from Ohio State.

On Slide 37, it is mentioned that historical control data are available for comparison. Can you comment on the extent to which historical control data were used in the analysis, if at all?

DR. SHARON OXENDINE: This is Sharon Oxendine, EPA. The point of this slide was just to give you a flavor of the sort of things that we considered when we did our review of the available data. We did not lean on the historical controls, per se. This refers specifically to the NTP cancer study, this slide.

DR. MICHAEL PENNELL: Can you comment on why you didn't? I mean, because there's a lot of information from, you know, previous NTP studies on historical controls.

DR. SHARON OXENDINE: I'm sorry. I don't get your point.

DR. MICHAEL PENNELL: Oh. Can you comment on why there's -- there was no use of any historical control data in the assessment or any sort of comparisons, given the large volume of, you know, available data?

DR. SHARON OXENDINE: Well, I guess we have a lot of confidence in the NTP study itself. And when they concluded that it's reasonably anticipated to be a human carcinogen, we felt pretty confident in that and didn't see the need to reinvent the wheel, I guess, is the honest answer to that.

DR. MICHAEL PENNELL: So my comment is specifically so that one particular study has just the limited set of animals, right? But the NTP runs a lot of studies, right -- very similar design, similar animals. There could -- comparisons could be made, right, to historical control data.

DR. SHARON OXENDINE: Yes.

DR. KATHERINE ANITOLE: This is Katherine Anitole. I'd just like to add that we did go through a thorough evaluation of all of the data that were available out in the literature. And at the time that we did that evaluation, we were finding that our evaluation of the data was consistent with what NIOSH was concluding and what NIOSH was using as endpoints of concern as well as ATSDR. So we felt that the data that we had were robust enough to use without having to reach back to do a comparison with historical controls.

DR. TALA HENRY: If you could possibly in either comments or any -- be more specific? I mean, I am a toxicologist, and I don't know what you're asking, really. What do you want us to do with that historical data, per se? And is it relevant to this 1-BP study, in particular? I guess I'm not crystal clear on what you're asking.

DR. KENNETH PORTIER: That was Dr. Henry.

DR. MICHAEL PENNELL: I guess I don't -- at this point, I don't -- I'm not trying to make an -- really, a recommendation. I'm just -- based on -- I just noticed that comment there. And it is -- I mean, there is, you know, in these studies, the NTP runs, they do, you know, have a control group. But obviously, it's going to be probably similar to control groups they've had in other studies so that, you know, comparing, like, one group of 50 animals, it -- so one particular study may have one group of 50 animals may -- probably comparable to another control group of 50 animals in a previous NTP study.

So you know, the information you would have about, like, a control response rate is probably stronger than what you would just get from one particular group from that single study.

DR. SHARON OXENDINE: Yes. And this is Sharon Oxendine again, EPA.

I believe they discussed that in their study, and we took -- we ran with that. We didn't feel the need to go back and make that comparison ourselves.

DR. MICHAEL PENNELL: Okay. That's fine.

DR. KENNETH PORTIER: Dr. Thayer?

DR. KRISTINA THAYER: Yeah, I was -- this is Kris Thayer.

I was just going to sort of basically make that comment, that sort of, often, there's consideration of the historical control levels, especially if there's some debate about how to interpret the finding from the actual technical report study.

I also had a question, though, on that slide. So I think what you're saying is that, in terms of historical control levels, it's sort of a factor that you look at, but it's not a requirement the study has.

DR. SHARON OXENDINE: Yes.

DR. KRISTINA THAYER: And then I had the same kind of question for the individual animal data provided in tabular format. Is that sort of a nice feature? Or if you had a fabulous study that you didn't have that, you would, you know, do what you could to try to get that?

DR. SHARON OXENDINE: It just makes it easier for our modeler.

DR. KRISTINA THAYER: So it's not necessarily an exclusion?

DR. SHARON OXENDINE: Correct.

DR. KRISTINA THAYER: Okay. And then that can also be applied to sort of the human literature.

DR. SHARON OXENDINE: Yes.

DR. KRISTINA THAYER: Okay.

DR. KENNETH PORTIER: And I have an associated question. This is Ken Portier.

I don't see any mention of kind of positive and negative controls in these animal studies and whether that's a factor because I know in a number of these reviews that we've done, often we find publications where there's no control and you ask yourself what did they really provide. Or maybe there's only negative control but no positive.

So is that taken into account in this assessment?

DR. SHARON OXENDINE: Absolutely. Yes. In fact, that was one of the problems that we found with the repeat of the mutagenicity study that was conducted by BioReliance 2014. The problem with their control data, in our mind, excluded -- well, it diminished the utility of that study, in particular.

DR. KENNETH PORTIER: Dr. Georgopoulos, thank you for being patient.

DR. PANOS GEORGOPOULOS: Okay. No problem. Maybe I should not be asking these questions since it's past noon right now. But it's a more philosophical question. I don't know if I'm going to get an answer.

But the point here is when we're talking about the health effects and biological effects, we extrapolate from rodents to humans. But when it comes to pharmacokinetic model, it was dismissed earlier because -- the pharmacokinetic for rodents, but we don't extrapolate that to humans.

So I think it could provide some information regarding, you know, after scaling the times of when you measure, it could be a way incomplete and certainly not enough to drive risk assessment, but it could be something useful in informing the risk assessment. But it was dismissed.

So there is some kind of inconsistency here as to the value of extrapolating from rodents to humans. In one case, it is dismissed. In the other case, it is accepted. Given this is the only data that we have, I was wondering this. Any comment back from EPA for this choice?

DR. SHARON OXENDINE: This is Sharon, EPA. I guess I need clarification from you on which rodent studies were excluded.

DR. PANOS GEORGOPOULOS: I --

DR. SHARON OXENDINE: I'm not sure what you're referring to.

DR. PANOS GEORGOPOULOS: There's only one pharmacokinetic model from bromopropane.

DR. CHRIS BRINKERHOFF: This is Chris Brinkerhoff. There is one pharmacokinetic study for rat inhalation. Unfortunately, we don't have toxicokinetic data to inform a model for either other routes or any other species. Specifically, humans would be our most interested species. And I say that in terms of the human data. There are not even in vitro metabolism data for toxicokinetics in humans. So therefore, to construct a PBPK model, we would be making assumptions in every piece of the extrapolation either route-to-route or across species.

There is concern about doing that because we would then possibly be reflecting back to ourselves simply our assumptions in the first place, which becomes not a particularly valuable model.

DR. PANOS GEORGOPOULOS: Ah. Thanks.

DR. KENNETH PORTIER: And here's where I'm going to butcher your name. Dr. Quiros-Alcala?

DR. LESLIAM QUIROS-ALCALA: So same slide -- and I may be getting ahead of myself if I rush some of the charge questions. But can you expand a little bit about how you decided that a study was adequate or robust? Because I see, for example, in Appendix M there is a table of different things you consider, different criteria. But it's not clear, at least to me, what happens when a study meets some of these but not all of them. Like, what -- did you use a ranking system or a systematic system, you know, by which you decided, okay, these studies are robust, these are going to be considered in our refining of the risk assessment or these are not?

So I was wondering if you could comment on that.

DR. SHARON OXENDINE: So our process -- we're actually in the process of developing our approach for systematic review. And for this particular assessment, we basically dove in. We started with the report on carcinogens, and we looked at what they had done. We collected those studies, and then we evaluated each on its individual merit.

In the case where you had a study that, perhaps, was somewhat marginal, we didn't discount it. But it wasn't weighted as heavily as, say, the other studies that were more robust. We tried to take a weight-of-evidence approach, and we used a range of endpoints to try to capture what we felt was the lay of the land, if you will, for the hazard story.

But we don't have a specific list of boxes to check in terms of whether it's in or out. That's the best answer I can give you.

DR. KENNETH PORTIER: Dr. Thayer?

DR. KRISTINA THAYER: Just one more question -- so sort of in follow up to that, I was wondering in terms of the report on carcinogens evaluations, sort of given that it's constructed under the sort of the same OMB guidance that you have to be vigilant to.

Can you just not sort of use the conclusions versus having to sort of go back and find -- you know, look at the individual studies cited in it and in terms of moving forward as you think about how to be efficient in using systematic review methodology?

DR. SHARON OXENDINE: Personally, I think that's a great idea. If you have confidence in the study in the way it was conducted, I see no problem with that. But in this particular instance, we did go back and get the individual studies, and it took a lot of time. We could have gotten finished a lot quicker had we taken your approach.

DR. KENNETH PORTIER: I was trying to remember if I read this or not. Is -- do you guys consider 1-BP a complete carcinogen? Or does it need promotion? Or is it a promoter? I mean, I vaguely remember one sentence in the report, and I wondered if -- and I realize that the mode of action is uncertain and all this other stuff. But I wondered where you were on that.

Please identify yourself.

DR. YIN-TAK WOO: This is Yin-Tak Woo, EPA. I think the mode of action is not totally understood. And the 1-BP is very interesting. It's a very difficult chemical to evaluate because, once you have the one hydroxyl group they're totally different. The usual bromopropane compound is just a -- you know, a kind of what we call a soft electrophile that reactive SH compound. So that's why GSH is detoxifying.

But once you have one hydroxyl group, if the hydroxyl group is just next to it, it becomes -- next to each other is a halohydrin. It can go from hypoxcide out if it. And also, the hydroxyl group could have go to other aldehyde it could be a bifunctional compound.

So we have looked at all of these possible -- the non-genotoxic mechanism, some immune suppression, maybe oxidative stress and also maybe the self-perforation. But there's no single one that stands out enough to say this is the mode of action. So that's where we stand.

DR. KENNETH PORTIER: And while I have you here, one of the public commenters mentioned inflammation.

DR. YIN-TAK WOO: Yes.

DR. KENNETH PORTIER: And I wondered -- and that -- I don't remember hear -- seeing that discussed in the -- as a potential mechanism. And I wondered if you had actually explored that.

DR. YIN-TAK WOO: I -- we haven't explored for information. But information usually requires very long process. It's unlikely to be complete by itself without any help from genotoxicity.

DR. KENNETH PORTIER: Okay. At this point, I'm seeing 12:20. And I think it's time for us to take a break for lunch. We'll reconvene at 1:20. I asked the panel to kind of do a quick lunch, not a long lunch, because it's surprising in this part of town how long lunch can be if you actually sit down for something. We'll be back at 1:20.

Thank you.

(Whereupon, at 12:20 p.m. a luncheon recess was taken.)

AFTERNOON SESSION

(1:25 p.m.)

DR. KENNETH PORTIER: So I'm going to call the meeting back into order. At this point we're missing only two panel members, and they'll be in in a minute. Before releasing the EPA presenters, I thought I'd offer the panel one last opportunity for questions on this morning's presentations if there's anything you thought about over lunch that you'd like them to clarify.

I'm not seeing any questions at this point, so I'm going to take the opportunity now to thank the presenters for this morning's informative presentation and thank them for pretty much staying on time. That was good.

At this point, we're going to close that part of our program and move on to the Public Comment section of this meeting. And we have -- on the docket there's a large number of written comments that have been submitted to EPA that I know the panel has gotten access to and gotten copies of. There's also -- just within the last two days there have been three or four new comments in, and Steven Knott here wants to make an announcement about something that just came in this morning.

MR. STEVEN KNOTT: Thanks, Dr. Portier. I just wanted to make the panel members and the public aware of some additions to one of the dockets that contains public comments for the meeting that include a large number of files, and it really wouldn't be feasible to print and distribute or even email.

So I'll make everyone aware of the docket number, and I'll also share that link with the committee members so this evening or through proceedings today you can access that docket to take a look at what's there. And the docket number is EPA-HQ-OPPT-2015-0084.

DR. KENNETH PORTIER: G-V-A?

MR. STEVEN KNOTT: I'm sorry?

DR. KENNETH PORTIER: G as in great?

MR. STEVEN KNOTT: No, EPA.

DR. KENNETH PORTIER: Oh, EPA.

MR. STEVEN KNOTT: I'm sorry. EPA-HQ-OPPT. Oh, is it on the -- it's on -- okay, even better. It's on one of the comments. And my recommendation is this is under www.regulations.gov. My recommendation when you enter that docket would be sort it by posted newest to oldest. That way these three additions to the docket should appear at the top of the list. And again there's a number of files there, and I'll follow up with an email for the committee members as well. Thank you.

DR. KENNETH PORTIER: Now as far as I know -- this is Ken Portier. As far as I know there is only one public commenter who's requested to address the panel, Ms. Christina Franz, on behalf of the American Chemicals Counsel. And I asked Christina to join us. Under the rules of these public meetings we typically provide each public commenter five minutes to make the presentation, but I've -- since we only have one commenter and we've allocated quite a bit of time to this, I've told Christina she can have six minutes.

MS. CHRISTINA FRANZ: Thank you, Mr. Chair. Thank you. So good afternoon. And as our chair or your chair has indicated, I'm Christina

Franz. I'm a Senior Director of Regulatory and Technical Affairs and the American Chemistry Counsel in Washington, DC, and thank you for the opportunity to comment. ACC represents the leading companies engaged in the business of chemistry, and as such we have a significant interest in EPA's work plan, chemical risk assessments as they're designed to inform EPA's regulatory decision making.

In so doing it is critical that EPA uses the best available science, applies transparent and objective criteria to evaluate the scientific studies upon which it relies, integrates hazard and exposure when characterizing potential risk and ensures that peer reviews of its assessments are independent and robust.

ACC submitted written comments to the docket on the assessment and on this peer review meeting, and I encourage the CSAC committee and the subcommittee members to review our comments as it considers this draft assessment. We recognize EPA has provided you with a collated set of comments that organize comments to correspond with a specific charge question. EPA has not sought our input on that, so unfortunately some of our important comments appear to have been lost in the translation.

Well, I will try to point out some important concerns. I encourage you to look at our complete comments in the docket and not simply rely on the collation. However, in the collation, we ask you to look at page 57, which provides suggestions to improve the charge questions that you will be addressing.

In the interest of time, I will note the following five key points regarding the draft assessment. First, while EPA has conducted some benchmark dose modeling, EPA's draft assessment of 1-bromopropane is really a screening level assessment. This is important as you consider Charge Question 1-2 and whether the assessment is fit for purpose.

This assessment is designed to inform regulatory decision making, which requires a high degree of rigor. However, in choosing the endpoints and studies to rely upon, EPA has acknowledged that the studies used by the Agency were those that provided the lowest human equivalent concentrations. It appears that study quality, relevance and methodology were not the most important criteria for EPA. Rather, the studies selected were driven by the desire to use the lowest hazard values and the highest exposure values to ensure that the assessment was protective of the 95th percentile.

This approach is not consistent with using the best available science. EPA has not provided a transparent and systematic review of the quality of the individual studies. ACC suggests that such a review of the quality, relevance and reliability of the individual studies is necessary before selecting the values to use in the margin of exposure calculations.

While these conservative choices may be appropriate for a screening level assessment, they are not representative of the best available science, and further refinement is necessary before EPA moves toward considering regulatory approaches. Therefore, we ask you to ask closely at the quality and reliability of the studies and the reliance on the 95th percentile values. Your comments on the scientific rigor will be important to help EPA refine this draft screening level assessment.

Point number 2, when evaluating exposure, Charge Questions 2 and 3, it would be helpful if this panel commented on the inputs and assumptions EPA has used in the exposure modeling. Many appear to be worst case assumptions that overestimate potential exposures. Further details are provided in our May 9th comments and in the comments provided by Albemarle, one of our member companies. And I believe those were one of the most recent materials that were uploaded to the docket.

EPA used inaccurate, outdated and unsubstantiated information regarding consumer exposures and should refine the assessment using current data and information in both occupational and consumer settings with the assistance of industry stakeholders. Please also see the comments submitted to the docket by the Consumer Specialty Products Association for further detail regarding consumer exposures.

Point number 3, regarding the cancer hazard assessment as noted in our comments, once all the data are considered there does not appear to be strong evidence for genotoxicity of 1-bromopropane. In addition, EPA must consider a more complete evaluation of the scientific database when looking at the relevance of mouse lung tumors. As was thoroughly discussed at a 2014 EPA workshop, there is very little concordance between humans and mouse lung tumors.

Four, for the non-cancer evaluation we urge you to look closely at the studies EPA chose to rely upon in its modeling approach. For benchmark dose modeling, rather than using the typical benchmark response, that is a 5 or 10 percent standard deviation, EPA used a relative deviation for the developmental and reproductive endpoint.

This construct is not even mentioned in the EPA BMD technical guidance and should be looked at closely. This choice has a significant impact on the final assessment, and yet EPA's rationale for using it has not been provided. Your comments on this approach will be extremely helpful.

Five, we also encourage you to look closely at the reproductive and developmental endpoints that drive the non-cancer assessment. If you look at the raw data supporting the liver, the live litter size endpoint, EPA's choice of a 5 percent benchmark response represents less than one pup per litter. We urge you to discuss not only the statistics but also if there is biological relevance when relying on this endpoint.

In addition, consistent with EPA

guidance, the level of maternal toxicity must also be considered. This will require you to look closely at the study data to conduct a robust evaluation. Further details are provided in ACC's comments, which have been collated to correspond with Charge Questions 4.2 and 5-1. We also provided comments relevant to Charge Question 4-2 and the need to ensure that EPA is relying on the best available studies and clearly and appropriately describing them.

And separately, apart from the assessment itself, with all due respect to Dr. Barone, since he led the risk assessment team that prepared the draft assessment his new role in EPA's office responsible for the peer review of this assessment does create a conflict. We hope he will keep an arm's length distance from the review. We appreciate the time and energy you are contributing to this work over these two days. We recognize the assessment can be technical and complex.

When EPA began the search for expertise for this panel, it appears that perhaps the neurotoxicity endpoint was the primary driver for the assessment. However, it now appears that the non-cancer driver in the current draft is the developmental and reproductive endpoint. If there are questions that cannot be answered during your in depth evaluation, we encourage you to seek additional experts to inform your review.

Thank you again for the opportunity to comment, and we look forward to further engagement with this panel. Thank you.

DR. KENNETH PORTIER: Thank you, Ms. Franz. I warned Ms. Franz that I would allow the panel to ask her any questions, and she said she'd entertain them as long as I allowed her to bring technical support if needed.

MS. CHRISTINA FRANZ: Yes, I'm not a toxicologist, so I have one here.

DR. KENNETH PORTIER: She's not a toxicologist, but she knows one or knows somebody who plays one on TV, right?

MS. CHRISTINA FRANZ: Several of them as a matter of fact.

DR. KENNETH PORTIER: So at this point, I'll ask the panel does anybody have any questions, clarifying questions. Dr. Blando?

DR. JAMES BLANDO: Sure. You mentioned about the discordance between lung tumors in rodent models and humans, and I wonder if you can just provide us with some more details on that particular point.

MS. CHRISTINA FRANZ: I am going to defer to Dr. Nancy Beck, who is a toxicologist with ACC.

DR. NANCY BECK: Hi, Nancy Beck, also with the ACC. A lot of mechanistic toxicologists have looked into this issue, and EPA has had a workshop on the topic. The mouse lung tumors seem to be mediated by cytochrome p450. That just doesn't exist in humans, so the model of using the mouse lung tumor has been questioned, not just for 1-bromopropane, for a lot of other solvents where you see toxicity in the mouse female lung but not in any other species or sex. So it seems to be very species specific. So there's been a lot of discussion, a lot of papers published, a lot of people looking into this.

MS. CHRISTINA FRANZ: And --

DR. NANCY BECK: Yeah.

MS. CHRISTINA FRANZ: If I can also emphasize that there's, I think, significant discussion of this in the Albemarle comments that were just posted to the docket.

DR. JAMES BLANDO: Just one additional clarifier, you mentioned that cytochrome p450 is not present in humans. Do you mean in the human lung? Is that --

DR. NANCY BECK: So yeah. It's a specific isoform. I think it -- I want to say 2F, but I'm not sure.

DR. JAMES BLANDO: Okay.

DR. NANCY BECK: I may be confusing my species, but there's a specific isoform in the mouse lung that people questioned whether or not it exists at all in the humans. And that may explain the very species specific effect that is seen in that animal.

DR. JAMES BLANDO: Okay, great. Thank you.

DR. KATHLEEN GILBERT: I thought that 1-BP was metabolized primarily by CYP2E1, which certainly exists in humans.

DR. NANCY BECK: This is correct, but there may be some specific -- species specific metabolism going on in the female mouse lung, right? So there may be some specific metabolites that could be causing the carcinogens you see. Again, more details on this and the discussions that have been had and EPA workshops are in the Albemarle comments that you received.

DR. KENNETH PORTIER: That was Dr. Gilbert who asked the question. Any -- oh, Dr. Thayer?

DR. KRISTINA THAYER: Hi. This is Kris. Nancy, that workshop, was that focused on sort of -- I think it was three other chemicals? I was sort of wondering how generalizable those comments are.

DR. NANCY BECK: Yeah, I think the comments are rather generalizable when you see that -- 1-bromopropane I don't think was one of the chemicals discussed.

DR. KRISTINA THAYER: No, I don't believe it was.

DR. NANCY BECK: But the workshop as not meant to be chemical specific. It was -- used some chemical specific examples for this case when you have these tumors in the female mouse lung but no other species.

So I think it is meant to be generally applicable, but of course in any toxicology data set you need to look at all the data. You need to look closely at the mechanism of action. You really need to understand what's going on with the specific chemistry.

DR. KRISTINA THAYER: Yeah, because I just didn't see any sort of general conclusion of that in the workshop report.

DR. NANCY BECK: You have to look at the workshop report.

DR. KENNETH PORTIER: Dr. Hossain?

DR. MUHAMMAD HOSSAIN: So as you said that only female mouse has developed lung tumors, and I think is there -- could be relation between there because there are hormonal differences between male and females, could be female hormone involved in this pathway.

DR. NANCY BECK: There could be.

DR. MUHAMMAD HOSSAIN: Call it a developing item.

DR. NANCY BECK: I don't -- there could be. Again, the idea is that you really need to look at the chemistry and understand the science and think about what endpoints you're using before simply making the assumption that yes, they're relevant to humans. In this case where there are female mouse lung tumors, there has been a lot of questions about the relevance to humans. So you're asking the right questions.

DR. MUHAMMAD HOSSAIN: Thank you.

DR. KENNETH PORTIER: Dr. Marty?

DR. MELANIE MARTY: Melanie Marty. So it brings a couple issues up. One is site concordance amongst species, so I'd like to point out that 1-bromopropane also induced tumors statistically significant in distal sites, so this argument about the lung tumors really is, in my view, irrelevant and particularly since CYP2E1 is present in the human lung.

So when you think about whether something is a carcinogen, if a carcinogen in multiple sites, then that actually is a lot more important information that where in the animal model the tumor is formed.

DR. NANCY BECK: So I absolutely agree with you 100 percent, and we're not saying that 1-bromopropane does not cause tumors at other sites. However, when you do the dose response assessment and you come up with your risk numbers, you have to question whether not the driver here is the mouse lung tumors. And then that's when it becomes important to talk about are we as confident in those tumors as we are in the other tumors and what is the right endpoint to use for the dose response.

DR. KENNETH PORTIER: Okay. I don't see any additional questions. Thank you very much for --

DR. NANCY BECK: Thank you.

MS. CHRISTINA FRANZ: Okay. Thank you.

DR. KENNETH PORTIER: -- bringing these issues before the panel. I guess I'll make one last call in the room to see if there are any other public commenters who would like to comment before the panel. I don't think there are any. Not seeing anyone, at this point I'll close the Public Comment section and we'll proceed on to the panel starting to address the questions that EPA asked us.

The general process is we're going to go through the questions in batches, so as EPA has done, they've grouped them -- every two or three questions into a batch. So the first question is on general issues on the risk assessment. Someone from EPA is going to read the question before the panel. We'll debate the two questions in this section, and then at the end, I'll come back to EPA and ask whether they have any clarifying questions of the panel of anything that we presented.

So, you know, we get to have our say and then they get to kind of do a little bit of cross questioning to make sure they understand and we understand what we said. So who's going to be reading the questions? Dr. Henry? No.

DR. KATHERINE ANITOLE: We have some slides that were on the end of our slide deck for the charge questions.

DR. KENNETH PORTIER: Coming up.

DR. KATHERINE ANITOLE: I don't know if I should wait until he gets those up or just go ahead and get started. Okay. So these two questions relate to general issues on the risk assessment. Question 1-1, please comment on whether the information provided in Section 1, Background and Scope, is appropriate and accurately characterizes the fit for purpose nature of this assessment for TSCA related uses. Please provide any specific suggestions for improving the clarity and transparency of the background information that describes scope and limits of the assessment.

DR. KENNETH PORTIER: The panel has identified four people to start the conversation, and

Dr. Holly drew the short straw. So she's going to initiate the conversation.

DR. HOLLY DAVIES: Okay. This is Holly Davies. I'm going to start with some comments on this. In general, I do think Section 1 clearly presents the scope, approach and uncertainties. I have some editorial comments that I'll include in my written comments.

While the Agency clearly explained where the information comes from, it's not clear how the Agency has weighted the different information. And in fact, in Appendix G it suggests a variety of sources are treated equally instead of weighting say a peer review journal more than just comments from somebody differently. So that could be improved.

I had a lot of questions that came up when I was reading this. Adding explanations about the authority that you have under TSCA. You refer to TSCA products. Of course you're only going to be looking at what you have authority for but continuing to say TSCA products really begs the questions of well, what's not a TSCA product. And that would be good to include for a general audience and what risk management options you have under this, so why are you getting this and what you can do with the information.

And then I will open it up to the next person, which was Jaymie Meliker. Where's Jaymie?

DR. JAYMIE MELIKER: Sure. So just a few other points, and this is mainly like, you know, I read through the public comments and I want to reiterate some of them. So questions were raised as to whether all the important industrial sources were identified and the extent to which we understand community level exposures in areas near by industrial or even dry cleaning operations. And I think that's something I know -- I think Delaware, the state of Delaware -- somebody from the state of Delaware submitted this public comment about nearby dry cleaning operations. And it sounded like they had some data that might be useful.

And then on the other side, there were some comments from individuals who question the extent to which dry cleaners were or will be an important source at all. So it seems like there's -- it's muddled I guess as to what an important source is, but I think we need to know a little bit more about that. And along similar lines, it would be helpful to describe the literature search process that identified that relevant literature sources because it's so muddled, it seems like, from the public comments about the different sources of this chemical, so explaining that process.

Another important point, which I think probably belongs here, is this question about biomarkers of exposure, which we talked about this morning, this N-acetyl-S-(n-propyl)-L-cysteine, which is now measured NHANES. It sounds like it is a metabolite of 1-BP, but -- and I don't know the literature on this, but how specific is this biomarker?

Can it be inferred to be a biomarker indicative of exposure to 1-BP and not something else? And if so, then that really does -- I don't know. I think it presents a lot of challenges for this risk assessment because all of a sudden it seems like there is much wider exposure, you know, if it is a specific biomarker.

In terms of dermal exposures, I would agree that they might be important as a contributor to overall exposure, but given that it didn't sound like data are available for monitoring or modeling efforts, I think it's okay, and I'm okay not including this root of exposure. Just wanted to comment on that, too.

DR. KENNETH PORTIER: Dr. Schlenck?

DR. DANIEL SCHLENK: Yes, Dan Schlenck. Overall I thought Section 1 was appropriate and accurately characterizes the fit for purpose nature of the assessment for TSCA related uses as mandated by the TSCA work plan. The background information was clear and transparent, at least in my viewing of it, and it accurately described the uses and production volume for this particular compound, the assessment and regulatory history of 1-BP and at least in this particular overall component, the scope of the assessment and why the Agency chose that particular direction and that exposure component.

The questions targeted for the assessment were clear, and the data is present, I think, that allows those particular questions to be answered, and I think the key is the data is there, which is why you asked those questions. That's a little circular argument to a certain degree.

So with regard to the limits, I would say there is some discussion regarding the inability to model dermal and oral exposures, which again would like contribute to inhalation as an additional exposure route in the occupational and domestic uses for 1-BP. In terms of additional limits, I think text regarding the data gaps, and again, I'm not sure where to put this is -- put it here or in your next question. But again, being an eco sort of person I think there's some data gaps that should be discussed primarily with these and other HPV chemicals. We just don't have the data that's there for a lot of things, and I'll go into more detail on that below.

The other thing I wasn't sure whether to talk about this here or also in Question 4.3, I believe it is, is the use of an adverse outcome paradigm which can be used in the problem formulation step for human health and not just eco but for human health based risk assessments that will again target uncertainties and data gaps, particularly for mode of action. And this has come up a lot actually in some of the discussions, which will help in biomarker determination I think in terms of being able to determine whether or not your biomarker is specific or not.

So if you can tease that out and actually put that here, I think that would be relevant. I think it also fits obviously in the weight of evidence component, and there's a lot of discussion, I know, with that paradigm, whether people should use it in formulation. I would say the unique aspect of this particular risk assessment is sort of a hybrid of an eco and a human health because human health doesn't usually put problem formulation.

So with the new model that's present now, I think it may serve its purpose in that capacity more so than just in the weight of evidence components that are normally used in terms of the human health. But I think that would hopefully identify some of the data gaps that are present.

DR. KENNETH PORTIER: Dr. Thayer?

DR. KRISTINA THAYER: Hi. So again I just want to sort of appreciate all the work that's gone into compiling the document. I learned a lot reading it. Probably not surprising I guess, sort of recommendation to move down the path of the systematic review just in terms of the transparency.

I understand this document was probably started before a lot of the work that Irish group has done in terms of coming up with guidance existed, and so certainly not suggesting sort of a do over all.

I'm just sort of suggesting as a moving forward.

And I think that a lot of, you know, at a minimum I know you can't really retrofit an analysis that's essentially done to be systematic review, but certainly there was a process for identifying the studies. It might not be the one that you use moving forward, but it was there and that should be described. And anything that you can add in terms of sort of the inclusion, exclusion levels. And that can be sort of an appendix.

And I think sort of moving forward on the systematic review, sort of adopting more elements of that. I'm not sure how much you've had a chance to bring that into the evaluations that you're starting now or what your experience is, but in our experience, it gets easier.

So I don't know how it feels for you now, but once you sort of have done it to a couple, you won't look back. It not only sort gives that clarity to your audience that they are really requiring, it's really more efficient from sort of a project management perspective. So I don't think you'll regret that. I will buy cookies for everybody in three years if you do regret that.

So let's see. And then I have some comment on the scope that I'm not sure if they're Questions 1-2 or 1-1, but I'll go ahead and say them now. So some of the scope, I think I was sympathetic to some of the public comments about sort of doing more to consider the residential or the general population and sort of the residential scenarios in particular living near a dry cleaning facility.

I understand that the data might not be there for modeling, but that should be explicit. And it wasn't clear to me, for example, on you know, there are other applications of model data in the document, but why could the example from PERC not inform a model based on sort of the co-residential. So just more clarity on sort of the decisions about when you chose to pursue a model or when you didn't. That would help.

And I think also for the dermal, the point raised by James earlier about sort of the occluded surface sort of being covered by clothes, I think that would be good to consider. And then the issue about the biomonitoring and trying to do more to draw that conversation into the document. I understand there's probably not a resolution, but it just needs to be mentioned. But I think you've probably already got that point.

DR. KENNETH PORTIER: Dr. Kissel? He grabbed first.

DR. JOHN KISSEL: One point on clarity. I thought in Section 1.5.5 there's a general description of use of MOE approaches, which is fine there, but on pages 26 and 27 of the executive summary it's actually presented in a confusing fashion. There's three different sentences in which a phrase something like "risks were below the benchmark MOE" appears.

MOE is not risk, so you can't equate the two things in the first place. MOE is a safety standard not a risk standard, and those sentences should say something along the lines that the estimated MOE was below the MOE benchmark. So when you say the risk is below the benchmark, it sounds like the risk is low when in fact the finding is that there's a hazard present. And so it's backwards. And that appears three different places, so it needs to get cleaned up.

DR. KENNETH PORTIER: Dr. Gilbert?

DR. KATHLEEN GILBERT: Thanks. Once

again, I really appreciated all the effort, and I also learned a lot reading this. It says peer review, so I'd be curious to know exactly who, you know, the target audience was because as far as transparency goes I mean I learned a lot, but it was -- I mean to me it read like it was written for other risk assessors.

And is that how it was written? Because I think as far as transparency goes, a little more background and explaining the whole process would've been useful for certainly the general public if that's who is supposed to be reading this and even for those of us which consider ourselves toxicologists but don't have extensive backgrounds in risk assessment.

DR. KENNETH PORTIER: Dr. Quiros-Alcala? Quiros-Alcala, I'll get it right.

DR. LESLIAM QUIROS-ALCALA: Hi. Along the lines with Dr. Gilbert, I had the same comment as far as transparency and also -- because there is a statement saying that, you know, this is not only available to risk managers, but also to people in the general public. And I don't think as is they could pick it up and do much with it.

Also there is, on Section 1.2, page 28 that talks about uses and production volume, there's a sentence that says in the past 1-BP has been used for, you know, other uses like fats, waxes, et cetera. I think it would be good to point out whether these uses could still exist and pose a hazard anymore because as it reads -- so it's saying in the past, but do they still represent an exposure hazard to people or not. Are some of these things still out there and could represent an exposure risk? So I think that would be strengthen that statement. And then I have other minor comments that I can submit later on.

DR. KENNETH PORTIER: Dr. Blando?

DR. JAMES BLANDO: So I have some minor comments that I'll include with my written document, but I just had three editorial comments that I thought maybe would be worth noting. The first comment I would make in response to Dr. Meliker's comment about the public comment about whether dry cleaning would be an important source of exposure.

And I just wanted to point out that in the dry cleaning industry, when we did our studies with dry cleaners and we spent a lot of time with dry cleaners, one of the things that's important to keep in mind is that if there is a ban in the air programs on the use of PERC is dry cleaning, for most dry cleaners the only option that they would have would be to switch, unless they bought a new machine, would be to switch to a 1-bromopropane containing solvent at the moment.

Many of the dry cleaners that we interacted with on a routine basis just reported to us that they just don't have the money to buy a wet cleaning machine or a hydrocarbon machine. So the potential concern that we had was when air programs, maybe rightly so, went to move forward with banning PERC they were essentially driving the dry cleaners to basically, who have a PERC machine, a Gen-3 PERC machine, to drive them to using 1-bromopropane containing solvents.

And that did represent a potential much larger number of people that could be exposed. In fact, when we looked at our Dun & Bradstreet database in New Jersey we found -- we estimated -- I'm trying to remember the exact numbers, roughly around 1,500 dry cleaners with a median of two employees per dry cleaner. So we're talking 3000 people that could potentially be switching out to a bromopropane containing solvent.

Now what happened is the PERC ban was delayed as you know, but it still exists, and I think the timeline, 2020 or something like that. So if there is still a move afoot to ban PERC in dry cleaning, it would certainly be worthwhile to check to see what the implication of that is in relation to bromopropane. So just in response to that question.

And then just the other two sort of editorial comments that I just wanted to make for your consideration. One of the other problems we found when we spent time with people who were using bromopropane in industrial settings was that this chemical at the time, and this is going back to 2008 but I think it's actually still somewhat perhaps true today, although correct me if I'm wrong, this chemical was kind of marketed as a green chemical.

Although this is a risk assessment process not a risk management process that we're talking about today, I do think it's important to note in the introduction section so that when you do start thinking about risk management -- I think there was a risk communication issue because most of the people that we interacted with who were actually using this chemical, they interpreted that it's a green chemical.

Their interpretation was it was non-toxic. And I think that really significantly contributed to some of the poor hygiene practices that resulted in some of the poisonings that we've reported in the literature. So I think that even though it's an editorial comment, that might be something worth explicitly noting in our introduction section, that when it comes to a risk communication standpoint to clarify, you know, if this chemical is continued to be marketed as a green chemical to clarify that.

And then just the other small little detail that I wanted to mention, and this is a little bit historic, that may be worthwhile to mention in the introduction and background, maybe not, is when we started in 2008 with our first two reported cases from our poison control center of bromopropane, early on there was some speculation in these cases that perhaps it was 2-bromapropane, which is a common contaminant in some of the processes and that maybe it was the 2-bromapropane that was actually causing the problem.

And this was raised to us when went to sample for 1-bromopropane. And in fact, as you may know, a gentleman, Gaku Ichihara, a Japanese neurologist, in 2005 published a review article that clearly showed issues with 2-bromapropane. And this was something that was raised to us. As a point of clarification for the paper we published on dry cleaning, I just wanted to point out that we only kind of alluded to the fact that we sampled for 2-bromopropane, but in fact we actually did sample.

We just didn't report it in the paper because it wasn't exciting because most of the results for 2-BP were non-detect. Of course non-detect is not particularly exciting, so we didn't really clearly define that in our paper. The reason why I mention that here is because it sounds like in this forum it might be interesting to point out that the argument that perhaps there's a contamination issue with some of the products containing 1-bromopropane, we actually did look at the potential contaminant and found it was non-detect in our studies. I don't know if I explained that clearly, but those are just -- some two editorial that you could consider for inclusion in the background document.

DR. LESLIAM QUIROS-ALCALA: This is just a quick comment. So this -- sorry, Lesliam Quiros. In some instances, and I don't know if it's here. Again, I found like there are a lot of responses that overlapped with other charge questions. But this was, you know, in some instances you say model results were adequate, or I don't know, it's just a lot of qualitative statements that don't really tell us what made it adequate. I think that would help us a lot. And I know that a lot of hard work went into this, so that would make it more clear and more transparent to the reader.

DR. KENNETH PORTIER: Thank you. I kind of had similar comments myself as I read it, and I wanted to make a recommendation about Section 1.1. So you talk about fit for purpose, but it takes quite a bit of reading to actually understand what the purpose is. And I think Dr. Kissel pointed out, there's kind of two purposes here for this document, for this assessment.

One is to identify unacceptable risks to humans and environment, but the other one, as somebody mentioned, is a risk management, a risk communication. It's to inform risk managers and the broader risk community of any unacceptable risks so identified.

And so as I started reading this

document, I kept these two things in the back of my mind, so I'll be commenting on sections when I'd find it unclear, you know, thinking if I were a risk manager, can I understand what you wrote here. And so I'm just kind of warning that in Section 1.1 it would probably be good to come back and look. Do I clearly state the purpose of the document upfront so people know what fit for purpose is really measured against?

And it's particularly bad in the first two paragraphs because you kind of bounce all over the place. You have a little bit of purpose, a little bit of history, a little bit of how we got there. In the last two, the history and how we got there kind of thing, you cover a lot more later on, so there's not a lot of reason to even mention that upfront. So I would recommend that.

Okay. Any additional questions, any additional comments on Question 1.1? Dr. Davies?

DR. HOLLY DAVIES: Hi. I just had one more thing I wanted to be more explicit on with explaining. You used a lot of different terms about what risks we're looking for because there's -- I mean the phrase in TSCA is unreasonable risk, as Dr. Portier just said, the unacceptable risks. There's questions about risks of concern, and so it would be nice to make it clear if those are different ways of saying the same thing or what exactly -- what level you're looking for.

DR. KENNETH PORTIER: Yeah. That's a good point. Okay. Let's entertain Question 1.2

DR. KATHERINE ANITOLE: Okay. Please comment on the scope of the assessment, in particular the conceptual model resulting from EPA/OPPT's problem formulation. Please provide any other significant literature, reports, or data that would be useful to complete this characterization and that may support expansion or refinement of the scope of this assessment.

DR. KENNETH PORTIER: Dr. Marty leads off.

DR. MELANIE MARTY: Melanie Marty. So I think the scope of the assessment is mostly appropriate for the consumer and work exposures. I have a few concerns, which I'll probably wait until a few questions down to mention. But in looking at the problem formulation diagram, it's not clear why emissions from operations that use 1-BP or manufacture 1-BP like degreasing, dry cleaning or emissive sources aren't considered for assessing risk to the general public.

And I heard earlier you guys don't think you have the data, but I'm not sure I'm agreeing with that assessment. So you know, it's a high production volume chemical. It's very volatile. All of the engineering controls involve venting out the stack, so it's pretty clear that it's escaping from dry cleaning and degreasing operations into the environment.

Lots of people are concerned about it. I can say the California EPA is concerned about it, especially because it's use is proposed as an alternative to PERC in dry cleaning, so we are seeing more dry cleaners in California using 1-BP. So I just think it's -- you really ought to rethink that, and I strongly recommend that you do something about assessing risk to the general public.

So there's a couple of issues around that. One is that there have been assessments done in California for "a typical dry cleaner" that could be very appropriate to do here for you guys. I know you really want things that are representative, but again, a lot of the data you have that you based exposure assessments on for other scenarios aren't necessarily representative. And you recognized that in your analysis of the uncertainties.

So CARB had emissions, factories from degreasers, which I mentioned earlier, I think those could probably be used to estimate exposures to receptors near the fence line and beyond. I don't think that it's going to be much less uncertain than anything that you guys have already done, which is a lot. I have to say it's amazing to me that you -- a lot of effort went into this.

Also, if you're looking at exposure to the general public, then you can consider infants and children and cancer risk from chronic exposure, residing near a dry cleaner for example or even in the same building as a dry cleaner. And in the 2005 supplemental guidance for assessment cancer risk from early life exposures, you would apply the age dependent adjustment factors because there's, you know, a certain probability that genotoxicity is involved.

And then, of course, you'd apply age appropriate inhalation rates. So it's not going to be a linear, you know, just sort of a proportional thing.

Well, the general public is exposed to 1/100, so therefore the risk is 1/100. It's actually going to be more than that because you're going to consider early life exposure, so that's something that I think is pretty important. Okay, I think I'll stop there. There's a few other things, but they're just as applicable to some of the charge questions later on.

DR. KENNETH PORTIER: Dr. Quiros?

DR. LESLIAM QUIROS-ALCALA: So I had very similar comments to Dr. Marty, and just to emphasize the chronic exposure to the general population, other reasons why they're really important. As Dr. Marty was saying, sometimes we have people living in the same building, or sometimes you have childcare centers in the same building as a dry cleaning facility, food establishments, so I think it's really critical to include this if at all possible in this risk assessment. And my other comments replicate what Dr. Marty said, so I'll submit them.

DR. KENNETH PORTIER: Dr. Schlenck?

DR. DANIEL SCHLENK: Let's see if I can get this without spilling stuff. Yeah, so basically my comments are going to primarily to the eco side of things on this. And this is something that is coming up more and more with emerging contaminants, particularly -- and this is based on the assumptions that again go back to the TSCA work plan model where you're basically looking at compounds that are, you know, if anything's below log, the KOW of 3, they're not considered for any sort of other route of exposure, route of discharge.

And these particular compounds, I think, actually fit something. And I know the data is not there, but I think this is something as you go forward with compounds of this nature, which you're going to have to do eventually, to consider some of these sort of concepts that have been coming out, particularly out of the emerging contaminant arena these days.

So again, the assumption here is that this, because of Henry's constant and volatility is that this is primarily an inhalation based route of exposure, and I totally agree with that, totally buy that from the human health perspective.

But if you look at the use patterns with this compound and the fact that it's also a high production volume chemical, it's very likely that you're going to get waste water movement of this compound into water at some point.

If you look at the fugacity model that's used, it's basically the same percentage estimate that goes into water as it goes in the air, so to discount any kind of water based exposure I think is a little bit, somewhat shortsighted. And again, this is something in the conceptual model that should come out at some particular point, so based up on just the fugacity component.

And again, the other component that's usually used again for these particular solvents and VOCs in general is that there's no persistence or bioaccumulation, which is very possible. But again, with a compound of a log KOW of greater than 1, in this particular case 1.5, that's still 50 times more likely to go into an organism that to stay in water once it's in an aqueous setting. So you do have the potential for exposure.

And a concept that's come out of, again, the emerging contaminant realm is this term called pseudo-persistence. And if you've got a compound that's a high production volume chemical, it doesn't matter really what the half-life is. At the point of discharge you are going to get exposure to aquatic organisms at that particular point. So again, this is something that needs to be addressed.

And I think maybe even in the appendices it said well, you know, there is acute tox data on this, and that's great that there is some acute tox data. But again, given what we've seen, and this is where again adverse outcome pathways come into play, if you know that this compound has developmental and reproductive toxicity with, at least in mammals, it's very likely that you're going to get a same mode of action across vertebrates in general.

So consequently, if you're thinking in terms of constant exposure, then sub-lethal types of toxic endpoints are data gaps that are missing here. You have acute toxicity, and obviously it's probably not a concern from an acute toxicity perspective. And again, without the data you obviously can't confirm that. My whole is that in discussing this, that's what the purpose of the conceptual model is, to put dotted lines like you have with dermal and oral exposure.

On the eco side, the only eco thing you have is coming from air, and I think, you know, to be complete and to present all data gaps that this would be sort of a valid way to do it in the future if you're going to be doing these compounds, which sounds like you are, in the future if you're going to be setting up a conceptual model to include all of those particular pathways and not just make assumptions based on, again, historical data and that it's volatile and not persistent so therefore it's not a problem.

But -- so those are things that are coming, again, through more the emerging contaminant issues as well, so I would maybe look -- check with people at Office of Water to see how they're actually dealing with those sort of concepts because that's obviously what they're having to deal with for now.

And again yeah, so you know, similarly how you have with dermal and oral and you can't do PVK predictions, and you've identified those gaps, I think you can also do that also with the ecological side of things, too.

DR. KENNETH PORTIER: Thank you. Dr. Thayer?

DR. KRISTINA THAYER: I think the only thing -- I agree with the comments made. I think the only unique thing I might have, and it's actually not unique since it was raised earlier, was -- it came up during the sort of clarification phase talking about, I think it was ExpoCast as sort of another place that you could sort of mention the article, sort of talk about other -- sort of the consumer product applications. I realize they might sort of not fall under sort of the TSCA probably, but I think it sort of of helps give a better picture of sort of the -- especially in the light of the NHANES data about other sources of exposure.

DR. KENNETH PORTIER: Dr. Gilbert?

DR. KATHLEEN GILBERT: So this brings up the point of the -- I know a lot of people are concerned about the general public exposure, and I certainly understand why that's interesting. It just seems to me that they've already got a fair amount of stuff to work with as far as their occupational exposure and the hobbyists and that I don't exactly know how the risk management part of this whole things works, but presumably, if they deal with those issues then the issue as far as the general public living near the facilities would essentially go away.

And I would hate to see a delay just to

accumulate more of that hard to get data when they already have a pretty good set of stuff to work with.

DR. KENNETH PORTIER: Dr. Marty?

DR. MELANIE MARTY: Yeah, I've thought about that, too, because I don't think that it -- we don't need more delays on this chemical in my view. But just a couple of things. So we do a general public risk assessment, all of a sudden your number of people exposed goes way up. So that's a pretty critical thing to think about, and I think it should be done.

And then one of the ways that you decrease worker exposure is you increase it venting out the air, so you actually sometimes make it worse for the general public by making it better for workers. So I mean the risks are not equivalent. The occupational exposures tend to be much higher, but it's kind of a catch-22.

DR. KENNETH PORTIER: Dr. Blando?

DR. JAMES BLANDO: Sure. This is Jim Blando. Just to mention quickly in support of comments talking about the general public exposures, I just wanted to note that EPA's urban air toxic strategy -- I have an old citation from 1998 that's in my written comments, but they pointed out that PERC was a significant driver for a very common air toxic in urban areas. And that was primarily driven by the presence of dry cleaners, a high number of dry cleaners in urban areas.

If dry cleaners were to substitute bromopropane for PERC, one could extend that sort of logic and thinking that this could be -- albeit we don't want to delay action for sure, but it still points to something that might be important to consider.

Just the other comment I wanted to make about this question was that if there was some ability to provide some more context in the document with regard to the acute consumer exposures, I think for those of us that do a lot of public health work -- because what will happen with this document is it's not just going to be EPA folks using it.

You're going to have folks in your public health department who's going to have a pregnant woman call them up on the phone very concerned about them using some consumer product. And I think if there was some context, for example, if exposure has to occur during a very specific window if that's the case -- I have to defer to the toxicologists for that.

But if the exposure had to occur during a very specific critical window in order for there to be an effect recognized, you'd probably want to communicate that so that a public health person who may be saddled with somebody calling them saying I used a product that had 1-bromopropane; I'm pregnant; I'm having a lot of anxiety over this, that they know how to provide the proper context to that caller. And if that is the case with these consumer exposures, it would be important to provide that, some context so that you could help make those types of consultations. Thank you.

DR. KENNETH PORTIER: Dr. Davies?

DR. HOLLY DAVIES: I wanted to support some of the earlier comments about including environmental releases and the general public or at least public close to manufacturing facilities or dry cleaners. I wanted to point out that Seattle King County Public Health has done a lot of work with dry cleaners, and I can provide the references for those studies.

And one of the things that they found

with those dry cleaners is 69 percent of the dry cleaners were in a building that also housed a business that sold or provided food. So that's a large percentage that could be included. Also the worker exposure during waste disposal, I don't think this is a state specific.

People can correct me, but in Washington state our dry cleaners take the vast amounts of waste, and they boil it or in some way separate it so that they get rid of the water. So now they have a smaller amount of hazardous waste to dispose of. And that seems like an exposure that should be added and that the state has just waste agencies would have numbers for that.

DR. KENNETH PORTIER: Dr. Georgopoulos?

DR. PANOS GEORGOPOULOS: Again, following up on this, I think it would be helpful if the life cycle approach to risk analysis which appears to be embraced by EPA, by TSCA and so on is discussed clearly and is identified during manufacturing. I mean obviously the exposures, occupational exposures, during manufacturing of the bromopropane and we haven't seen anything about it. This could be very significant exposures.

Then it uses intermediate in industry. Those industries with cosmetics, whether it's used or not, it starts with it because the numbers that are presented reports that about 90 percent is used in spot removers and cleaners. But the actual percentages are questionable. I mean we need to get market data, actual data. It is a good fact that it's going to be from 2016 reported in TRI for vent emissions, but we need this cradle to grave or life cycle analysis during manufacturing, during transport and eventually after disposable. And after disposal it will find its way in the general environment, so it will continue to have exposure remotely.

So even identifying and listing clearly the data gaps and knowledge gaps associated with each of the steps of the life cycle analysis is helpful in putting in context. I'm not saying that we should wait for a perfect risk assessment in order to make a decision, but the fact that we are missing so many exposures should be further factor that will justify a decision based on high exposures associated with only a snapshot or a cross or a slice of the possible exposures.

And in terms of risk management,

clearly today despite some claims that were made in the public comments, you can go online and you can buy various and have delivered gallons of this stuff at your home, you know, by ordering in a couple of places on the Internet. I went to allbrands.com, and you can order Ever-Bloom, you know, it is a major constituent. So somebody said, oh, it's only used by professionals. No, it is not.

I mean I know stuff like this is used in fast food restaurants to remove, you know, stains from, you know, the dishes. They don't send them to the professional dry cleaners every day, so there are uses that are not accounted for, and they can contribute to exposures substantially. And it's very easily -- you can buy it very easily.

It's available to major source on the Internet, so -- and it's marketed. Actually, one of the things that you can find is that there are no dangerous components in these products. It's green. It's an alternative.

They use the SNAP designation. It's a -- not ozone depleting, so it's good stuff. It is marketed today as a green chemical, so given this fact, we should not wait. However, listing all the data gaps and filling these gaps will reveal additional exposures and risks would be helpful in communicating and putting the risk in context, and those calculations are represented here in context also.

DR. KENNETH PORTIER: Dr. Davies?

DR. HOLLY DAVIES: Oh, sorry. I just put it down.

DR. KENNETH PORTIER: No, she's done.

DR. HOLLY DAVIES: Sorry.

DR. KENNETH PORTIER: I wanted to add a few comments to this. As I was reading this section, and this is more again about clarifying. You know, first, you look at Section 3.4 -- 1.4, and you've kind of got this list of nine users, and then you have the seven questions. And you know, as I looked at that section, I really like the seven questions, and I think the list of nine users doesn't add a whole lot. The users are implied in the questions, and the questions are what you're answering in this document.

So I would kind of focus on that. Make sure you have the right questions asked, and in fact Question 7 could actually be reformulated to be very similar to the occupational questions one through 6 with a little bit a -- without too much work.

The other thing is in Section 1.5 you begin by discussing selected scenarios, but it seems like you use the terms scenarios and uses the same. And so I went and looked up what do we mean by uses, and what do we mean by scenarios. You know, scenarios are defined as a postulated sequence or development of events whereas a use is defined as the action of using something or the state of being used.

And I think for risk assessment you're doing a lot of scenarios. You're not talking about use. You're talking about scenarios. You're assessing the risk under a plan, a play. So I think you want to be careful when you're talking about scenarios you're really using the word scenario. So again, it's just kind of making it easier for people to understand what's going on.

On the environmental risk, it's kind of mentioned in two or three different places, and in fact, it probably belongs in Section 1.4 more so that Section 1.5 where you're talking about the scope of the assessment. You know, Dr. Schlenck brings up a lot of points that probably need to be discussed later in like a Section 1.5.4.3, right, because it becomes part of the conceptual model.

But you kind of mention it. Then you mention it. You don't mention it. I got the feeling that you're being defensive against it or something. You just need to say it was not in scope and move on from there if that's the way it's going to be.

In Section 1.5.4.1, you use the terms exposure and exposure pathways synonymously, and I'm not quite sure they mean the same thing. You have exposures and then you kind of have pathways to exposures, and you're going to want to look at that. The section could better be organized by discussing first what exposures are included in this risk assessment and then discussing which exposures are not included with justifications.

And I think part of what I've been hearing is that you've excluded some exposures, but you don't add a lot of justification for why they got excluded. You just kind of say we're not doing population, and it's not always clear whether the exclusion is because you've kind of subjectively decided there's not a lot of risk here or whether you've decided there's no data here.

And I think it would be clear to be

able to say we're not doing it because there's no data. There might be risk. We don't, you know, we're just not going to go that route because there's no data. It's going to be a waste of our time.

Yeah, and case in point seems to be the general population exposure for BP releases from manufacturing. You point to concern for risk but also lack of data, and then ecological assessment is brought up again there and it doesn't need to be. So there are just some minor things.

Any additional comments from the panel? Okay. At this point, I'll turn it back to EPA. You've gotten everything from editorial to substantive components. Are there any questions? I saw you taking notes, so I thought maybe you had questions you want to ask the panel on their comments or for clarification. Dr. Henry is rapidly going through pages.

DR. KATHERINE ANITOLE: I'm trying to color code. I think the general thing is that we just sort of need an eco section that's a little more cohesive in and of itself, addressing it one way or the other. I think I heard that as a general thing. And Dr. Georgopoulos, I think you talked about how we needed some additional market data. Do you have any insights or references on where we might get that?

DR. PANOS GEORGOPOULOS: Okay. Unfortunately -- for general cleaning supplies and so on, there are the labor statistics. There's the spending -- consumer spending index. That's at least what we are using in our modeling for general. Then again, however, figuring out which of these products actually contain bromopropane, I think, it's something the total industry can provide. I mean I wish I had that kind of data. Usually we note it.

However, information from the Department of Labor, the spending index data provide way -- useful information viability because this has census blocks, census tract level data across the United States. And you realize that there are very different amounts people will spend or buy a lot of different depending on where they live. And so that can help in building distributions of exposure. At this point, the consumer exposure is not done on a distributional basis, but it could help eventually.

However, I think that getting data from industry or from market organizations -- sometimes, this information is for sale, and it's usually something that we cannot afford in academia when we do projects. But maybe there are ways in getting that information.

DR. KATHERINE ANITOLE: No. Yeah, we do subscribe to something that was mentioned earlier, Economist or Dun & Bradstreet is one of our usual sources. Okay. Thank you. Maybe that's the kind of thing we can get the industry associations to help ferret out.

Dr. Blando, you also mentioned that you had some unpublished data around the occurrence of 2-BP within 1-BP, so of course in order for us to use such information we would need to have access to that.

DR. JAMES BLANDO: Sure.

DR. KATHERINE ANITOLE: And it would need to be able to be shown.

DR. JAMES BLANDO: If you just tell me who to send it to, I'd be happy to do that.

DR. KATHERINE ANITOLE: Beautiful. That would be fantastic.

DR. JAMES BLANDO: Okay. Sure.

DR. KATHERINE ANITOLE: Thank you, should that issue arise.

DR. KENNETH PORTIER: Very good. Mr.

Macek?

MR. GREG MACEK: Dr. Blando, you had talked a couple times about the dermal and I guess looking at where it could be occluded. And so anything you have along those lines that could help us sort of, you know, if we do add that to the assessment, sort of construct, build an assessment, it would be very helpful.

DR. JAMES BLANDO: Sure. I was going to mention this later, but I can certainly mention it now. I think the specific scenarios I was thinking of was in our MMWR that we published in 2008, which I'm not sure if it was cited in the document or not, we detailed a vapor degreasing case in Pennsylvania and a dry cleaning case in New Jersey.

In those two cases, I think our feeling from being in the field with those folks was that our dry cleaner was essentially using -- so the scenario I'm thinking. I'll tell you, and maybe this is not a practical thing or maybe this is something that can't be modeled. I'm not a modeler, but our dry cleaner was using rags soaked in 1-bromopropane to clean down his machine.

And because it was a green chemical he

figured it wasn't toxic. In that case, I'm not sure that the evaporation from the skin is a good way to model that because he was soaking the rags in the solvent and holding in his bare hands because it's a green chemical, was holding in his bare hands cleaning the material down. So I think in that case, our feeling was that we thought the dermal exposure could have been important.

In our vapor degreasing case, and again, this is perhaps not something that can be modeled because as you can imagine a lot of industrial hygiene situations sometimes we're responding to poor practices or things that are not working the way they should.

Our vapor degreaser, the cooling coil was broken, so as he was reaching down into the bath to immerse the boards from the wave solder room, because the cooling coil was broken, he was getting condensation on his hands.

And he reported to us that, you know, he actually complained about the liquid that would always condense on his hands as he's doing what he probably shouldn't have been doing but was doing this with the vapor degreaser.

I understand that you probably aren't going to want to model in this type of exercise. You might not want to model like people doing things really poorly, but I just wanted to make you aware of a situation that you could consider as you're thinking about this particular scenario.

DR. KATHERINE ANITOLE: Certainly any references, especially if there's a MMR report or something, we'd appreciate that. Of course, we would have to get the tox data to go along with it to really pursue this pathway, so --

DR. JAMES BLANDO: Sure.

DR. KATHERINE ANITOLE: But the MMR reports, those are useful when we consider the scope of things that --

DR. JAMES BLANDO: Sure. I have the citation for that in my written.

DR. KENNETH PORTIER: And we may want to revisit that discussion when we talk about the vapor degreaser scenarios later on today or tomorrow morning, you know, as to whether the panel things it might want to recommend such a scenario. I mean there's nothing that says we can't say that we think that's a good idea.

Okay. I have 2:37 on the clock. We're scheduled for a 15-minute break at 2:45. I'm going to go ahead and call the break right now. We'll come back in -- at five minutes to 3:00. Why don't we come back at five to 3:00? Thank you.

(Brief recess.)

DR. KENNETH PORTIER: Okay. Let's reconvene. We've only lost three members of the panel, so that's not too bad. I'm sure they'll be here in a minute, but we're going to go ahead. Let's first make sure that those are not the three members that are going to start the conversation. Well, one of them is. We'll skip and come back. Let's see what happened. Her computer's not connected. Okay. Let's go on to question 2.1.

MS. KATHERINE ANITOLE: Okay. 2.1. Please comment on the approaches used, and provide any specific suggestions or recommendations for alternative approaches, models, or information, references, that could be considered by EPA/OPPT for improving the workplace exposure assessment, including estimations for bystander/non-users. For example, women of child-bearing age.

DR. KENNETH PORTIER: Dr. Blando.

DR. JAMES BLANDO: Okay. Well, thank you. So I have a number of comments, and I apologize for the number I'm about to read off to you, because I spent a lot of time out in the field with folks, using this chemical. So anyways, so I guess I'll just read them off. So when we talk about spray adhesives, I noted that in your assessment you stated that sprayers had higher exposures than the other two occupational groups that non-sprayers. And this is with the spray adhesive occupational cohort.

In Table 2-2, you showed the data from these two groups. And I just wanted to make the comment that, although some of the non-sprayer data is in fact lower in that table, it's also important to note that you also had, for non-sprayers, less than half the number of samples that you had for the sprayers. And the only thing I wanted to point is that, because you had a lower number of samples, it's in fact possible that you may have not gotten the full distribution of data you may have gotten if you had more samples, which is something that's typical.

And my comment would be it's unlikely that the difference is noted in Table 2-2 between the sprayers and non-sprayers are really truly meaningful, and I would argue that they really essentially had basically the same exposure.

As indicated in the NIOSH HHE reports, and specifically the STN Cushion Company report, and you also noted this in your limitation section as well, that many workers in these favorites may not be discretely assigned as a sprayer or a non-sprayer. They may work together, or they may go back and forth between the two work tasks. So with that being in mind, and with the data in Table 2-2, and especially having fewer number of samples for the non-sprayers, I think you might want to reconsider raking the sprayers and non-sprayers as one being higher than the other. Kind of more of an editorial comment.

One of the other things that I was very interested in was the assumption of the 90 percent removal efficiency for pre-EC and post-EC analysis, especially in spray drying. It appeared to me anyway, from reading the document, that this 90 percent removal efficiency was based on the paper by Peter Sheff from 199 -- or I forgot who the first author was in 1988, quite a long time ago, where they had slot hoods, and they were using TCE. That's what it appeared to me from what I read.

I'm not so sure that, especially for spray-drying operations, that slot hoods would necessarily be a workable ventilation solution, and I also am not sure that there's a good comparison between TCE and 1-bromopropane, which is more volatile in terms of emissions capture from ventilation, and this is all related to your assumption of that 90 percent removal efficiency.

I found it interesting to note that in the NIOSH HHE for STN Cushion Company, it appeared to me from reading that document that the removal efficiency they attained in their spray-drying operations was more about 60 percent. So it might be appropriate to just, you know, reevaluate that, maybe take a look at that HHE report and reevaluate what's possible in terms of engineering controls when you're think about the assumptions that you're going to make in terms of control efficiencies or removal efficiencies.

Just moving on the dry cleaning occupational exposure assessments, another note I had, which was really somewhat minor, but it is good to note that there are a number of dry cleaning shops, when you're trying to estimate the number of workers that actually are called "drop shops", as you probably are aware of, where they actually don't have -- they might be included as dry cleaning workers, but they might not actually work in a facility that actually has a machine or a plant in their facility. There might be estimates about how many shops are drop shops versus how many shops actually have a plant where they do cleaning, and that might something you could look in terms of refining the numbers of workers that may be exposed. I did mention that we use a Dun and Bradstreet. I think iSelectory was the last name I remember for that particular product in terms of assessing those sorts of numbers.

On page 47 on line number one, you mentioned that a conversion of a PERC machine to 1-bromopropane is no longer recommended by the manufacturer. I just wanted to point out that for most dry cleaning operators, if PERC were banned, they would not have another option, other than converting to 1-bromopropane, because they would need that drain-and-drop solution, unless they were going to buy a new machine, and many operators are not going to necessarily be able to purchase a new machine.

So whether it's recommended or not

recommended by the manufacturer isn't going to change the behavior necessarily of what the workers are going to have to possibly do to keep themselves in business.

In the assessment of the dry cleaning inhalation exposures and modeling of these exposures, it would assume -- at least it appeared to me from reading the document. It was assumed that the releases in the near-field were from the front door of the machine and during spot cleaning and finishing. I would note that, just clarify, that the paper we published in 2010 and in 2008, that we, in fact, found significant leaks from the machine from decayed gaskets, and in particular for the GEN3 machines we assessed and discussed.

And the papers we published were often times behind the machine, and we felt at the time that that contributed significantly to the background concentrations in the room. It should be noted that one of the problems people reported to us, and we mentioned this in the papers, is this tends to happen because a lot of the gaskets materials are severely damaged by Bromopropane, especially if you're using rubber weave and saw cases of viton gaskets getting destroyed. So that might be something else, when you're thinking about the modeling, to consider.

I noted that, also in the occupational exposure assessment, it seemed to me, if I read it properly, was that charging of the machine was not included. In other words, because dry clean operators, this chemical is so volatile, and because you tend to get leaks in your machine as a result of damaged gaskets, most of the -- every operator we visited had to add anywhere from five to ten gallons of new solvent every week to their machine, because they would just lose it from the volatility of the solvent.

As you probably noted, in our 2010 paper, we clearly demonstrated in that paper that you get a really significant spike when you charge the dry cleaning machine. In fact, what most dry cleaners -- matter of fact, every dry cleaner we observed, how they would do it is they'd kick open the front door of the machine, and just dump a five-gallon drum into the front door of the machine, right into the drum of the machine. And that paper, I think, demonstrated a significant spike. And you might want to consider when you're modeling if that could be something you could consider adding to your model, because that it wasn't just when they interrupted the cycle or just when they opened the doors, but I think that initial charge of the machine could result in some high exposures.

I also just made a note here that you discussed pre-engineering control and post-engineering controls in the document, in the assessment. And I just would make an editorial comment that I think engineering controls are probably not terribly feasible for most of our dry cleaners.

I know at one time NIOSH was talking and had their engineers looking at ventilations systems that you could put on dry cleaning machines, and I think our experience, in practice, from being out in the field, is that I don't necessarily think that's a realistic assumption, that there's a post-engineering control scenario for most small dry cleaning shops.

The modeling based on the bridal shop, which assumed eight dresses were cleaned per day, we typically observed -- in the study we published in 2010, we typically observed two to three garments with each load. So if you had a shop that was doing 14 loads, just mathematically that's a lot more than eight that they would be doing spot cleaning on. And the modeling approach appeared to assume, and I may have read this wrong. But the modeling approach appeared to assume that the occupational non-user does not ever enter the near-field.

Typically, what we found is that when the garments come out of the machine, often times the clerk or the tailor would come over and help, you know, come over to the near-field and basically help get everything sorted and everything put on. Of course, they were there less than the user, but they still were there enough that you might want to think about if there's a way to make an assumption about how often does this occupational non-user actually come into the near-field, because I think we observed them doing that.

For degreasing, in-line degreasers, as described, having lower exposures than batch degreasers, it's just important to note that that would likely be the case if those in-line degreasers were vented, if there was an emission capture system. If you have an in-line degreaser that doesn't have any emissions controls on it at all, it's just the box sitting in a room, that vapor is going to go somewhere. So I would just caveat your statement regarding the controls, that you're kind of assuming that there's some sort of ventilation associated with that in-line degreaser.

It was also noted in the NIOSH health hazard evaluation for Trilithic, which I also have that site, which you have in your document, which was assessing coal-degreasing operation, it was noted that, in their particular assessment, that when the parts were removed from the bath in the degreaser, they were allowed to drip-dry while they were still in the ventilated room.

So there was still some capture that was done as the pieces off-gassed, in terms of the carryout. I would just note that you're making that assumption, because for an industrial hygienist thinking about exposures, that's an important assumption to be aware of. I've been to many degreasing operations, not necessarily ones using BP, where people aren't always so diligent about letting things drip-dry before they remove them to the unventilated space.

You also clarified already for me that the CARB emission factors in the AP-42 were 1-BP specific, and I already noted -- oh, this is a repeat. I already noted that the 90 percent removal efficiency based on the Wadd and Sheff and Frankie paper from 1988 might not be appropriate necessarily here, and it might not be appropriate even for degreasers, since 1-BP is more volatile than TCE. And I think that's all I had on that. Thank you.

DR. KENNETH PORTIER: Dr. Georgopoulos.

DR. PANOS GEORGOPOULOS: Sorry. Thank you for pointing the mic. Jim covered, actually, more extensively what I had to mention. The one thing that certainly I would like to bring up, I think it was mentioned before, is the issue of co-located residential exposures, especially for scenarios where the dry cleaning operation is in a residential building. In some cases, you hear about the family that's living above it, and it's with these people we have extended exposure, both occupational and secondary during that. I think that is scenarios that should be included, as they would probably be on the high-end of the risk.

Other possible scenarios that would have to do, and I think Jim probably covered it more thoroughly, with cases of poor or substandard operation of a facility, or whether that can be defined, probably, but not to the point of having an accident, but when something is routinely taking place, an operation not following the standards of the practice. But the most important one that I think EPA should seriously consider to incorporate is co-located residential exposures. It's quite common, especially in the northeast, New York, New Jersey areas. I have some editorial comments that I will include in my written comments.

DR. KENNETH PORTIER: Thank you. Dr. Kissel.

DR. JOHN KISSEL: So for suggestions, I'll fall back on the clarifying questions I asked earlier. I would suggest that the Monte Carlo analysis be explicitly two-dimensional, meaning separation of true population variability from uncertainty, and show more details, rather than just report the 50th and 95th percentiles when you're done, and include a graphical comparison of the modeling versus the biomarker data. I think all those things would improve the presentation.

This question, like many of the questions in the charge, is a plea for more information from us, which, in some ways, is kind of futile, because the information you're asking for doesn't actually exist anywhere. It's not, you know -- academics do specific integrations in specific locations, and that's not a systematic treatment of an industry, and so you don't get the kind of information you want. And so I guess I'd like to make a little plea to -- we had this discussion earlier about the purpose of CSAC, and is it a purview just review of these documents, or is it the larger picture of the Tosca world?

It seems to me that the EPA should be giving substantial thought to how you do data call-in if you want to know these things. The people that know these things are the people that sell this stuff, and you're going to run into CVI kind of issues when you start asking people for, what does your industry actually do?

But really, if the larger society's going to understand chemical flow, materials flow, and society -- we have to start doing that. So data call-in would be an obvious thing.

A second piece would be agency people -- and I don't know to what extent this is a problem at

EPA or not, but I've talked to somebody that I respect at another federal agency and asked him, why has your federal agency funded so and so for all these years? Because it was a ten-year project where somebody produced stuff. A lot of papers, all based upon a basic incorrect premise, and bad physical chemistry. And the guy kept getting published or kept getting funded to keep doing that. And so I asked the guy who worked on the research side, as opposed to the grants funding side, why is agency was funding them. And he said, "Well, we never talk to the funding guy, so I have no idea what their priorities are." And I suspect that happens at EPA also. And so you're asking us for questions when -- or for answers, when EPA has a funding mechanism. Maybe not a big one, because of agency budget issues. But you should be directing those questions to the external funding people at EPA, and say, "Look, we need these bits of information to do our job, so why don't you put out specific proposals on these topics?" Because waiting randomly for academics to happen to stumble upon the data you're looking for isn't going to get you there.

And one other soapbox that I will get on, just because I have the microphone, the -- much of the information that's missing here is on the exposure science side. I mean, you can always do more tox testing, but an awful lot of the questions here, the inability to do risk assessment with any moderately small confidence intervals about it is severely impacted by the fact that we just don't know how to estimate things, because we do exposure science at the nine home at a time kind of scale, and that doesn't really get you very far. And so there is a -- the director of NTP is sitting over there.

A rhetorical question that I will ask is, why is there NEP at NIH? Why is there no National Exposure Program? Where is there only a National Toxicology Program? And I don't actually expect anybody to answer that, but that's part of the issue here. With inability -- I mean, this is a classic case of "let's do a risk assessment, and what we find is the questions throughout the whole charge are, do you know any more information that we can do this with?" And personally, mostly I don't have more information for you, but that seems to be the big issue. To do this well requires more information, and that means talking within the agency, talking across agencies, and trying to change priorities for gathering information. So enough speech.

DR. KENNETH PORTIER: That's what I was expecting from John. I -- Dr. Quiros.

DR. LESLIAM QUIROS-ALCALA: So one thing that I noted was this was with regards to estimating the potential number of employees at dry cleaning facilities. You mentioned that there was a survey, the americandrycleaner.com survey, that revealed about 1.1 percent of respondents indicated that there were currently using 1-Bromopropane, but then in the appendix it refers to what seems like the same survey but different references, and it indicates two percent.

So I wasn't sure if it was the same survey or not, even though the reference is different, because there were other instances where a reference was indicated, but it was not the right one. So I would urge you to double and triple check all the references and values.

And then that same sentence where I started talking about how you estimated the number of potential affected employees using this 1.1 percent, in the appendix in that same survey it said 4.1 percent of the respondents indicated that they would use it in the future, and this was back in 2009. And so I was wondering why, in the absence of data, you were going for 1.1 rather than 4.1 percent, even though it's still a small percentage.

And, let's see, there was one public comment submitted by Dr. Mark Stelljes, and I'm sorry if I'm butchering his name, but he said, "Currently, there are fewer than 25 establishments using 1-BP as a dry cleaning solvent and fewer than 100 employees that could be exposed." So maybe it's worth trying to confirm where he's, you know -- what sources he's using to base these numbers on, because that's clearly a source of uncertainty here, in terms of estimating how many people are exposed. Let's see.

So for a lot of dry cleaning facilities, a lot of them are family-owned and operated. And I know that you did make a statement saying, "We do know that in some cases they work 12-hour shifts instead of eight," but you split it into two eight-hour shifts with a four-hour overlap. But there was nothing done for those people who work 12 hours straight, and often times it's six days a week and not five. And given that you used modeling, maybe I was wondering why didn't you consider allowing that parameter to vary, instead of just saying eight hours? And maybe going, you know, part-time eight hours and 12 hours. And by the same token, on one of the other parameters, you assumed 14 loads based on this one study, but then you -- in the same column, you say, you know, "The range - the number of loads ranges from" I believe it was one or two to 14. So why not also allow that parameter to vary? I wasn't sure.

So it wasn't clear to me why certain parameters were allowed to vary and others were not. So if you could clarify that in the report, that would be -- that would make it a lot better. And you also mentioned different distributions you used, but there's no really reasoning for it.

Again, some type of explanation would help. And then I have some other minor comments that I'll submit. Oh, and you asked about references. There's been some studies published since you've finished your literature review. They're all 2015 studies. They're Chinese though, but they may be worth looking at. They are occupational exposure, so they may or may not be relevant. And I'll provide them to you.

DR. KENNETH PORTIER: Thank you. Dr.

Marty.

DR. MELANIE MARTY: I would like to second some of what Lesliam just said, particularly the 12-hour exposure thing. My grandparents had a French laundry in San Francisco for decades, and they worked more than 12 hours a day, not with 1-Bromopropane. I appropriate EPA trying to bracket the exposures based on modeling and the monitoring, given that the engineering controls and the NIOSH studies, they walked in, and the engineering controls weren't all working.

Some of them were all clogged up with the spray adhesive. You can expect that to be reality in the workplace. So I think it's good to have at least some scenarios where you do have exposures that are based on no engineering control, and I commend the agency for all the work they did on that. And also, agree it is appropriate to use the third-generation perc machines that have been converted, because a lot of these places, and California is another example, most of them are small mom-and-pop places.

And then EPA used data where they had to apply a distributional approach. In some cases, it's -- well, in a lot of cases, it wasn't clear why they decided to use uniform or triangular distribution, where the data weren't good enough to have an empirical distribution. So you might want to add a little more detail there. Thanks.

DR. KENNETH PORTIER: Thank you. Any other questions?

This is Ken Portier. I wanted to make a few comments. So the first one is that, you know, the beginning, that first paragraph in Section 2.1, kind of links you back to Section 1.5, and I would recommend that you tie the two together. For some reason, in 2.1 you list the six occupational users, but then you only add comments on three, and the other three you kind of left open, and I wondered why you enhanced three and didn't enhance the other three. So it's a minor thing.

In the five-step process described in Section 2.1.1, there's no discussion on model validation, even though you do model validation in a number of places. So I would add that to the description of the methodology. There is a mention of short-term and partial shift exposure monitoring data that you can't use, and I think you might want to think about how that might be able to be used to enhance model validation. There's probably some scenarios where you can run a model, a partial model, and compare it to the partial data, which would give you greater use of that data.

So Sections 2.1.2 through 2.1.7 are really where you're supposedly describing the scenarios, and I'll come back to the scenarios. Remember, it's a sequence of events. But when I read the 2.1.2 to 7, I see the events, but I don't see the sequence. It's very hard to figure out what's the sequence of things that you're actually modeling here. So I think what -- you know, I'm going to recommend that you think about kind of the standard way of describing the scenario. Not just the users, but what -- how the -- when the users are doing certain things, you have it all here. It's either in the text, or it's an appendix somewhere, but I think you kind of need a standard format so that a risk assessor reading this says, "Oh, that's what they -- that's where this data monitoring data came from. That's the sequence from the scenario under which NIOSH, whoever, collected the data, or that's the scenario that we model.

I found it very hard sometimes to read

through and try to figure out in my mind what was the real scenario that was modeled. I see the pieces and the tables, but I don't always see the linkages. And in my mind, I'm actually seeing, you know, little dots and lines that said that they did this, and then from there, they went here, and we modeled this much time spent in this task, and this much time in that task, and something like that.

Okay. And the final thing -- and I don't even know. We talk about the mom-and-pop dry cleaners, but is there a bimodal distribution here? Are there other larger dry cleaners that have more than one machine? And I would think that multiple machine exposures, if they're sequenced right, you could really produce a four field concentration that would be a lot higher than anything we got with a pulsing near-field one machine scenario.

So I don't see any discussion around the one machine. It's an assumption you make, and you mention it, but it kind of begs the question, you know, why did you make that assumption? Where do you actually say, "We don't have any data on multiple-machine establishments"? It'd be nice to say that. Any additional comments? Yes, Dr. Davies?

DR. MELANIE MARTY: I just, again, wanted to bring up the Seattle King County Public Health, which does have information on numbers of workers per dry cleaner in that county, including that about a quarter of them have no employees. So those are really, you know, one person working multiple shifts. And to echo the request for more explanation around how that was derived in that section of, you know, two eight-hour days and that people work a little bit here and a little bit there, and where that came from.

DR. KENNETH PORTIER: Dr. Blando?

DR. JAMES BLANDO: So just, Ken, in response to your question, I think what we typically observed when we were out in the field was that most places were one machine. They were small shops, one machine. However, there were some folks that did tell us that they had other places larger that did have two machines or whatnot. But I think the typical scenario was one.

I did, just as an antidote, because you'll find it interesting, I did have somebody call me from Arizona once, because they apparently have places that have do-it-yourself dry cleaning machines, where you put in money, and you can use the dry cleaning machine yourself. But anyway, just another odd side note you'll just find interesting late in the day.

But so the one point I wanted to just make about Dr. Quiros-Alcala's comment about the shifts is if you were going to go from two eight-hour shifts with a four-hour overlap, instead wanting to go to a 12-hour shift, something that you think might be more representative, and I might commit a little bit of heresy by mentioning this, but you might want to consider, at the risk of offending our friends at NIOSH, but you might want to risk considering something other than an eight-hour time-weighted average and maybe just a straight, raw time-weight, just a pure time-weighted average for the 12-hour shift, rather than following the OSHA guidance for compliance.

The OSHA Guidance, which I have cited in my written document on extended shifts, is designed for regulatory compliance. Now, this is a little bit of more personal opinion. Maybe it's more of an academic exercise, but I don't believe that the OSHA guidance on extended shifts are necessarily the most representative way to calculate an averaging time when you're doing risk assessments, especially for extended shifts, if you were doing a 12-hour. So that might be something you might want to consider, and maybe work with NIOSH on what is the best way for this purpose, when you're not doing regulatory compliance, am I complying the PEL, when you're doing this kind of work. Is there a different way to average that data if you are going to do extended shifts?

DR. KENNETH PORTIER: Okay. I think at this point we'll move on to Question 2.2. Yes? You have a question or a comment, clarifying comment?

DR. HOLLY DAVIES: Question, or ask, or clarification. I think it was Dr. Blando, early on here in this section talked about reconsidering, I think the way you put it, ranking the sprayer versus non-sprayer. I guess I would ask, you know -- I'm not asking you right this minute on the spot, but if you have any recommendation as to whether or not perhaps we should consider combining those two populations, even though they were broken out in the HHE, given the data. This occurred to me when I saw the table. Is it really different? My end could go up, that kind of thing. We would appropriate that.

And then these co-located residential scenarios. Several people spoke to -- this was one of the public comments, and they referred to an assessment using perc. Again, there -- if you're reading through all that, considering it, if you could speak to whether you think that is a good model to consider following. And then, again, Dr. Blando, if you had any reference about the one machine versus multiple machines. If it's in any of your papers or anything like that, we would appropriate that.

DR. KENNETH PORTIER: Okay. I thought Dr. Blando was going to jump in and answer all these questions, but he's just making notes. So let's go ahead and move on to 2.1. 2.2, I mean.

MS. KATHERINE ANITOLE: Question 2.2. Please comment on whether there are any additional occupational exposure scenarios that EPA/OPPT could address that have not already been quantified. Please also provide specific references and/or data to address such additional exposures.

DR. KENNETH PORTIER: Dr. Kissel?

DR. JOHN KISSEL: My associate discussants have already mentioned some additional scenarios, and I expect that they will reiterate those when they speak. So I will -- I just want to take my shot now at the dermal exposure bit. And rags and clothing have been mentioned, but the obvious one is gloves, and naïve gloved use is actually worse than no glove use, especially for volatile chemicals, and there is a literature on that. I can point you to some things which say, you know, if somebody wears gloves and gets them dirty on the inside, they actually get a bigger exposure than if they weren't wearing gloves. So that would be an obvious thing.

The other piece here is that we have multiple occupational uses of this compound, and the big one, or one of the prominent ones at least, is adhesives. And adhesives also can exclusive -- occlusive, in that you can get a film on top of the solvent on top of the skin, and that could increase uptake.

There are lots of literature which would suggest that, for instance, dirt can be occlusive with respect to volatile compounds, and so more goes into skin, even though there's partitioning, adverse partitioning, to soil. And so you would expect that driving force goes down. The exposure can actually go up, because you've reduced the volatilization to a greater extent than you have reduced the amount -- the rate at which the material's going in the skin. So I would think adhesives potentially could be coating the skin in a way which prevents the rapid volatilization, and so therefore would not be protected.

Now, having said all that, I think those things -- I still have my doubts, other than the extra case where maybe somebody's using soaked rags, and you have basically maximum flex through skin during that window. This stuff has such a high vapor pressure, meaning it has such a high solubility in air that the lungs are taking it in at a very great rate. And so it's really hard for dermal to catch up to that, for this compound. That's not universally true, but for this compound that's true. But I think you could, for the adhesive and for the glove cases, do at least a scoping analysis, and put some numbers into the report, and say -- instead of just saying, "Well, it volatilizes, so we're going to throw this away," "It volatilizes, and here's what some of the numbers look like, and this is why we're going to throw it away."

DR. KENNETH PORTIER: Thank you. Dr.

Blando?

DR. JAMES BLANDO: I don't think I have anything to add beyond what's already been said, other than I did note that in your report, you did have a citation. The F-R-A-S-C-H, FRASCH, had all the 2011 paper. I thought that might have had some data that might be useful to you if you were going to try and do as Dr. Kissel said, you know, evaluate dermal exposures. But I don't have anything else to add other than what's already been said.

DR. KENNETH PORTIER: Dr. Georgopoulos?

DR. PANOS GEORGOPOULOS: Since John also mentioned it, I will repeat the question about whether it would be possible to consider model exposures from carpet cleaning crews. That would be both occupational and related to residential, from the residential of the house or institution. I mean, it happens not only in houses but in churches and places where people assemble. And it appears that it's a product that is advertised for carpet cleaning operations, so that could lead to a combination of both occupational and residential exposures, especially, you know, the number of children in the family and number of carpets cleaned, and so on.

DR. KENNETH PORTIER: Thank you. Any additional questions? Comments? I'll read mine. It's Ken Portier.

You know, it's interesting, because I was sitting there reading. As I read the document, again, thinking scenarios, saying, "Well, what additional scenarios come up as I'm reading this?" And the first one that came up was the reference on page 43 to the TVL of 0.1 part per million set by the American Conference of Governmental Industrial Hygienists for spray adhesive sprayer and non-spray exposure levels. And I thought to myself, "Well, what does that end up -- if you could achieve that level, what does that -- what would happen there?" You know, can you model that scenario?

Because obviously the hygienists say that the target, so if you're a good operation, you should be able to be achieving. And what's the risk associated? Nowhere do you address that risk, so I -- or what that looks like.

So in Section 2.1.3.3, I was uncertain of which scenario the 95th and the 50th percentile exposure estimates of 50.2 and 29.8 parts per million eight-hour TWA actually represent. You know, as I go through it, and I read this, and then I went to the appendix and looked at the parameters, it wasn't sure which parameter settings went with 50 percent and which went with 55, and when did you hold things at a median, when did you hold things at a high level. So, you know, again, reiterating that when you -- once you've got the scenario laid out, you need to link it back to those tables and say, you know, "The high-end exposure would have been produced by these kinds of settings." Or if you're doing a Monte Carlo, then I understand that, but then you need to be very clear which parameters were held constant and which parameters had a distribution, and what was that distribution, and why did you choose that distribution?

This is another point, and it has to do with a readability of the document. So in the body of the report, you present model scenarios with one sequence, like dry cleaning, spot cleaning, vapor degreasing, coat cleaning degreasing. But then when you go to the discussions in the appendix, they're mixed.

So I can't follow that sequence of discussion in the appendix. I have to kind of read around. So vapor degreasing might be the third thing discussed in the appendix with the first thing discussed. It's a little bit of writing stuff, but, you know, I get the strong feeling that somebody wrote the appendix, and somebody wrote the body, and they never talked to each other, and it comes out really clear when you're looking at that. And it's specifically appendices J and K are what need to be synchronized.

The post-EC scenarios, you really don't discuss them. They're only mentioned in footnotes, in Table 2.5 and then I think again in another table, 2.7. You know, it's like star, star. You read the bottom, and it says 90 percent, but nowhere in the body do you really say what you said this morning, what Mr. Merrick said this morning, that, "Well, we took the exposure and just divided by ten, and we assumed that we had efficiencies of 90 percent in reducing that." It took me a while to come to that conclusion, because you didn't tell me. I had to kind of infer that by reading through the table. So I would strongly recommend having a section for each of these where you really -- even two sentences about post-EC, so I understand what you're really doing there.

So I was assuming that another aspect of engineering control might be changes from third-generation or modified third-generation to fourth-generation EC machines. And, you know, from Table and Appendix K-5, you see that unloading the machines, we see a difference in cylinder concentrations of 8,600 parts per million for the third-gen machine and 300 parts per million for the fourth-gen machines. And what it seems you did in the Monte Carlo simulations is you run a uniform distribution from 300 to 8,600, and all I was thinking of is this is a bimodal distribution, and that might be third-generations. It might be, you know, from 8,000 to 9,000, and fourth-generations might be 180 to 400. But instead, you kind of modeled the whole thing.

So I think you confounded generation with exposure in the simulations. And you might want to do a third-gen or modified third-gen scenario and a fourth-gen scenario to kind of look at what the reduction in exposures might be if that kind of engineering control were put in place. You pull the old machine out, put a new machine in, and that -- if nothing else, that'll help your risk managers later on.

Okay. Don't worry about that. I will say that the vapor degreaser discussion on the post-EC scenario is the most extensive, and it was the clearest description of the post-EC scenarios that I was able to find. But again, the clearest description is in the footnote to Table 2-10. It should be in the body.

So I have here for the code cleaning degreasing scenario, we have from page 66 the quote, "To model exposures during 1-BP code cleaning, an exposure reduction factor, or if with uniform distribution from 0.032 to 0.571 was applied to the vapor degreasing model. So I went to Appendix J to kind of figure out what the RF factor was. But then I went back to page 55, which refers to emissions from coal cleaning ranging from 3.2 to 57.1 percent.

So to figure out what your RF was doing, you had to go to three or four different places to kind of finally figure out what was going on, and I think that needs to be combined. And I got very confused, because from Figure 2-11, I'd assume that the RF factor would apply to your G, which was your outgassing from the device, right. If you closed it, you don't get as much outgassing if it's open. But it could also have been just conceivably applied to the near-field concentration, and I couldn't figure out from the write-up where the RF factor was applied, whether it was applied to the outgassing or to the near-field concentration, and I think that needs to be clarified.

And then I said I'm surprised that the what-if scenario of a vented booth, discussed on page 69, was not modeled. So there's a discussion of a scenario, but then you didn't model it, and I was wondering, why didn't they model that? So give you some other things to think about. Any additional questions? Any questions from EPA on 2.2?

Yes, Dr. Quiros?

DR. LESLIAM QUIROS-ALCALA: So I have one minor thing, and I don't think that necessarily you need to go ahead and calculate this; it may be worth a sentence. So in many, or in some family-owned and operated dry cleaning facilities, it's not uncommon for you to find children there under 16, right. It may be that they're helping out the family, or they came from school, waiting around for their parents.

And so I think that the calculations were done for pregnant women, and obviously exposure estimates for a pregnant woman are not going to be the same thing as for children under 16. So it may be worth a sentence saying that in your limitations of, like, "Look, this may be a possibility. However, this was beyond the scope," or, "We didn't calculate this," or, "Be aware that exposures are going to be higher in this population."

DR. KENNETH PORTIER: Yes, Dr. Barone.

DR. STAN BARONE: So I wanted to clarify -- and these are really comments in reference to some of the comments or questions that Dr. Kissel raised about a request for data and identifying data gaps.

So I've been a peer review coordinator for the work plan program for the last six years, and we have received data from the peer review panel, who have identified publications and/or other data sources that have facilitated the revision of our risk assessments, exposure assessments specifically. So we find that useful.

We also find useful -- and I say this because I'm talking about generically, for the CSEC, how we would like to go forward with some of these basic principles that are not just for this assessment but for other assessments, because I think that's what you were speaking to, is sort of those generic issues. For the panel to also identify priorities for these data gaps, what we find actionable and useful is where the peer review panel actually says, "We believe this is a really critical data gap," versus just giving us a laundry list of data gaps and sort of talking about a research program that may be for the next ten years.

I also want to remind the panel -- at least this came up in the overview presentation. When we're talking about the work plan assessment program, at least as it is today under current existing Tosca, we're talking about existing data tools and models. We're not talking about a DCI authority or data collection, per se, going out and collecting additional data and doing an assessment over and over and over again.

And then you also raised the issue of EPA has funding, and EPA funds research, and that is true. And you somehow indicated that the researchers and the program scientists are not necessarily involved, at least in another agency, is the funding decisions. That is true generically, but there's a separation between those grant organizations, grantee organizations, and in-house researchers and the in-house programs. But I would also like to make transparent that we are involved in the relevancy review, at least with the EPA funding initiatives. So we do provide scores and ranking. Not on the science, but on the relevancy of those funding decisions. So there is, just for you all's transparency, and some of you know this, but some of you apparently don't, that that's a component of the grant's program. Those are my comments.

DR. KENNETH PORTIER: Thank you. Are we back up on our webcast yet? We're going to take a two-minute breather here while we get back our web audience. It looks like they've been connected eight hours, and it automatically dropped them. And so that takes a little bit to reestablish, and then everybody at home is, like, wondering, "Where did they go?" And so let's wait a few minutes. They'll bring it back up, and…

(Brief recess.)

DR. KENNETH PORTIER: Okay. At this point we're going to move on to Question 2.3.

DR. KATHERINE ANITOLE: Question, 2.3, for the exposure assessments based on monitoring data, are you aware of any additional sources of occupational exposure monitoring data that EPA OPPT could consider in its assessment?

If so, please provide specific literature, reports or data that would help us refine the exposure assessment.

DR. KENNETH PORTIER: Dr. Blando.

DR. JAMES BLANDO: I guess for this question I would certainly like to commend you guys. I think that you had done a very good job on obtaining information and a fairly thorough job and a fairly, a very thorough job on your literature review. So I don't really have much to add. I'll just say a few things.

I did note that there are one or two papers that I have in my written citations that didn't seem to be in there but may or may not be terribly useful to you, but they'll be in the written documents. You can certainly check those papers out. In particular, I was thinking about the Ichihara paper that I mentioned in 2005. I know you have lots of his papers, but this particular one was not in there. He did a review and I think there could be perhaps some occupational information you might be able to use.

I also noted the MMWR that although it didn't have any exposure monitoring data that MMWR report does have for the two poisoning cases, does have some of their clinical parameters, like their serum and urine bromide levels, may or may not be helpful to you, but it's certainly easy enough to get a hold of.

You guys are very well aware of obviously the NIOSH criteria document that's currently under peer review as well. I'm sure you work closely with them.

The only other things I wanted to point out to you that may be useful to you is with regard to the identification of the population that may be exposed, the number of shops and folks that may be working in the industry.

You already answered one of my questions, which is you already used the Dun & Bradstreet databases, which I think can also be helpful. And truthfully I've honestly found them sometimes to be a little bit better and more accurate than some of the labor, Department of Labor type sources.

But the other source I wanted to point out to you is I was thinking about the undocumented workers I've seen in a lot of these facilities. And as you can imagine, they are notoriously very, very difficult to get a good number on. And I just wanted to mention two data sources that I've seen epidemiologists who've I've worked with utilize to try and get some estimate of undocumented workers. I have to be honest with you, I've never had good luck with this, so I just forewarn you I'm not suggesting that you waste a lot of time or spend a lot of time utilizing these data sources, but I have worked with epidemiologists that do seem to think that they've been able to estimate undocumented workers using the -- let me give you the name -- using the DataFerrett tool from -- where was it -- the DataFerrett tool from the Census Bureau and also using the Public Use Microdata Sample, the PUMS samples from the American Community Survey. I'll just leave it at that.

I've never particularly found them to be super helpful, but I have worked with epidemiologists that have seemed to tell me that they really felt like they were able to get estimates of undocumented folks in various environments by utilizing those tools. I'm not really quite sure how they did that, but I do know that they were pretty adamant that they thought it was great.

I know when I've tried it I haven't found it that helpful. But just food for thought for consideration. And I don't have anything else to add.

DR. KENNETH PORTIER: Thank you. Dr. Kissel?

DR. JOHN KISSEL: So I don't have additional biomarker studies to add, but on page 43 there's a list of biomarker studies which are essentially discarded because of other shortcomings of those papers. They lack full details. But I think they could still be useful in that you could, even without a full pharmacogenetic model just doing simple study state throughput given molecular weights of biomarkers and parent compounds, you could make a crude estimate of what kind of biomarker levels you would expect in the populations that you're modeling and then just put those in a table next to the ones that are actually measured in the studies where there's measurements and see if they're in the same ballpark or not, just as kind of a scoping exercise.

So I think you should maybe do a little more with the existing biomarker data that you already identified.

DR. KENNETH PORTIER: Thank you. Dr. Quiros?

DR. LESLIAM QUIROS-ALCALA: So again, there is about six recent articles. Some of them are in Chinese, but they may have relevant exposure data that you could use. And there's also an exposure monitoring and health risk assessment of 1-bromopropane as a cleaning solvent in the workplace. It was a human and ecological risk assessment. This was published in 2014, 2015. It was done in Korea, so I don't know if you have access to this or not, but I have it here for you.

And what's unique about this is that they sampled 10 different workplaces and took five samples per facility, and so that may or may not be helpful to refine the exposure assessment. And that'll be in my comments.

Oh, and sorry, one last thing. Again, in the public comments somebody actually said that they may have data and they're open to sharing it, so it may be worth looking into. It's Comment 19 by Dr.

Mark Steljes, and he's indicated that he's also done exposure monitoring of 1-BP in dry cleaning facilities, so it may be worth taking a look.

DR. KENNETH PORTIER: Dr. Georgopoulos?

DR. PANOS GEORGOPOULOS: Just citing to recent articles, though exposure is not very well defined whether biomarker measurements. This study in Taiwan for exposure to 1-bromopropane golf club cleansing workers, again in the same biomed, the Korean and the Taiwan. The tags are the only ones in English. This is in clinical toxicology project, and so that's pretty much everything comes from the Far East these days.

DR. KENNETH PORTIER: Golf club cleaning, huh? Okay. Anyone else? Any comments from EPA? No? Let's move on to Question 2-4.

DR. KATHERINE ANITOLE: Question 2-4, for the exposure assessments based on modeling, are you aware of any additional sources of data that EPA/OPPT could consider in deriving the parameter values used in the modeling?

If so, please provide relevant literature, reports or data that would help us refine the parameters used in the modeling.

DR. KENNETH PORTIER: Dr. Georgopoulos?

DR. PANOS GEORGOPOULOS: Now, for the types of scenarios that were considered in the occupational exposure assessment, EPA has probably collected and quantified in distribution steadily with the very limited available information.

There is that information I have for evidence to recent article by Hillborne and Averill on the viability of parameters that affect the VOC vapor dispersion in the workplace, including the velocity diffusion, co-efficient and so on. And they also actually mention bromopropane as one of the VOCs that they considered, but it's doubtful that the information there will affect in any substantial way the calculations and the outcomes of the modeling that was performed here.

However, so even though no other different parameters exist, I think that codification or the definition of parameters and distributions can be improved. For example, if you look in Appendix K, I have some consensus of the definitions of some parameters. The distributions, for example, in a couple of places look normal. Distributions are defined with a range from zero to infinity where in reality, you know, you really have one worker exposed and you don't have an infinite number of workers and so on.

And what we do in this case, we can still fit lognormal, but use a truncated lognormal distribution. I mean, there's no need to use this. At least, I feel very uncomfortable when I see some of the selections and distributive state forward.

The second thing that could also be done with existing available information and some of the information is in the exposure factors handbook or instead of using some of the point values, of course, the Monte Carlo modeling and occupational settings, it's kind of mixed. It's for a number of individual parameters, point values are assumed in the distributions.

But in some cases, I think somebody mentioned earlier that instead of using eight-hour work day to use something, and one can use a distribution with most probably value of eight, but could be from 6 to 12. I mean, there are things -- and that probably could capture some of the high end of the viability.

So replacing some of the point

estimates with reasonable distributions and justifying or modifying the selection, as I think it was mentioned before, yes, that the section of a uniform distribution in some cases where you would expect more of it by model distribution or even a triangular is not reasonable. And these corrections to the Monte Carlo I think should be doable. It's not a major task.

Now, for some of these parameters, it's clearly viability. In some other cases it's most uncertainty. So this is where we come to the suggestion of doing it two-dimensional Monte Carlo analysis separating variability from uncertainty and actually summarizing some of this information.

The big advantage of doing the many runs of Monte Carlo simulation in this one is that you have a global sensitivity of the system, at least for those parameters that you don't assume play point values.

I mean, I know for the -- we'll discuss tomorrow for the deterministic residential or consumer exposure related to sensitivity analysis, but for the Monte Carlo analysis of the occupation, we get distribution, but we don't get -- at least maybe I'm missing it, some information on the uncertainties of how different variables or parameters affect the outcome.

And if we've done a million rounds, I mean, you have all that information actually in those if that is extracted appropriately.

The final thing that also can be done, and this is missing, if it has been done, is asking the Excel code or net risk. But a problem that we often have in a Monte Carlo simulation is in a particular run using, selecting random values for the parameters that are inconsistent with each other; for example, you know, having a high volume -- I mean, in this case I think I think it was good, but a high volume of workers than just one worker or something like this.

Usually establishing rules that make sure that the proper combinations of parameters are used in Monte Carlo and not just running a crystal ball with the distributions because they're -- crystal ball, they just don't know, I mean, this restriction. This is more of a common sense characterization and maybe it has been done, but I don't see it documented.

So I think if it has been done, it

should be explicitly listed, otherwise, sometimes we see that it affects the calculation. So the rules that ensure consistency of the combination of parameters needs individual Monte Carlos simulation would be useful.

Something, a final comment, something that is more recommendation, the available data and the scope of this don't really justify the use of a more sophisticated model like a computation fluid dynamics model. So I agree the selection of the consumer exposure modeling, as far as this, is appropriate and reasonable. But what we do in these cases are not your limitations, maybe regulatory or guidelines.

I mean, it has developed in Europe a number of models for exposure assessment in Tier I models like ECOTOX or ConsExpo and similar to E-FAST and they have somewhat different parameters. So running that model for a specific, like a subset of scenarios can help provide inside a non-case because some of the parameters are different. If the models concur, at least we say, okay, the models point to the same direction. If there's some kind of substantial division, it makes you question it and look at it further. And these are models that have the same level of requirements or inputs as eFAST, approximately. They are models that are designed to run for Tier I calculations in a data pool environment.

So I don't know if you run any of these European models, but they are available and they can provide an interesting comparison, just as -- at least when I see three different models provide the same numbers, starting with different parameters and with a different subset, you know, we must be in the ballpark. So these are my comments regarding the modeling.

DR. KENNETH PORTIER: Dr. Blando?

DR. JAMES BLANDO: I don't have anything else to add beyond what's been said.

DR. KENNETH PORTIER: Dr. Kissel?

DR. JOHN KISSEL: I could add one thing, once again, about the dermal bit. I published a paper in 2011 and then there was one follow up on which Fred Frasch was the lead author in 2014, involving a parameter we call "in-derm," which is a ratio of the rate of -- or the availability of the load on the skin compared to the loss processes which could include both absorption and volatilization.

And so it's a way to characterize the availability of material and whether it's likely to sustain uptake. And that might be useful in discriminating whether dermal needs to be considered or not be considered and I can give you those citations.

It's actually in the Fred Frasch paper that's on 1-bromopropane. He invokes the concept without actually using quite the same language. So I think it does fit here. And in that 2011 paper, one of his arguments is that this stuff is just evaporating so fast that it's not going to be absorbed, but that's exposure to the neat compound and with some modification you could apply the same analysis to the occluded case and maybe learn something from it.

DR. KENNETH PORTIER: Any additional comments?

I wanted to kind of support what Dr. Georgopoulos said about this feasibility space for the parameters. I thought about the same thing as I was looking at it and, again, thinking at it from a scenario. The scenario should be able to not only say what the steps are but where the parameters are feasible, combinations are feasible and infeasible. I think that'd be very important.

And the other thing is really clarifying where you're modeling uncertainty and where you're modeling variability. It's no always clear right now. They kind of come together in the Monte Carlo simulations, but you need to be a little clearer that, you know, this is a variability estimate, population size, how many are working in the place? That's a variability estimate, whereas some of them are uncertainty, I mean, real uncertainty estimates in a parameter that went into the model.

So yes?

DR. JAYMIE MELIKER: I'll just say one thing. I mean, to me what was nice is that your model, even though, you know, lots of people have given suggestions to tinker with it and things you can do, did a pretty decent job in matching the monitored data.

And I think to that, when I see that, I'm feeling okay, because there's always ways you can tinker with a model. There's always ways to improve it and sometimes you don't even know if the things that people suggest will end up improving the model. You at least have a way to verify the model by comparing it with the monitored data. And I think it's reasonable. It seemed reasonable to me just looking at that comparison.

DR. KENNETH PORTIER: That was Dr. Meliker. This is Ken Portier.

I tend to agree, and that's why I mentioned the validation part. But, again, you have to make sure that what was simulated that you're comparing to what's monitored, where they match up. And I wasn't always sure that what was simulated matched up with the monitoring scenario.

So I think if you tighten that up a little bit, we'll believe the model a lot more and then we'll believe the model results a lot more. By "we," I use the global "we," not just us at the panel.

Dr. Georgopoulos?

DR. PANOS GEORGOPOULOS: Yeah, just, you know, reiterating what Dr. Portier said, we want also the model to predict the right results for the right reasons. Sometimes conversation of ours can lead sometimes. Very often we get a new parameter, we're getting those, we improve the model and we say, oh, it doesn't agree so much. Yeah, well, because something was hidden there.

So getting the right results for the right reason is also important and that's part of the transparency here, being all the visibility or the consistency between parties, et cetera, because then you can be sure that you can apply the model to other situations for which you may not have data to compare with.

DR. KENNETH PORTIER: Yeah, what's nice here is that the models are not super parameterized. So, I mean, there's a reasonable number of parameters, so I'm not too worried that you over parameterized and then things were compensating and you're getting results but for maybe like you say the wrong reasons.

And here, I think this is a rational design and you can follow the parameters very well.

Any additional comments? Not seeing any. Turn back to EPA. Any comments or questions on this?

So we're debating whether we want to move to Section 3.1, whether the panel is ready to go there. Sometimes the panel likes to digest the afternoon's discussion and go back and going to rethink the questions and come in fresh the next morning. It's 4:15. We have 45 minutes. We could probably cover one of these questions. But maybe I should look at the -- look to the leads for those questions and say are you ready? You know, Dr. Georgopoulos or Dr. Kissel.

DR. JOHN KISSEL: I'm not ready to discuss 3.2 at this time.

DR. KENNETH PORTIER: 3.2, yeah. Dr. Kissel says he's not quite ready for 3.2. You know, I think I'm going to do an executive decision here and say, yeah. Dr. Schlenk says break. I think we'll call a break. It'll give the panel a little bit more time to kind of come together.

The second day of the discussion is always much better if the panel has an opportunity to think about what we've said already and kind of come back.

I'm going to give them that 45 minutes to go back, rest and then rethink and we'll come back. We have two sets of questions to deal with tomorrow. Well, yeah, three, yeah, three sets. But we've been doing two questions an hour, so I think we have plenty of time tomorrow to get through the four questions.

Is EPA okay with that? You guys okay with that?

So I think at this point we'll end the meeting for the day. We're going to reconvene tomorrow morning at 9:00, same location. I thank those of you who have sat through the webinar. You'll be able to hear us tomorrow. We don't hear you, but we'll hear you tomorrow. Thank you.

(Whereupon, the meeting was adjourned for the day.)

DAY 2

MR. STEVEN KNOTT: Just as another reminder, as I mentioned yesterday, there is a docket that contains all the meeting materials for this meeting. In fact, there are two dockets. And I've put up on the screen our CSAC website which contains the meeting materials and identifies the two different dockets that contain information that's related and has been shared with the Committee members.

So I think that was it. At this point, I'll turn the microphone back over to Dr. Ken Portier, our chair.

DR. KENNETH PORTIER: Good morning. Welcome to Day 2. We'll begin our meeting this morning by going around the room and identifying ourselves so we have a record of who's here. I'm Ken Portier, Chair, vice-president, statistics and evaluation Center of the American Cancer Society and I'm a biostatistician. We're start with Dr. Thayer to my left.

DR. KRISTINA THAYER: Hi, I'm Kris Thayer. I'm Deputy Director of Analysis at the Division of the National Toxicology Program, which is headquartered at NIEHS.

DR. JAMES BLANDO: Hi. I'm JAMES BLANDO, an associate professor at Old Dominion University in Norfolk, Virginia.

DR. MUHAMMAD HOSSAIN: I am Muhammad Hossain from Northeast University, Northeast Ohio Medical University. I am an assistant professor in the Department of Pharmaceutical Sciences.

DR. MELANIE MARTY: I'm Melanie Marty, Cal EPA's Office of Environmental Health Hazard Assessment.

DR. MICHAEL PENNELL: Michael Pennell, Associate Professor of Biostatistics, College of Public Health, the Ohio State University.

DR. LESLIAM QUIROS-ALCALA: Lesliam Quiros-Alcala from the Maryland Institute of Applied Environmental Health at the University of Maryland.

DR. DANIEL SCHLENK: Dan Schlenk, Professor of Environmental Toxicology in the Department of Environmental Sciences at the University of California, Riverside.

DR. JAYMIE MELIKER: Jaymie Meliker, Associate Professor at Program in Public Health in Department of Family Population and Preventive

Medicine at Stony Brook University.

DR. JOHN KISSEL: John Kissel, Professor of Environmental and Occupational Health Sciences, University of Washington in Seattle.

DR. KATHLEEN GILBERT: Kathleen Gilbert, Professor at the University of Arkansas for Medical Sciences.

DR. HOLLY DAVIES: Holly Davies, toxicologist, Washington State Department of Ecology.

DR. KENNETH PORTIER: Thank you. And running late this morning is Dr. Panos Georgopoulos from Rutgers Biomedical and Health Sciences. I'm sure he'll be here in a minute.

Before we jump into the next set of questions, I thought I'd look to our EPA representatives here and ask if you had any questions on yesterday's discussion that may have come up as you've reviewed the material, which I know you did.

I'm looking at Dr. Henry here. She says no.

DR. TALA HENRY: I don’t think so.

DR. KENNETH PORTIER: Good. And I'll look at the panel and say does anyone have any remarks that you wish you had said yesterday that now you have your opportunity on Question Sets 1 and 2 before we move forward? So I don't see any. We said what we said yesterday and we're ready to move forward. That's good.

So at this point, we're going to continue with the EPA questions. We're now in the consumer exposure assessment questions, Question 3.1.

DR. KATHERINE ANITOLE: Question 3.1: Please comment on the approach used and provide any specific suggestions or recommendations for alternative approaches, models, or use information. For example, information on duration, number of user events, amount used that could be considered by EPA/OPPT in developing and/or refining the exposure assumptions and estimates for spray adhesives, aerosol spot removers, and aerosol spray cleaners and degreasers.

DR. KENNETH PORTIER: And there he is. Panos, we're waiting for you. We're ready to go. It's going to probably take him a second. I don't know, John, are you ready to -- Dr. Kissel? Have you guys consolidated?

DR. JOHN KISSEL: I'm not ready to discuss my portion yet.

DR. KENNETH PORTIER: You're ready?

DR. PANOS GEORGOPOULOS: Yeah. Sure.

DR. KENNETH PORTIER: Okay. Dr. Georgopoulos is our first discussant, Question 3.1.

DR. PANOS GEORGOPOULOS: First of all, since we are talking about a consumer exposure assessment, I think a more appropriate title for this section is residential exposures to this specific products: cleaning sprays, spot removers and so on.

Please, I need to take a breath.

DR. KENNETH PORTIER: Catch your breath.

DR. PANOS GEORGOPOULOS: There was an emergency at the office I had to deal with. So that is one thing that is important because this consumer exposure probably only captures a slice of the actual range of consumer exposures. In terms of other information, EPA's ACTR database, the Aggregated Computational Toxicology Resource has information on uses and consumer products containing the chemical of concern.

And so I was not able to identify these products. They list a number of cosmetics that could contain 1-Brompropane. It should probably be consulted, along with the other information, the biomarker information from international study that we discussed yesterday to put the consumer interest and potential exposures in context and clarify that the exposures considered in this modeling analysis is only a subset of the potential exposures and risks associated with the chemical. That to start with.

The second thing, this is an exposure, a calculation done deterministically, but this, again, as we mentioned yesterday, in the tables, the high and central estimates are given as you present the 90th and 50th percentile, that is not correct. There are certain values that are used in the parameters that correspond to 50th and 90th percentile of distributions of inputs, but a lot of other parameters are only using point or average values that I'm not sure that they are that representative.

So we cannot claim anything quantitative like the upper estimates in the 90th percentile in any way. It's a representative number of high-end exposures probably, but the added quantitative characterization that is given by a numerical value is not there. So that table should be corrected.

I would also urge EPA to consider expanding the deterministic calculation into a probabilistic one because I think some of the values that are considered are probably are restricting the range of outputs of calculations. Especially, we are concerned about children in a residential environment. We have seen in a similar study that was conducted recently for cleaning space containing, you know, products and that also children are not the users of the product. They end up getting the higher dose per body weight because they are smaller in weight, they stay in the residence longer, their inhalation rates are higher and so on.

So using an average inhalation rate, I believe, since I'm not looking at my notes, I think they are using an average body weight of 80 kilograms for men and women. That certainly is not appropriate when you try to capture exposures and doses at the high-end, especially for children. So I think it is worth considering variability and a certainty in the parameters that are affecting consumer exposures.

Now, I understand that there's tremendous lack of data. EPA did a very good job. I was impressed by identifying a list of products that are available to the consumer. I actually checked the websites and they are very easy to order and get delivered to your home very quickly. And I'm sure there are users that are not -- of this product that are not captured by the analysis, but because of variability that one expects in a residential setting, it's probably larger than the variability in occupational settings. So pretty much, you have a defined range of processes. I think we should consider expanding the residential analysis and they keep using this term instead of consumer exposure, to account for variability in that, especially to capture potential exposure to children and so on.

I don’t know if this is feasible within the time frames, but I think it is doable. I mean, it’s not more complex. It's actually less complex, given the scenarios that they are using than the occupational Monte Carlo analysis they performed. And I also would recommend, additionally, to check the concurrence or the agreement of different models.

Again, in Europe, they have been models developed for Tier I calculation of consumer exposures, or residential exposures from use of things like cleaning sprays that involve certain events that have quite limited data. Of course, the parameters that they are using probably correspond to distributions, house sizes and so on, but at least they can provide a comparison of estimates that could be useful since we are lacking comparison with -- we cannot do comparisons with actual measured -- there is no real information that has been collected.

These are the main things. I have a number of editorial comments. There are some things in the table, some of the things I will provide with my written comments, but from the top of my head, I think this captures the main issues. But I struggle to clarify the title, talking about consumer exposure, especially when there is not an EPA document where I can go to the actual website or the IACSS Board and get information for bromopropane and you get that consumer exposure is driven, not by these products, but by others. That's again, a potential calculation that are very possibly made more clear on this point.

DR. KENNETH PORTIER: Thank you. Dr. Kissel?

DR. JOHN KISSEL: I don’t have much to add to that. Panos covered all of the basis there. I would reiterate that I think it would be -- it's a little incongruence to do part of the risk assessment probabilistically and part of it deterministically. And I think it would be better to do both of them probabilistically. And I also think that EPA should take into account the O'Boyle Paper with the pregnant women, where 99 percent of pregnant women show a marker of Bromopropane. It's late information, but I think it should be incorporated into the study because I think it tells us things. I'll say more about that with Question 3.2.

DR. KENNETH PORTIER: Thank you. Dr. Quiros.

DR. LESLIAM QUIROS-ALCALA: Hi. So I had some more comments. And also, just to add to that, I know that it was assumed that bystanders, including children and their exposures would happen when they're present in Zone 2, which is referred to as the rest of the house. Is there a reason why you didn't do calculations for assuming that the child was present in the same location?

So that's just a question. And also, again, given that there is widespread detection, I wasn't sure why chronic exposures weren't calculated. And also, let's see. I think those are my main points and other minor editorial comments that I can provide. And again, I also have a problem with the word "consumers" because it assumes that everybody exposed is actually applying them when it may not be the case.

DR. KENNETH PORTIER: I'll open it up to the Panel. Any comments? Dr. Blando?

DR. JAMES BLANDO: I noticed that the consumer behavior pattern parameters were from a Westat survey in 1987. And I understand that that may be the only data that was probably available, is what I'm guessing. But I'm just wondering if it was possible -- if there is any updated information or if not, what limitation that that might present for some of these exposures? Because I can only imagine that, you know, things have changed quite a bit since that survey was done.

I don't know if folks think that that's important. I guess it's kind of more of a question than a comment is do folks think that that is a significant limitation for this or not.

DR. KENNETH PORTIER: Anybody want to comment on that?

DR. PANOS GEORGOPOULOS: Unfortunately, we have done similar studies. And as I mentioned, we do not have data specific on this product. I mean, one can see correlations and patterns with the use of cleaning products in general from the Department of Labor, the Consumer Spending Index and then look over the years and see trends or calculate variability. There is certainly -- there are factors or each of them and I don’t want to go into is specifically for this, but you may find out that people who cannot afford dry cleaner may try to do some more of these things at home. And so consumer behavior is driven by economics and location. There are factors that can be used to refine consumer behavior, but data specific to these products are not readily available.

DR. KENNETH PORTIER: Dr. Marty.

DR. MELANIE MARTY: I'd like to second the comment about kids. Assuming the children are in another part of the room, especially older kids and adolescents, they might be out there helping their parents.

Maybe I have this wrong, so forgive me if this is incorrect. But it seems like the assumptions in the model were that a person only uses these products one day and that's it. And then I'm not sure how many times in the day it was assumed that people spritzed the product and whatever they were working on, but I'm just thinking that it might be a good thing to calculate exposure for somebody who is using the product like, imagine like a degreaser. You know, there's a person who's working on a project that's a do-it-yourselfer, and the project goes on for a week or two and they're using it here, there and everywhere.

So it might be a better idea to consider multiple uses per day and per week, rather than they're just using it once because I just don't think that's realistic. I mean, maybe for something like a spot cleaner, it's not, you know, just one or two spritzes. But for something where it is a do-it-yourself project, it could be quite a bit more than a single use in a single day.

And then the other issue, I'm not sure how to get around it, but I'll just bring it up so that if you assume the peak exposure, if there's one or two peak exposures in 24 hours and then you model the concentration out over 24 hours and that's what the person is exposed to, it's kind of of like thinking a short high peak exposure is equivalent to a longer lower exposure or Haber's Law for the adverse -- the extent of the adverse health effect.

And Haber's Law is appropriate to apply for relatively shorter extrapolations like, you know, an exposure of a few minutes to a half-an-hour or two, maybe several hours. But if you're going to talk about a really high peak exposure for less than a minute of use, what does that mean over 24 hours. That's a pretty large extrapolation. So you kind of get a little bit concerned about dose rate effects. But again, I don’t have a better idea of how to get around it.

And I did notice that the worker exposure was assumed to be eight hours and then the residential exposure is assumed to be 24 hours. And when you do that, it kind of drives that longer extrapolation in terms of exposure. So maybe it's worth looking at it a different way. Maybe not. I'm not sure. That's all.

DR. KENNETH PORTIER: Dr. Meliker.

DR. JAYMIE MELIKER: Yeah. I'm just going to reiterate what Dr. Marty said. Your formula for the acute exposure calculation is the same for workers as it is for the consumers, the residential exposure. The only difference is this averaging time.

So if you divide your workers' averaging time by eight and you divide your consumers by 24, the same concentration in the "air" is going to result in a one-third lower average estimated exposure. And I think that's wrong. In fact, I think that's a faulty assumption, especially if you're talking about an acute exposure. I think I would treat them similarly, again, to an eight-hour period where they're working. If you're going to treat one as eight hours for acute exposure, I'd do the same thing for the other.

DR. KENNETH PORTIER: Dr. Georgopoulos.

DR. PANOS GEORGOPOULOS: As a clarification, we're talking about the exposure, the way it integrates over time. So again, I understand what you are saying, but when exposure is calculated, it will take into account that a longer time period has been used for the average. You end up with the same result.

I mean, the point is because usually we calculate intake or uptake on a daily basis or on an annual basis, you need to specify the fixed time period to the averaging. But that point that was done by the previous speaker is more relevant to it, but it relates to the effects. I mean, that's a high peak.

It has the same effect. And also, we may be losing something there in the interpretation.

However, we try to calculate daily or annual average exposure. I don’t think it matters how we divide.

DR. JAYMIE MELIKER: But if it's called acute, right, if it's called an acute exposure calculation, I think you would like it to be similar for both the workers and for the consumers, right? If they're exposed for an eight-hour period, you should average it for the same period to calculate acute.

DR. PANOS GEORGOPOULOS: But it's a matter of definition. Again, I mean, it's daily exposure of this. I mean, the word "acute" means very different things and it all depends upon the effects of the chemical. So we do daily, we do monthly, we do annual, we do lifetime, but in terms of residential consumer exposure in the eight-hour period, it doesn’t have a specific connotation.

DR. KENNETH PORTIER: This just reminds me of all these discussions we've had on pesticides where you have, you know, one application and there's a peak concentration or is it an area under the curve. It's the dose. I mean, that's what's going on here, right. And with the -- and it sounds like with the occupational exposure area under the curve makes sense because there's that background concentration that is maintained for quite a while, not because they're applying it, because the chemical is there in a vat, right. But the home exposure, that's a lot more like, you know, one shot of pesticide and then you're done. The problem there is you're not doing that in your house, right?

The difference here is you're doing it in the house at 2:00 in the afternoon and you're still going to bed and it's not until 8:00 the next morning before you actually leave the house. So the exposure could be, you know, 12 hours or something. Eighteen hours or 24 hours for that matter.

DR. JAYMIE MELIKER: But that's different, right? I mean, that's talking about the actual exposure duration, which is in the numerator. The averaging time is in the denominator. So literally, the same concentration in the air at work as at home, your acute exposure value will be one-- third lower at home than it is at work because of the way the equation was calculated because of the way it was parameterized.

DR. PANOS GEORGOPOULOS: No. The point is you're at work for eight hours; at home, you can be there 24 hours. So it's the duration also that is different. What you spray is basically, when you do a spray, you have an exponential type of decay, but you are exposed continuously over the time period you are in the house.

DR. KENNETH PORTIER: I mean, I get Dr. Meliker's point, though, is that actually, the way it works is the 24 hours at home, you end up with lower exposure, right?

DR. JAYMIE MELIKER: I'm just saying, that's the way the model was parameterized, right? No? I mean, I'm looking at Slide 30 that you showed yesterday: Acute exposures for consumers are estimated assuming a 24-hour averaging time.

DR. EVA WONG: So the exposure concentration is calculated as Dr. Georgopoulos mentioned, you're in the home for 24 hours. The duration of which you're spraying is going to depend on the product, but it is assumed in this model that you're in the home for the full 24 hours and the concentration is calculated over that time period.

DR. JAYMIE MELIKER: You're estimating everything over the 24 hours. You have an average 24-hour exposure.

DR. STAN BARONE: So also note that the MOE, the adjustments are for eight hours or for 24 hours. So it's in then numerator and the denominator for the risk estimate and they cancel out. So there are comparable adjustments on duration adjustments on both numerator and denominator.

DR. JAYMIE MELIKER: I made note of that in my notes, but still, I think when you're comparing concentrations if all of a sudden it looks like your residential. But so long as everything is 24 hours in the numerator and denominator for this acute exposure at home, I think you're fine.

DR. KENNETH PORTIER: So to me, the bottom line of this discussion is maybe we need to think about writing that up a little clearer in the write-up just so we're a little clearer of what's going on.

DR. JAMES BLANDO: Ken, may I ask just a point of clarification?

DR. KENNETH PORTIER: Yes, Dr. Blando.

DR. JAMES BLANDO: I'm sorry. So I guess the thing I'm kind of unclear about with the discussion is the exposure duration and the averaging time terms. I was under the impression when I read that the exposure duration term and the numerator for occupational was eight hours and that the exposure duration for the consumer, that's what I'm unclear on. What was the exposure duration? Because it's essentially a proportion, really, is what you're calculating numbers, isn't it?

DR. EVA WONG: So the exposure duration for the consumer, we assume they're in the room of use for the amount of time, depending on the product. And then they're in the house --

DR. JAMES BLANDO: For amount of time they're using the product?

DR. EVA WONG: For the time they're using the product. And then they're in the rest of the home, depending on the activity pattern, for the remainder of that day.

DR. JAMES BLANDO: Right.

DR. EVA WONG: And the exposure -- the air concentration is calculated based on that activity pattern and that time of use.

DR. JAMES BLANDO: Right. so that would be a proportion of 10 minutes over 24 hours if they were using the product for 10 minutes, right?

DR. EVA WONG: Correct. But they are still being exposed, even as they're moving throughout the room, depending on the decay of the chemical concentration.

DR. JAMES BLANDO: Right, right, right. Now, for the occupational setting, are you assuming that the numerator is eight hours? That they're at work for eight hours?

MR. GREG MACEK: Yes, that's correct.

DR. JAMES BLANDO: Okay.

DR. KENNETH PORTIER: Any additional comments?

(No response.)

I have some editorial comments as well. I found, especially Section 2.2.1.4 kind of confusing. As I read this section as a non-risk assessor, you know, but as a scientist, I'm figuring well, can I duplicate what they did? The E-FAST software is available, so I should be able to download it. I should be able to read through Appendix L, multiple tables, find all the parts, plug it, and I just do it.

So I would, you know, part of my comments just encourage you to think about how do I restructure the writing so the scenario is clearer and that a risk assessor reading this document could actually duplicate what you did to convince themselves that you did it right. I mean, there's no reason why you can't do that. But I won't read through my half-a-page of comments on that. I'll just include that in the discussion.

Any additional questions? Dr. Blando?

DR. JAMES BLANDO: So I just had just a minor point. I noticed that in some of the assumptions you made that there was a 1 percent overspray assumption. And I was just curious, for the exposure assessors, if they thought that was realistic for some of the aerosol products in particular.

I imagine, although I have to be honest, I didn't do a literature search to check this out. I probably should've, but I imagine there is probably some literature somewhere that somebody -- I wasn't sure what that was based on, what that assumption was based on. So I guess my comment would be is if there's some literature to support that assumption, that would probably be beneficial to include in the risk assessment.

DR. KENNETH PORTIER: No one wants to take that one up?

(No response.)

So I think the bottom line here is that it maybe needs more reference in the document. It means a better description about why -- I think I did look that one up, though. You have to go from the main body where the assumption is made, the Appendix L, and actually, there are two tables in Appendix L; one that describes the parameter and then later on in the document, it actually discusses that assumption. I picked up on that as well. So it's in there. A lot of the stuff is in there, but you really have to do a little hunting to find everything.

I was trying to find my notes because I think I made a note on that as well.

Yes, Dr. Kissel?

DR. JOHN KISSEL: I would just say that if this was done probabilistically, you would be using a range for that number instead of a single value. A single value is kind of hard to defend.

DR. KENNETH PORTIER: I found my notes and it will be actually tracking that down as my first bullet item. Okay. Any questions from EPA on that or any clarifying questions?

DR. EVA WONG: A number of you have recommended doing a more probabilistic assessment, which I understand. If you could, in your write-up, perhaps provide some specific recommendations or suggestions on how best to parameterize that particular model. I think that would be helpful.

DR. KENNETH PORTIER: Dr. Henry.

DR. TALA HENRY: Similarly, again, I think we're all aware of the NHANES biomarker study. If any of you have knowledge as to whether or not that particular metabolite is specific to 1-BP, that would be much appreciated. I don’t think we know that. Secondly, as you can well imagine, you have to link that back to some of these products or uses. So if you know of information -- you know, we just don’t know quite how to incorporate that because, you know, here you have a body burden or a dose rate and to back calculate that to one of these particular use scenarios or whatever. So any kind of advice on that would be appreciated.

DR. KENNETH PORTIER: Dr. Thayer.

DR. KRISTINA THAYER: Not particularly helpful advice, but I think even sort of assuming you can't find the information about how specific the metabolite is, then I think that sort of still it raises uncertainties that I think sort of tips it toward really trying to acknowledge sort of the residential, you know, expanding the scope beyond, as it is currently outlined just because it suggests that there could be. And again, it just sort tips and balances of expanding the scope. Even if you can't find numbers to help with the modeling, better numbers that you have, I think it still sort of suggests you should try to do something with what you have.

DR. KENNETH PORTIER: Dr. Marty.

DR. MELANIE MARTY: I tried to figure out last night how specific that particular metabolite was to 1-bromopropane. I mean, I think that's one thing that you guys could try to figure out, look into the literature. I found a 1959 paper that looked at that metabolite and they looked at 1-bromopropane, 1-iodopropane, and 1-chloropropane and found it from all three of those.

But as you're aware, if it's not a metabolite that's specific to 1-bromopropane, then it's hard to say yes, this is from 1-bromopropane exposure. So a little legwork on figuring out what other chemicals result in that metabolite would be really good as part of the write-up.

DR. KENNETH PORTIER: I was thinking about smoking and whether it's one of those metabolites that might be linked to smoking, both occupationally and residentially. For some reason, I just keep thinking, in none of these scenarios that interaction with personal tobacco smoke or workplace or residential tobacco smoke and these VOCs, well, I don't know what to think about that. How you would even model it. But in the background I keep thinking about that.

Okay. I think we'll move on to Question 3-2. Thank you for those clarifying statements. I'm hoping the Panel will be able to provide some additional comments on that.

Question 3-2.

DR. KATHERINE ANITOLE: Question 3-2: Exposure estimates were developed for three consumer uses: spray adhesives, aerosol spot removers and aerosol spray cleaners and degreasers. All products are aerosol sprays and appear to be available for sale and use by consumers in the U.S. There were no current reliable data regarding the consumer exposure scenarios.

Please comment on the consumer uses selected for this assessment and provide any specific suggestions or recommendations for additional uses (including information on duration, number of user events, amount used) that could be considered for evaluation.

DR. KENNETH PORTIER: Dr. Kissel.

DR. JOHN KISSEL: In thinking about this question, I'm actually drawing back to the prior question. So the new information that we have from the Boyle, et al. 2016 paper is a geometric mean of 2.6 nanograms per mL of this biomarker of unknown specificity in 99 percent of pregnant women who were sampled, which is a suggestion that it's a ubiquitous exposure.

That level, for starters, one of the biomarker papers, and I didn't get through all of them, but one of the biomarker papers that was discarded earlier, Hanley, et al (2009), provides data both on the cysteine biomarker and bromide ion and provides a little bit of a Rosetta Stone for interpretation.

So at least at the high level, they track each other very, very nicely, which would indicate that at high level exposures that it is a very good marker for 1-bromopropane exposure. Now, that might break down at very low level because of other potential sources, but it's certainly true at high levels. And then if you interpret it as a marker of exposure, then you could at least overestimate what the exposures to those consumers were to 1-bromopropane.

And in trying to do back of the envelope calculations, it turns out that that 2.6 nanogram per mL is three to four orders of magnitude lower than the biomarker level that you would expect in the occupational exposures and has been reported in occupational exposures. So there's ubiquitous exposure at very low levels compared to the occupational, which is useful to know. And it raises a couple of questions.

One is where is the stuff coming from? And Panos has suggested a bunch of uses that are not listed here. You expect if it's ubiquitous, this spray adhesive thing is not really the answer because that's an episodic sort of use. And some of the population would be nonusers. They would never do that. So it's not averaging out of that that's being projected.

I should note that in the -- there was a maximum value reported, which was over three orders of magnitude larger in the Boyle, et al study. And so that could be somebody who is either occupationally exposed or is somebody who is using adhesives or other things at home and that's kind of plausible.

The numbers that are presented in the scenario are expressed as average air concentration instead of biomarker numbers. So there's some translation that has to be done to interpret. But my sense is that probably those average air numbers are not too far off for the short-term use kind of scenario and are plausible numbers based upon the high-end reports from Boyle. They're still lower than the occupational exposures.

With respect to the widespread use, 1) it hasn't been brought up yet, which I will offer up. Our key -- or one of our key occupational exposures is these people that are putting furniture together. If you think about that, you've got two phone blocks that are probably four inches thick and you spray the one side of each of them and then slap them together and make a sandwich. And the bromopropane is volatile and would want to escape, but the easy place to escape would be through the plane, and that's full of adhesive and so that's clogged up, which means now the only way to get out is through four inches of foam, which is going to take a long time to happen via diffusion, even though it's a volatile chemical. Which means all that furniture is a permanent source of 1-bromopropane in all occupied spaces. And so that could explain why everybody is exposed at a low level.

So there are probably other things like that out there. There are other uses that are going on, but it's not surprising, and this gets back to my comments yesterday about a flow of materials in an industrial society. We need to understand what's going on when people sell things if we're going to understand how people are exposed and whether we're going to do anything about it or not.

So once again, the plea here is for further investigation of these kind of odd pathways that you don't think about until you do get into a situation like this and you're forced to think about them a little bit. So generally, I think, despite all the limitations of the consumer exposure scenario, I think probably the numbers are not terribly bad for the scenario that was run and I think maybe some expansion to incorporate or at least to frame that in light of the Boyle, et al report to suggest that there's widespread other exposures at a lower level going on. We need to understand more about that.

Dr. Schlenk wants to join in on this.

DR. DANIEL SCHLENK: Yeah. So if you look at the structure, my sort of background is in metabolism and I was going to deal with this when we get to AOPs a little bit later in the weight of evidence stuff, especially some of the mutagenic things too.

If you look at that metabolite, that's a glutathione conjugate derivative is where that's coming from. That sulfur-based pathway. So any halopropane is going to form that metabolite. So if you're confident that 1-bromoprane is the only halogenated propane that people are exposed to, then yeah, yeah, that's totally fine. But there are a lot of chlorinated by-products in drinking water that we have no clue how much is there and exposures taken place and all it takes is one 1-chloroproapne or even 2-chlorpropane.

You can get migration of that halogen

to the one position. So it's a very common metabolite that's present on any halogenated propane compound. So it is exactly 1-bromopropane? Potentially. But I think there's other possibilities that you've got to weed to make sure it is that particular metabolite. So just my little two cents there in 1-BP metabolism.

DR. KENNETH PORTIER: Dr. Davies.

DR. HOLLY DAVIES: My major comments have been covered by everyone else in most of this discussion. I did want to make some comments, though, about -- I do have editorial comments on organization. I spent a lot of time flipping back and forth between the chapters and the appendix in a way that was hard to figure out what was going on and where things were. It was not helped by the chapter referring to Appendix K instead of Appendix L in places. So things like that I will include in addition to agreeing with a lot of what else was said.

DR. KENNETH PORTIER: Dr. Georgopoulos.

DR. PANOS GEORGOPOULOS: Yes. What John said covered most of what I was thinking also. Some of it goes back to doing, expanding the probabilistic analysis because, again, the question is specifically asking us for more uses. And everything here is scenario based. I mean, we have anecdotal evidence of people doing weird things sometimes. And I know present cases of people using (inaudible) in a way that it's not covered by this case. And of course, we cannot cover the extent, but I think it helps looking at different scenarios and multiple uses and the probabilistic analysis that both John and myself mentioned before could help in that. In the lack of any specific data or surveys, I don't think we can give more information about time, duration, number of use events and so on, but I'm sure it's going to be more valuable than what we usually suspect in the beginning.

The issue of the ubiquitous number -- of that metabolite, that is something that again, as I was reading the paper from the NCS study, is something that is worth a lot of consideration. I understand the concerns about having, this may not be unique to 1-bromopropane, but it's worth examining the potential of exposures in the range of contaminants. It should not be dismissed on the fact that it is not unique to 1-bromopropane. It's the best thing that we have out there.

I know that this is the first year with

TRI emissions, will include 1-bromopropane, but I think -- I hope it’s going to be used as soon as data is available for some calculations of exposure. Probably it's not going to happen for a year. I understand that, but it will probably show that because we have seen in calculations for others has shown that dry cleaners, especially in urban areas and so on are a major local source. So if it is used extensively, maybe that's a major contributor to this background concentration for the general population that we see in the international study.

So I don’t want to make more comments. Basically, more scenarios in probabilistic analysis probably would give some more information and insight, but again, I want to, because we keep bringing up all these studies, I was very impressed by the good work, especially with all the amount of work that it took because when you don’t have data and you try to provide estimate based on this, it's very hard. So I do appreciate the effort that has gone into this. And making comments about what is missing should not be viewed as negative. I mean, there is a lot of good and useful information in these calculations.

DR. KENNETH PORTIER: Thank you. Dr.

Blando.

DR. JAMES BLANDO: So I recognize, as Dr. Georgopoulos was saying, that it's not possible, nor realistic to include every single scenario that we can think up this morning that we could suggest for you guys to include. The only thing I was thinking of when I read over the consumer exposure scenarios was, in particular with the brake cleaners and some of the automotive products. I guess I'm not aware of any literature to support what I'm saying, however, when I put my written comments together, I'll do a literature search and look and see if I can find anything.

I was kind of thinking of hobby folks, like gearheads that may work on their automobiles. Obviously, I'm personally biased because I have friends who are mechanics and I think about the amount of time they spend in their driveways working on their cars and I thought the time estimate for the use of brake cleaners for that particular more extreme population of people, albeit a smaller group, because not everybody is working on their cars extensively, but I thought that the time estimate for the use of brake cleaners was somewhat short for a population of folks that might spend a lot of time working on cars hobby. I didn't know if that was something that should be considered as sort of high-end consumer use. I just wanted to say I'll mention that in my written comments and I'll quickly look in the literature to see if I can find anything on auto hobbyists to include. I'm just not aware of anything, but I just remember having the inclination at that time period for the brake cleaner use in particular seemed a little short to me for that population of folks.

DR. KENNETH PORTIER: Any additional comments?

(No response.)

My wife frowns on it when I try to clean the brakes in the kitchen sink. I was sitting there thinking, "We've probably done that at some point in the past."

I was sitting and thinking about the comment of getting distributions for parameters. I mean, that's a challenge on this. Thinking back to the statisticians, they think about these Bayesian approaches, right. In a Bayesian approach, you would bring in a panel of experts and have them kind of help you come up with a prior distribution on these parameters. I would've thought that for a lot of the

E-FAST stuff, probably that's been done. I suspect it's been done for some of the residential pesticide use stuff. And some of that could be carried over if it's not already encoded into the program. Some of these other things you've asked about, I keep thinking, you're not to going to get data, you're not going to get published data on that, but you could possibly develop subjective prior distributions through working with small teams of people who maybe know this kind of stuff like Dr. Blando has been talking about. That's the only source I could think of.

I'm looking at Dr. Pennell because he's more of a Bayesian than I am. That's the only thing I can think of there. Any additional comments?

Yes, Dr. Henry?

DR. TALA HENRY: I just wanted to clarify or get clarification from Dr. Georgopoulos. With regard to the TRI data that the first year collection will not be until 2017, are you recommending that we wait to complete this assessment until that data is available. Then I would also like to hear from other panelists if that was indeed the recommendation.

DR. PANOS GEORGOPOULOS: There was no recommendation to wait. There is a lot of interesting stuff that is coming out of this. I would be very much interested to see in analysis what exposure associated with emissions from all the sources that will report and how this compares with available data as soon as this information is available. I don't know if EPA is going to do it. I hope it is done because it will help answer some of the questions that have been posed here.

So maybe I'm looking at this as a scientist not as a regulator. I mean, you know, and the timeframes, but I think it may say give it a yes or no answer to this question on the ubiquitous exposures can lead to levels that will observe in studies like NHANES or international studies. Of course, since you asked me a question, I think it is also essential for the longer term for a year from now or so on to have, to do work on a pharmacokinetic model that will link biomarker levels to inherit concentrations that will allow. Even if this is incomplete model, you know, having a rough screening model is better than not having anything at all. At least it could help in the model calculations.

So steps beyond completing this phase of the assessment for the future, I think it will be important to have both, an analysis of TRI data and build upon the existing pharmacokinetic model doing an extrapolation to humans in an exploratory -- again, I'm talking about this from the perspective of they are known scientific questions that need to be answered.

I mean, if somehow bromopropane disappears or any of these questions become available, that's another issue that has to do with the science, but with respect to understanding the information that is out there right now, I think these are the two steps that should be taken, even after this risk assessment after this particular task is completed.

I don’t know if I answered your question, but don’t wait, but I think we need to see what the TRI will tell us about general population exposures.

DR. TALA HENRY: Of course. We have a lot of chemicals on our work plan.

DR. KENNETH PORTIER: Dr. Davies?

DR. HOLLY DAVIES: I just wanted to add on that I don’t know how fixed you are once you start some sort of risk mitigation measures, but I would say, agreeing with Panos, not to wait on the risk assessment. But as you get information, if that can affect and guide the actions that you're taking to mitigate the exposures, that would be good.

DR. KENNETH PORTIER: I think that's more of a policy question. I was just sitting there thinking of a risk benefit, cost benefit kind of thinking on this. I think our general feeling is exposures are higher, occupationally, and you're going to move forward on that anyway. And residential exposures are lower. There's no reason to hold up the whole risk assessment while that part of the risk assessment gets fine-tuned. So I think that's part of the thinking there. But that's your thinking, not our thinking. We recommend that you use the best data that's available. And if that new data is coming up, that'll be good.

Anyone else want to add?

(No response.)

Okay. I think we've got your answer to Question 3-2. I see 9:55. I'd like to move onto the next question if we could, 4-1. Now, we're moving into hazard and dose response assessment.

DR. KATHERINE ANITOLE: Can we just have a minute to move people a little?

DR. KENNETH PORTIER: Sure. Well, maybe we should take a break. What do you think?

We'll go ahead and take a 10-minute break so you guys can get your team reorganized and we'll get our coffee. We'll reconvene at five after the hour here.

(Brief recess.)

DR. KENNETH PORTIER: Okay. Let's reconvene if you please. So we smell something in the room here. I'm not quite sure what it is. 1-bromopropane, right? Some kind of cleaner somewhere. We're going to leave the doors open, if we can, to kind of clear that out. One never knows, right?

We're going to continue then with Question 4-1. And I think we've got an new EPA Panel -- half a new EPA Panel here. So that's good. New people. Dr. Anitole?

DR. KATHERINE ANITOLE: Question 4-1. EPA/OPPT concluded in the risk assessment that 1-BP carcinogenesis occurs through a probable mutagenic mode of action based on the totality of the available data/information and the weight of evidence.

Please comment whether the cancer hazard assessment has adequately described the weight of evidence regarding the mutagenic mode of action.

DR. KENNETH PORTIER: Our discussant lead is Dr. Thayer.

DR. KRISTINA THAYER: Hi. This is Kris Thayer. So I guess sort of my two major suggestions would be to consider broadening the description to maybe genotoxic rather than a more specific mutagenic. And then also, probably, too, as I mentioned yesterday, make better use of existing analyses rather than a sort of start from scratch. Let me just sort of expand a little bit.

I think in terms of the description of mutagenic or if you consider changing to genotoxic, I think that although there were some other pathways implicated yesterday and maybe there is not absolute consistency with the data, it seems reasonable to me. Surely nothing to suggest, I think, sort of taking something different than a linear approach would be warranted. There is no suggestion of that.

And just for kicks, some of the language from the report on carcinogens and monograph was that available data provided some support that 1-

bromopropane is genotoxic as induced mitogens -- sorry, mutations and bacterial in mammalian cells and DNA damage in human cells and then 1-bromopropane either directly or via reactive metabolite causes molecular alteration to the carcinogenicity, including genotoxicity, oxidative stress, glutathione depletion, immune suppression and inflammation.

So just in the language that I think that you've brought into yours already, I would consider, certainly keep that language, even if you go with sort of the genotoxic as the primary mode. But then in terms of use of the existing RSC monograph, I make the suggestion not only because it's sort of an NTP product, but it's actually fairly recent, since September of 2013 it was finalized. It was also constructed using peer review processes that are fall under OMB guidance, so applicable to your own.

In sort of a going forward approach, I would encourage you to sort of aggressively try to use other evaluations done by other agencies for the same reasons. Perhaps, being vigilant that you might have to not just be able to lift their label, but probably have to sort of look at the science that is used to support their label and make sure it matches your criteria.

And also, and this is sort of a more general approach for how you might be able to sort of apply this in future assessments because we've wrestled with the same issue, in terms of how to use the tools of systematic review most efficiently. So I'll just sort of tell you where we've landed and then you can just tuck that away. So for example, if you have a 2013 document and let's say that you're updating literature, it could be that you do that and if it not a particular controversial health outcome or something that is likely to change the scape, then maybe you just document that there is no new evidence that contradicted that conclusion.

If it is a more controversial outcome, then you probably have to take a deeper dive into that literature. But I think the idea is to sort of, the recommendation would just to sort of be efficient as you apply the tools of the systematic review, moving forward. So don’t obligate yourself to data extraction and quality assessment for every individual study, especially when you have lots of literature.

I say this, some of you on the panel who might not sort of prepare these documents might not appreciate the time involved. So it could take, you know, 30 minutes to an hour and a half to summarize a study, just the data in it, especially if it's a complicated study, especially if it's poorly written. And if it's poorly written and presented, then it's probably not going to really feed into your analysis.

And then you've got an additional 30 minutes to an hour and a half to do sort of a robust study quality assessment, especially if it's an epidemiology study where you probably have to engage with a topic-specific expert to deal with the nuances of the exposure assessment confounding. So, you know, for one study, it can take three hours. And so you think about scaling that up and sort of saying do a systematic review and do a quality assessment on every study that's relevant, then now you've really worked against your ability to produce these in a timely manner.

So just a recommendation to be efficient. And I think that you've already got steps. I'll imagine you'll have steps for trying to maybe sort of present an analysis plan on new chemicals. So you could always get feedback from people on whether that sort of efficient use of those tools are reasonable. And they will tell you if not.

So I bring that up -- and this is a bit repetitive too. The other reason I bring that is that I think the document would be -- there is no structured approach for synthesis in the current analysis. Again, this is sort of a by-product of when this was initiated, a lot of the work that's been done by the average program or other entities really hadn't sort of fully developed on their guidance. I understand. But the lack of having a structured approach for evidence synthesis is a vulnerability to this document.

So again, another reason to sort of use an existing one that reached a conclusion of "reasonably anticipated," which is very similar to your "likely." In terms of the structured frameworks going forward, you know, we use something modified from grade, the IRIS program, from my understanding, they're using something that's maybe not specifically linked to grade, but I've looked at it and it's very conceptually similar.

So I think that anything toward, especially because you're EPA, anything that you can do to sort of harmonize toward the approach used by IRIS, which would be consistent with the approach used by NTP and other agencies would be great. And just to sort of not to raise expectations too much for the audience. As you see these, I think in terms of the systematic review, it's very easy to bring more clarity to how you identify the evidence and look for inclusion criteria and maybe how you applied said equality tools to the individual studies.

I would probably be remiss if I didn't say that in terms of the -- if you use a structured approach for evidence synthesis, it can help with how concise the document is, but it's probably still going to be a dense read. I mean, I think these approaches work best when you're talking about -- if you can meta-analyze the data, then you can sort of get a concise summary or figure. But when you can't because you've got lots of different endpoint, the evidence synthesis will probably -- it's still going to become (inaudible), probably. And I think it's going to take us a while to get there in terms of conciseness. But you have to start somewhere.

Let's see. I think the other thing, too, is a few other points, again, sort of maybe more of a moving forward one that you might also want to consider, Martin Smith had a publication come out recently about key characteristics of carcinogens as a basis for organizing data on mechanisms of carcinogenesis. And this publication seems like it's getting -- you know, we're looking at it and IARC is looking at it in terms of way to map the mechanisms. You might want to look at too, probably people in IRIS have already made headway on that.

Also, in terms of the terminology and weight of evidence, I think there was a suggestion in the NAS report to IRIS to sort of maybe consider using evidence synthesis because weight of evidence -- none of these words are easy to define, but weight of evidence is particularly, maybe harder to define. And so for us, we move toward evidence synthesis because it's sort of describes a process of what you're doing rather than a thing. But I'm sure that you would probably -- a higher priority with you would be trying to map to other parts of EPA, in terms of the terminology.

Those were my main thoughts.

DR. KENNETH PORTIER: Thank you. It's interesting, I always think weight of evidence, I want to see a weight. Give me a quantitative number of how good this thing is. And what you're suggesting is getting away from that terminology allows you to just say I'm looking at the holistic literature here and kind of giving you some relative importance. But I'm not going to weight this one or rank this one above that one.

DR. KRISTINA THAYER: Right. It's the process, the thought process.

DR. KENNETH PORTIER: You're getting at the process. That's a good point. Dr. Gilbert.

DR. KATHLEEN GILBERT: I think Dr. Thayer has done a much more thorough evaluation than I did. And I'm looking at it more from the point of a biologist. I understand why you picked the mutagenicity as the endpoint, but it wasn’t completely convincing. I mean, obviously there is some evidence that you do get mutations if you culture cells with it. On the other hand, there was the 2011 NTP report where they looked and didn’t find mutagenicity in some bacterial mutagenicity assays or in the erythrocytes in the mice exposed.

So that kind of suggests, well, maybe it’s not really mutagenicity, but then I understand, as far as the other possible mechanisms that is really like the immunosuppression, there just isn’t enough data to say one way or the other, so I have to concede that looking at what's actually available that the mutagenicity makes the most sense in terms of the endpoint, even though it’s not completely convincing from a biologist point of view.

DR. KENNETH PORTIER: Dr. Marty.

MR. MELANIE MARTY: Yeah. I probably found it a little more convincing than Dr. Gilbert, in part because of this weight of evidence or evidence emphasis, however you want to call it. So one thing to note, I think that there was an adequate description, but it could've used a little more detail that may have been a little more convincing. It's really hard to test very volatile chemicals in these cell-base assays, as different standard assays.

So back in '81, the publication by Barber, they looked at an unenclosed system versus an enclosed system and in the unenclosed system they tested 10 VOCs and only two of them were positive. And when they used the enclosed system, seven of out ten were positive. So it’s just an indication from that actually rather seminal paper on doing this kind of stuff. Then there is based permutations that were observed with the mass lymphoma assay. When you look at some of the human data, again, if you dig a little deeper and provide a little more detail on some of the papers, for example, Torresen (2006), when they looked at various ways to measure exposure, they did find positive associations between 1-BP exposure at the individual levels. So this is just not air exposure, but personal exposure and DNA damage and leukocytes. Some of those associations were statistically significant but they were all in a positive direction.

So having a little more detail I think will help your case. And also, the entity report on carcinogens had a little bit more expanded description and they had a few more studies that I didn't see in your report. So for example, formation of globin addicts in workers exposed to 1-BP, and also observed in rats.

Okay. So I think that given all of the information you had, structural similarity to other compounds that are genotoxic, metabolites that are genotoxic and some are carcinogenic in carcinogenicity bioassays, that fact that it is an alkylating agent, so we always worry about alkylating agents because they react so well with cellular macromolecules. I think you are on good ground for saying that there is a probable mutagenic mode of action. But also, I would like to note that unless you have really compelling evidence that it acts as a threshold, you're going to use a linear model anyway. So that's sort of standard risk assessment practice.

Okay. Thanks.

DR. KENNETH PORTIER: Dr. Schlenk.

DR. DANIEL SCHLENK: Yeah. Just to throw in my two cents on this. I think given the evidence that, again, it goes back to the biochemistry of this with CYP 2e1 activation being a fairly important mode of action in terms of activating it. And I'll talk more about this for the non-carcinogenic endpoints, but again, one of the ways I think you can do that, and I'll mention this a little bit more, again, is using an adverse outcome pathway type of approach where you actually do link each of the pathways together which, qualitatively, can be used in a weight of evidence approach.

So that, again, I think if you do that you can see that there are multiple genotoxic and non-genotoxic pathways involved here. I don’t think it's one or the other. Obviously, from a regulatory perspective, you have to pick one, I guess. But if you look at the mode of action of this, it's very likely that's it's genotoxic, as well as mediated through oxidative stress. I think the data is an immune suppression. I think all of those fit together with an adverse outcome pathway of activation by 2e1. Very, very similar.

Actually, I'll talk a little bit more about this, or through glutathione depletion. You don’t even need an enzyme, actually, to deplete glutathione with this compound. It will actually bind glutathione directly, leading to oxidative stress, which again, you may not see addicts with that. You'll see, you know, hydroxyl wanting addicts from oxidative stress. Or hydroxynonenal, which is again, lipid peroxidation by a product, which is -- you're not going to see that.

So again, mechanistically, if you draw those boxes and put the little lines through the boxes and just show, figuratively, how these things can work interactively, you can do that qualitatively. That's not a problem. No new data, just a different way of presenting what you have in text. But what it does, I think, is when you connect those lines, you can actually see they all lead to the same endpoint. And again, the goal, at least with the AOP pathway, is to eventually quantify those linkages. I mean, that's the ultimate goal. Obviously, that's not what you guys are going to be doing, but other people in ORD, for example, would be doing that type of things, which eventually, hopefully would move in that direction.

So I agree that genotoxic is a good word, but I think there's also evidence for non-genotoxic types of pathways here as well. If you do the adverse outcome pathway, it actually shows you that sort of paradigm and that probability, at least qualitatively. And then eventually, you know, you can actually do your quantitative measurements or estimates based upon that qualitative data.

Anyway, I'll go into more detail on the non-cancerous stuff a little bit later, but it fits in this question as well.

DR. KENNETH PORTIER: Dr. Marty, do you want to follow-up on that?

DR. MELANIE MARTY: Yeah. I just was going to say yes, indeed there are other mechanisms. There are many mechanism of carcinogenesis. And we really don’t know which ones are predominate. The data to get that is just prohibitive. And also, the predominate mode of action may differ by life stage. So that's, to me, a really important thing, life stage, physiologic status, disease status, et cetera.

So we always use linear dose response because we can't ever really answer the question is there or is there not genotoxicity somewhere involved. Even inflammation, you get reactive oxygen species, which produce the oxy addicts that you just mentioned. So it's not very simple.

DR. KENNETH PORTIER: Dr. Davies.

DR. HOLLY DAVIES: I wanted to comment back on the mutagenicity. I was convinced by the evidence presented, but it was hard to find it in both the organization and the repetitiveness. Just an example, the hazard identification has a huge list that's kind of more this all of the evidence more so than the weight of evidence section that is a couple of pages later. So it's both repeating it. And I would've put the list there. But then in Appendix O, where a lot of stuff is again repeated, the NTP monograph is mentioned. So the fact that NTP monograph has determined it's reasonably anticipated is not mentioned in either of those sections and founded. So just the organization, as Kris has mentioned. I'm putting that in.

DR. KENNETH PORTIER: Dr. Thayer.

DR. KRISTINA THAYER: Yes. I guess just to follow-up on what you said, I would support genotoxic and non-genotoxic, and making it clear that nothing to suggest working -- that you would use an approach different than a linear model.

DR. KENNETH PORTIER: Dr. Meliker.

DR. JAYMIE MELIKER: So this is really a question for the Committee because I'm not a toxicologist. But it seems like in the end, a lot of the risk assessment is based on these animal studies that came out of the NTP. There were three of them and I just don't know, you know, how good they are. I think really, I think those are really what we're basing it on, right? This is Table Appendix 03. This is the dose response that you end up building everything off of. So I just want to make sure that we're confident in those data, at least reasonably so.

DR. KENNETH PORTIER: Dr. Thayer.

DR. KRISTINA THAYER: Yeah. I would think that for sort of any key study, it would be good to sort of apply whatever tool you have for said equality to it. That being said, I think NTP studies are considered to be cancer studies, sort of gold standard. I mean, they undergo -- there's a draft document with draft conclusions that undergoes public comment, public peer review. So they're pretty well vetted.

DR. KENNETH PORTIER: Yeah. And I would also say that, you know, they're typically vetted twice. So the technical report goes through a peer review and they definitely look at whether there are any warts in the study, anything that would lower it. So you have that opportunity to go read that document to find out really how good the study was. And I didn't see a summary here, but it might not be bad to refer to that technical document and pull some conclusions forward, just as again, part of what we're calling the literature synthesis, just being able to say, you know, not only are NTP studies in general good, but this study was graded good because that's what's more important. Not all NTP studies get five stars, for a lot of reasons. But I'm pretty confident this one did.

You know, Dr. Marty, as I was listening

to what you were saying, I was wondering whether the recommendation is to put that kind of summary in the body or is that an appendix where that kind of detail is laid out and then pulled forward. I keep thinking there is communication here. What you were talking about is pretty extensive. It's a nice little 30, 40-page report. Does that go in the body of the report is or is that an appendix?

DR. MELANIE MARTY: You know, I personally have trouble flipping back and forth between the body and appendices. So I think Dr. Davies mentioned the same thing. You know, if you could bullet a lot of stuff in the body of the report and then put the detail in the appendix, that's fine.

I did not mean to add 30 or 40 pages of the document.

DR. KENNETH PORTIER: Any additional comments from the Panel?

(No response.)

Any EPA clarifying questions?

DR. YIN-TAK WOO: I actually came into this project in the middle of the process. I actually find this a very interesting chemical in the sense that if you look at the -- my personal background is on structure-activity analysis. And I've looked at all these chemicals. And the first thing I look at was the 1-BP series, methane is very mutagenic. It's NHANES positive like how it's not carcinogenic.

The ethane is also NHANES positive, but seems to be acting by some other mechanism. Now, we come to the propane and then we come to the butane, is also mutagenic in the NHAMES test. So we have some in between this somewhere so that that's the original thing that we think there is a reason to support NHANES. But again, the complication of having a closed system. And I understand that (inaudible) is a new submission.

So we didn't actually depend on the NHAMES test at all because that seem not to be crucial thing. And also, as we mentioned that there is absolutely no evidence that this genotox -- non-genotoxicity is a mode of action. So basically, we only need to fight for this rating whether it be genotoxic or non-genotoxic, but we just look at the available data.

And also, (inaudible) provided the additional chrome map assay showing positive data, although there's some question of whether it's positive because of cytotoxicity or not. But basically, they have that information coming in.

One other thing I look at the -- I'm talking about the 1-bromoalkanes series, but then what make 1-bromopropane so different, that's the (inaudible) oxidizing to the hydroxyl group. And the hydroxyl group can do a lot of interesting things. first of all, the hydroxyl group, when it's next to a halogen, this is called alpha -- you know, halogen, and it could make it very reactive and also could cyclize and get HCL, HBL and becomes epoxide.

So that's a different story because as I mentioned yesterday that as a 1-bromopropane, it's expected to be what we call a soft electrophile that will react as SH compound first. That's why it's reacted to glutathione. So you need to deplete the glutathione to make it connect.

But once you put it in the hydroxyl group it become a different story. It becomes possible to have an epoxide. In fact, the NTP work that suggests that there's potentially epoxide and that changes the story. And also, in addition to epoxide, there is also a possibly of aldehyde or ketones. And normally aldehyde or ketones are very reactive, but when you have something next to it, alpha halo, it makes it an even more reactive. But also makes them short-lived. So that means the studies are very difficult.

For example, one of the things that we look at, the in vivo bone marrow micronucleus that tend to be negative. But people are probably putting too much weight on the in vivo study because cases like the bone marrow micronucleus, if the reactor (inaudible) is too reactive, it cannot go into the bone marrow.

And in fact, Dr. Baninni (ph) in Italy has a recent paper that indicate that the in vivo, micronucleus and bone marrow is not a good indicator for potential carcinogenicity. But anyway, come back to that. In addition to, we basically -- in addition to available data, which we realize that not perfect, but it’s enough to support some -- actually, when I first looked, I did call it genotoxic carcinogens. I think I have to change to mutagenic, but basically, it's not much difference.

Anyway, we would look at the whole pieces. We called it weight of evidence, but basically we had to look at the whole thing, why it could be considered supportive of genotoxicity and also why some of the in vivo study may be negative. Some of the other in vivo negative studies cited a drosophila, but drosophila is not enough (inaudible) and very incident sensitive.

So that's basically what we came up with this. I would, you know, first time they would call it possible rather than probable, but because of the quality of data is not what I would like to see, but is sufficient, in totality, to support those views.

DR. KENNETH PORTIER: Dr. Thayer.

DR. KRISTINA THAYER: A quick comment. And again, I'm stop talking about this, but if you were to try to sort of maybe sort of craft some of what you said in terms of a systematic review framework and with a drosophila, you could sort of use their insensitivity as a rational for excluding that model system. You know, so there are ways to really sort of think about your inclusion/exclusion criteria so that you're really getting at the most applicable information.

DR. YIN-TAK WOO: Yeah, that's a good point. I guess we would basically have to list whatever is available and then maybe we could exclude a drosophila, actually put the weight away from the negative in vivo because the fact that most of the reactive metabolite that they look at will be very short-lived and very unlikely to go all the way into the bone marrow. And I did this with a lot of experience when I would look at this infection by-product when it's a correlated compound, when you see all those being next to the aldehyde or things like that to make it so much stronger.

DR. KENNETH PORTIER: Dr. Schlenk. And then I think we'll move onto the next question.

DR. DANIEL SCHLENK: Yeah. I'll address this in the non-target because it still fits with a carcinogenic, non-genotoxic mechanism. And because you actually list the paper in the report. The Lee, et al paper actually shows splenic, a decrease in splenic cellularity with glutathione addicts and oxidative stress that leads to immune suppression.

So you're actually getting activation in the spleen, probably through 2e1 or 2f1 or 2f2 if you're looking in mouse that can lead to, again, it's a non-genotoxic mechanism that leads to immune suppression which could actually cause that. Again, that's not really flushed out. Again, I would go to a diagrammatic viewpoint with the boxes with the lines that actually show those links because then you can see okay, you're trying to compartmentalize non-cancer thresholds to immune suppression or immunotoxicology. But immunotoxicology can manifest itself in carcinogenicity. So I think those are linked and you need those lines to draw those lines between the boxes.

So again --

DR. KENNETH PORTIER: Point made again. Point made. Why don’t we move onto to Question 4-2. I think we're kind of bleeding into the next questions here, so let's move forward.

DR. KATHERINE ANITOLE: Question 4-2. EPA/OPPT identified liver toxicity, kidney toxicity, reproductive/developmental toxicity, and neurotoxicity in the risk assessment as adverse human health effects for risk characterization. EPA/OPPT used these endpoints to calculate PODs to assess non-cancer risks associated with chronic inhalation exposures.

As part of the review, please comment on the choice of these endpoints as PODs for assessing risks in humans associated with acute and chronic inhalation exposures to 1-BP. Are there other data that EPA/OPPT could have considered for the hazard identification and dose response associated with chronic inhalation exposures?

If so, please provide specific data and references.

DR. KENNETH PORTIER: Dr. Hossain, we haven't heard from you very much. Here's your opportunity.

DR. MUHAMMAD HOSSAIN: Thank you. I think EPA appropriately focuses on the several non-cancer endpoints, including liver toxicity, kidney toxicity, reproductive and developmental toxicity, and neurotoxicity for assessing human risk associated with acute and chronic inhalation exposure to 1-BP.

Based on the literature, liver and kidney toxicities are very important endpoints of 1-BP toxicity, but appears to be less sensitive for determination of human risk. It seems that EPA/OPPT properly uses several reproductive endpoints including decrease in prostate epidermal, seminal vesicle weight and sperm mobility in male and also a prolonged ester cycle and decrease antral follicle count in female, and decreased litter size for both response study and OPPT determinations.

Neurological symptoms following acute and chronic inhalation exposure to 1-BP are the key concern for the risk of human health that are presented in the appendix or indicates that the adequate dose response analysis who are selected for POD determination of non-cancer effects.

In the most cases, adverse neurotoxic effects are observed in both the humans and animals at the concentration at 100 bpm and above. Neurobehavioral and deficits including decrease motor function and cognitive deficits in laboratory animals, along with neurochemical and structural changes in the brain can be used as chronic, neurotoxic endpoint to predict neurological impairment in human following long-term, low-level occupational exposure. Likewise, the developing brain is more sensitive to several environmental neurotoxicant at the level far below those that are known to harm adults. That's concern for developmental neurotoxicity could be an important consideration in the assessment.

Furthermore, high bromine concentration was observed in PND 1 (inaudible) following gestational inhalation of 100 bpm, 6 (inaudible) they throw out the (inaudible), 1 to 20. This data came out this year from a Japanese group. I think therefore, long term, low-level exposure could be the good things to look at for developmental study, and whether it has long term consequences in later life. That's it.

DR. KENNETH PORTIER: Thank you. Dr. Gilbert.

DR. KATHLEEN GILBERT: Okay. Some of the comments I'm going to make are going to bleed into the next section because it's tough to talk about endpoints or points of departure if you're nuts about the endpoints that they're using.

A lot of the data was based on the WIL study, which was a very impressive study; 25 rats per gender per four different concentrations, F0, F1, F2, a really impressive study. And so as far as the points of departure for the reproductive -- I thought that they were really good choices and I thought the data was very strong there.

As far as the neurotox endpoints, I thought that the functional endpoints were much more powerful than the brain weights. The WIL study noticed that they got decreased brain weights in several of the groups, but those numbers were absolute. As they noted, they were not compared to total body weights. So the significance of that wasn't as impressive as some of the other endpoints. So the functional endpoints, in terms of grip strength and things like that, seemed to me, much more useful.

In terms of the liver toxicity, I found the WIL study to be really unimpressive in terms of describing liver toxicity. They noted the increased incidence of vacuolization in some cases, but they also went on to say that these changes were probably reversible.

Now, of course, they did not follow the rats for a lengthy time. Most of the rats were, I think, sacked at post-natal Day 21 post-natal Day 28. So it's possible that hepatotoxicity could've developed into something more important. But that seemed to me, especially when you're talking about reversible changes, it just didn't seem like the liver toxicity was that strong.

Now, there is the Lou paper, where they looked at multiple strains of mice and they actual got necrosis in the liver in their exposed mice. And so it wasn't clear to me, once again, it goes to Dr. Thayer's point of inclusion and exclusion. I realize that there much fewer mice per group in that study and I was wondering if that's why the WIL study chosen over the more robust liver toxicity study or the Lou study.

So overall, though, I didn't think the liver toxicity was that noticeable and I don't know if for a risk management if the idea is to make sure that you get as many different endpoints out there as you can because if it were me, I'm not sure I would include that one. The kidney toxicity was a little more convincing. And I thought the points of departure for that were pretty good. So I think that's all I had to say.

DR. KENNETH PORTIER: Thank you. Dr. Meliker.

DR. JAYMIE MELIKER: I think I have just a little bit more. I think in general, pretty similar to what people have said. My reading was that, you know, let's find and look at the different endpoints that you did. The most sensitive seemed to be neurologic reproductive and developmental. When I look at the human evidence, I look at the animal evidence, I look at the doses. And it seemed like that was in line with what you were doing.

There was this question about litter size and how to relate that to humans, which I think is a question, and perhaps, paralleling your analysis with litter size with other endpoints like fertility and infertility. It might be nice as a way of saying, okay, at these doses, this is what we're seeing in endpoints that are more clearly relevant to humans.

The function of neurologic endpoints I thought were appropriate of what Dr. Gilbert just talked about. They've been used for some time with regard to inhalation exposures from VOCs. There's clear human relevance there. There is also human data there for these neurologic functional endpoints. And I think I would use that as your POD, you know, your point of departure value or use those human data, then you don't have to just divide by 10, which is what you're doing now with your uncertainty factor. I think that division by 10 produces -- I see Dr. Barone saying "no," but that's what I would do.

DR. KENNETH PORTIER: Dr. Schlenk.

DR. DANIEL SCHLENK: I agree with most of what folks say, although I'm a little more inclusive of the hepatocellular vacuolization because I think it fits with the mode of action of the compound. I'll talk about that with the weight of the evidence a little bit later.

I think the real key here, and this is all been mentioned, I think, but it is using an acute endpoint for chronic endpoint. The developmental aspects, I think it's warranted in this particular case because of the potential for critical windows in development. I think that’s a very, very good way to go with that. Again, this comes more to the weight of evidence component.

So I also agree with Jaymie on the human relevance here. And again, the linkages between the behavioral modification that you see in laboratory and the linkage to human impairment that seems to be consistent. Although, I don’t think I'd use the human, I'd actually use the animal just because you have more data points that are present. It gives you a little more certainty there, but definitely the human thing.

I don’t know, if you could cut to maybe to three, I don’t know, on the uncertainty factor. I don’t know. Honestly, I haven’t looked at that data to say that. But having human health data definitely helps; particularly, again, with the qualitative mode of action kind of endpoints there.

So the neurological components, I think, are important. And that said, developmentally, I think, again, I don't know if you got the data or not for the developmental endpoints there, but I think that's going to be a real big likely target primarily because you have CYP 2e1 in the placenta and you actually have it in the fetal organism. So there's that.

So again, bottom line, I'd say development are your best, I agree, development is your best sort of threshold here and the PODs and the VMDLs that you have I think are totally fine with that. I think, again, the multiple reproductive endpoints that you've seen here, again, provide more weight of evidence for that, which again, is the next question, but I think again, it provides evidence so that you can use a dose response analysis to do the POD determination. So again, there's some progression there.

So yeah, overall, I think using a QPOD for developmental toxicity appears to be protective of other chronic toxicities resulting as present.

DR. KENNETH PORTIER: Thank you. Dr. Marty.

DR. MELANIE MARTY: I have a couple of comments. First, in response to what I heard from Dr. Meliker, the concern about the decreased live litter size being relevant to people. So generally, we only have one kid at a time, as humans, but it a measure of fecundity in the animals and it could be the result of male repro effects, female repro effects and effects on the actual fetus and embryo.

So it is overall an indicator of a problem with reproduction. So I don't have an issue. And actually, EPA's Guidelines include that as one of the endpoints. And I think other people said there's a number of other endpoints, all around the same -- sort of the same point of departure. So I'm okay with that. Using human studies -- so for dose response assessment, it's really always hard to use a human study because the exposure assessment tend to be really difficult. So I understand why EPA didn't use those for the dose response assessment, but I think you could look at the measurements made in the studies, like for Ichihara (2004), and say okay, here's our point of departure from the animal studies and here's the exposures that were measured in people that had neurological effects, sort of as a check against the human data. And just a warning about the uncertainty factor because you used an HP study. It's workers. It's usually all males. It's usually -- there's no kids. So there is still a huge variability in the human population which I don’t think even gets covered by a 10-fold intraspecies uncertainty factors. I just wanted to put that out there.

Then in terms of the points of departure, maybe I'm bleeding into the next question, I'm not really sure, but the general applicability when you're using the BMDS software, if you look at that visual fit, the P values, you want them to be high in this case. And the AICs. So I'm not sure that that was evenly applied.

If you look at the table, there's one case in particular, decreased body weight in the FY male pop in the WIL study, where the BMDL was actually lower than the one that was chosen. With the Hill model -- so one of the Hill models with a 5 percent relative deviation. So I was just curious about that maybe you want to expand a little more on why you didn't decide to use 23 rather than 31 parts per million for that case. So that -- I think it had a bit higher AIC, a better P value but it was larger ratio of BMD to BMDL. So that's another thing that people look at. But if that's why you didn't choose it, you need to say why.

Thanks.

DR. KENNETH PORTIER: Thank you. In listening to what the Panel said, you've addressed the question. You commented on the endpoints. Other data; I heard reference to a new paper that you thought might be considered. Is there anything else here that they should consider that they didn't consider in the discussion?

Dr. Marty?

DR. MELANIE MARTY: Just one quick thing. It won't drive the risk, but it was interesting that you didn't look at hematological or immunotox as one of the endpoints for the PODs. Because you had some evidence there that you have immunotoxicity and you have evidence that you have decreased blood cell counts. So I wasn't clear why you didn't decide to use the BMDS software on some of those studies.

DR. KENNETH PORTIER: Dr. Gilbert?

DR. KATHLEEN GILBERT: Along the same lines, it would've been really useful to have mentioned some of the reasons why you didn't include some of the things like the immunotox in there.

DR. KENNETH PORTIER: So I'm hearing a lot of support for your endpoints and no new data. Any comments?

(No response.)

Well, oh, Dr. Gilbert?

DR. KATHLEEN GILBERT: I'm still curious as to why the brain weight was included in there as a point of departure.

DR. KENNETH PORTIER: They may not be prepared to answer that question at that time. But if you can do it pretty quickly.

DR. SHARON OXENDINE: Sure. This is Sharon Oxendine, EPA. We actually came across a clinical trial study that showed major histopathology in the brain. And that, I guess, queued us to deeper. And because, generally, the brain is spared, it seemed like something that we should pay attention to. Not only that, it was demonstrated in different studies and across generations so we thought that it was worth including.

DR. MELANIE MARTY: But did those changes actually result in changes in the weight in the brain? I mean, how would you translate that?

DR. SHARON OXENDINE: Yes.

DR. KENNETH PORTIER: Is that human clinical trials?

DR. SHARON OXENDINE: Oh, no. This was a clinical trial study, a '97 contract study that showed pathological changes in the brain with rats.

DR. KENNETH PORTIER: Dr. Hossain.

DR. MUHAMMAD HOSSAIN: So is there any possible data that -- whose brain region is specifically target for 1-BP? Maybe it is, I think overall, decrease the brain weight, but its specific brain region could be affected and because of that maybe an effect on neuro function. So that needs to be looked at.

DR. KENNETH PORTIER: Dr. Gilbert.

DR. KATHLEEN GILBERT: I hate to keep harping on this, but in the WIL study, they didn't see any kind of cellular changes in the brain.

DR. SHARON OXENDINE: Yes. There are some issues with sensitivity with different rat strains. Generally, the rat strains that have a higher P450 level, decreased glutathione levels, decreased GST levels tend to be more sensitive.

DR. STAN BARONE: So you referred to neurotox, and I want to also remind you of the neurotox risk assessment guidelines so the Committee is also aware. Brain weight is considered a pathognomonic, pathological finding and is generally used is risk assessment by the agency.

Brain weight, also as our neurotox risk assessment guidelines indicate, is not corrected for body weight. So we use the absolute brain weight, not corrected for body weight. And again, to Sharon's point about sparing, particularly in developmental studies, brain weight, the brain is usually spared as far as the absolute weight in comparison to other organ systems.

So that's a generic thing that the Committee needs to appreciate in all of our peer review assessments as we go forward.

DR. KENNETH PORTIER: Thank you. I think we're done with question. We'll go Question 4-3.

DR. KATHERINE ANITOLE: Question 4-3.

Please comment on the WOE analysis for the choices of non-cancer endpoints for the acute and chronic risk scenarios. Please provide additional data, data interpretation or information that would have informed the WOE analysis and selection of critical studies for the PODs.

DR. KENNETH PORTIER: Dr. Gilbert is the lead.

DR. KATHLEEN GILBERT: So we sort of talked about this a little bit already. So the WOE for the developmental reproductive toxicity was, of course, based on numerous studies in mice and rats, especially useful was, once again, the WIL study. And they reported exam in both F0 and F1, rats in both genders and they found many significant differences in infertility, puff weight, weights of several reproductive and growth-related organs. Very convincing.

In another two-generation inhalation study, exposure of rats also showed altered numerous reproductive endpoints. So the strength of the WIL report, in conjunction with similar findings by several other studies concluded that the development reproductive toxicity was a really good endpoint.

And then, of course, there was a study looking at women, associated, that used 1-BP in a glue spray gun use. And they experienced several -- I think that study was only three women, but they experienced serious neurological and reproductive effects.

Let's see. One other study looked a pregnant rats, they showed that fetal rates were decreased. Various skeletal variations. And then, of course we already talked about the fact that the NHANES study showed that 99 percent of women that are pregnant had a metabolite. Whether or not that's specific for MBP is apparently still up in the air.

The evidence in one MBP causes neurotoxicity. Also, very convincing. Identified as a critical factor, numerous rodent studies, including the WIL, as well as cross-sectional studies in case reports in humans. A study in Chinese workers with passive sampling showed neurological effects. Multiple and consistent adverse neurotoxic manifestations have been described, including peripheral weakness, numbness and ataxia.

So once again, the neurotox seems very clear-cut, seeing the reports in humans as well as in rodents.

As I sort of said before, I thought the WOE for hepatotoxicity was less convincing and there was one study in humans, Lee in 2010, which didn't find and deliver toxicity. And the kidney toxicity I also found less compelling. And there were a couple of studies in humans that also failed to demonstrate renal effects, making those two less convincing endpoints.

So in conclusion, the selected endpoints of neurotox and developmental reproductive tox seemed very well justified based on numerous animal studies. And in many cases, human case control studies and case reports. I think that's it, except, like I said, I think the kidney toxicity and hepatotoxicity were less convincing. And I wasn't exactly sure why they were included.

DR. KENNETH PORTIER: Thank you. Dr. Hossain.

DR. MUHAMMAD HOSSAIN: I think most of the comments are covered in 4.2. So I think since liver and kidney toxicity is very less sensitive, so I think we need to focus on mostly neurotoxicity. And with that, several symptoms comes after the acute toxicity, but I'm not sure what is that mechanism. It is not clearly understood, I think. So it is very critical to understand that. Please ask mechanism for neurotoxicity.

DR. KENNETH PORTIER: Dr. Quiros?

DR. LESLIAM QUIROS-ALCALA: So to follow-up on that, there are some recent studies, human studies, and these deal with neurotoxicity. I'm not sure what the outcomes were because these were not available to me and these are in Chinese, but they may be worth looking at.

One by Miao (2015) on electrophysiological effects of 1-BP unexposed workers and the other one by Wang, et al (2015), neurotoxicity associated with exposure to 1-BP in the Gulf Club Cleansing Workers.

In Section 3.3, the WOE, multiple lines of evidence supporting the critical effects section, it covers reproductive, developmental and neurotoxicity as well as cancer endpoints; however, there is no mention on other endpoints that were considered in this risk assessment calculations in that section. It was sort of mentioned before, but not in the WOE section.

So somehow, we combined those two sections more effectively. There is also one recent liver/kidney toxicity pertaining to the liver toxicity endpoint. Fang et al (2015), they looked at the effects of 1-BP on liver and kidney function on exposed workers. So it may be worth looking at. I don't believe they found anything, by the way.

Again, more transparency as to how things were selected or not selected would help. And again, because -- due to the fact that I wasn't clear on how some studies were selected and how others did to make it, I wasn't sure also how immunotoxicity didn't end up as one of the endpoints.

That's it. I think the other points we've already covered.

DR. KENNETH PORTIER: Thank you. Dr. Schlenk.

DR. DANIEL SCHLENK: Okay. So two WOE evaluation discussions for non-cancer endpoints are provided in the assessment.

For reproductive/Developmental toxicity, dose-related decreases in live litter size, postnatal survival, and pup body weight, brain weight and skeletal development were used to confirm the occurrence of reproductive toxicity.

In addition, the reported decreases in the number of implantation sites, and increases in 'unaccounted' implants for corresponding ovulatory events, reported as the difference between the total number of implantation sites counted and the number of pups born were interpreted as an indication of post-implantation loss, which I agree with.

Similar effects were observed in other studies with rats with increased implantation loss in rats and in mice, multiple species effects. Very consistent with causality. Given the consistent observation of similar effects in multiple species, a causative association between 1-BP exposure and developmental toxicity is likely. So I agree, that was a fabulous section.

The Second WOE discussion for non-cancer endpoints was for neurological endpoints. In this case, the agency used 15 years of behavioral, neuropathological, neurochemical, and neurophysiological studies in rodents as well as cross-sectional studies and case reports in humans to establish a causal association with 1-BP and neurotoxicity. Great piece of work on that. Again, the only thing -- well, I'll talk about this a little later.

The studies appear to link electrophysiological impairment with behavioral modification in animals. Mechanistically these studies appear to be consistent with human symptoms observed after high dose exposures to 1-BP and confirm peripheral neurotoxicity as an endpoint of excessive 1-BP exposure.

In addition, there are also WOE data available, particularly in this assessment for liver, and immune function particularly, again if the adverse outcome pathway paradigm is utilized, which can be linked to the cancer endpoints, I think. For example, it all boils down to what's called the molecular initiating event, the MIE, which again, is CYP P450 mediated.

So I think if you follow where 2e1 is, particularly in development, I think that's a real critical aspect. If you see when it's expressed, what organs is expressed, and I think what's really fascinating, just some of the literature reviews that I've just seen is that apparently it's later in development, at least in the fetal development, which is very consistent with the CNS depression and reduction of brain wave because that's obviously a later developing organ, developmentally. So I think it’s a pretty neat linkage there.

Again, what I'll do, in my notes, is I'll actually draw you out one. I'll tell you in a minute. So basically, I think there's great data for neurological liver as well and immune function, particularly if you use this paradigm, and the key is 2e1, which why I think you see the effects in rats and rodents but not in humans, particularly in the liver and the kidney responses because rodents obviously have very high 2e1.

So if 1-BP undergoes bioactivation epoxidation reaction that 2e1 would generally do, and 2f1, by the way; I'll throw that in there, too, just for grins. And you get subsequent conjugation with GST. And this can occur directly or -- sorry, in glutathione, this can occur directly with GST enzymatically or non-enzymatically. I think glutathione depletion is another sort of secondary molecular initiating event that takes place in this pathway.

And I think it governs, again, not only

the cancer endpoints, but these non-cancer endpoints as well, particularly given the target organs here. And the reason why I say that is primarily because of, I think it's the Lee, et al paper that actually looked at oxidative stress and lipid peroxidation. This is completely and totally linked to hepatocyte vacuolization, which was seen in the WIL et al study. So you have a linkage to vacuolization, which is a lipid peroxidation-based pathway.

Again, just connect the dots, right. And then you have necrosis observed in mice, I believe, is the other one, which again, this is just a little bit further down the line. And again, this seems to be species-specific because again, the 2e1 component in the liver and not necessarily in humans that, particularly in adults.

And similarly, for the immune components, and I mentioned this earlier, glutathione depletion was observed in spleen from 1-BP treated animals. Again, this would likely result in immune suppression. They saw a decrease in spleen excel type, which again points to -- and again, I don't know if this is possible or not, but to do white blood cells measurements as a biomarker would seem to me to be a pretty interesting thing to look at if you have that from NHANES data. I don’t know if there is white blood cell data out there. Again, not my area. I think that would be a real good component there because it would give you some indication of immune suppression and whether or not the animal data fit the human data in that regard.

Again, my point is that this definitely represents a non-genotoxic pathway that's present through immune suppression, at least in the animal studies. Additional results occur, again, as I mentioned the neurological targets since 2e1 is also present in the brain, inducible in the brain, and it's present in the developing fetus in humans. Again, more so later in developments through second trimester. And I'll include some references on that but it seems to be consistent with that.

So again, this may again point to 2e1 as your molecular initiating event, which, again, you can run lines off from that to different endpoints, depending upon your targets, which you have them, at least in text, anyway, in the report. And again, the figure just makes it a little easier for people to see the lines, the dotted lines where you're not sure.

And where your uncertainty lies.

So anyway, the other component of this whole pathway that this is an AOP wiki that you can actually submit this online and get basically an internal and an external evaluation of this, real time. I think it's a pretty cheap and effective way to determine whether or not your pathway makes sense and whether or not, you know, again, pointing to the point of departure values that you point on this, this is a good way to actually get some feedback in real time on these types of things.

I think also, and I mentioned this yesterday, I think it will also help you identify potential biomarkers. For example, if the white blood cell count is something that, you know, if you seeing immune suppression through this pathway that points you to white blood cells counts as a potential biomarker, perhaps.

And it also, I think, eliminates the biomarker, particularly with this particular glutathione that is likely present in any halogenated propane that you're going to be seeing if you believe that molecular initiating event is the 2e1 glutathione-based molecular initiating event, then that metabolite, you could say okay, well, if that metabolite is there, are there any other compounds that give you that metabolite, which I think if you look in the literature, you'll find there's other halogenated propanes out there that could give you that. But again, that's just a guess based upon my little AOP, sort of evaluation that's present.

So that's all I got.

DR. KENNETH PORTIER: Okay. Dr. Gilbert?

DR. KATHLEEN GILBERT: So somebody who does immunotoxicity, I'm all about immunotoxicity. I always loved to include it in anything; however, I must admit, for this particular study, I'm just not seeing that much data. And as an immunologist, seeing a decrease in glutathione on the spleen just would not cut it. And looking at white blood cells is an excellent idea, but if you're actually seeing changes at that level, you are darn well going to being seeing a lot more robust alterations in different kinds of functions. So I would be very surprised that that would happen.

I love the idea of using the immunosuppression, but on the other hand, I hate to see them dilute what they've got is really good endpoints with ones that may be interesting and may really be useful, in terms of figuring out the function in the long-term. But for right now, the risk assessment, I think they've got plenty to go with.

DR. DANIEL SCHLENK: Yeah. I'm not saying they use immune suppression or replace the neurodata that they have. I think the neurodata, obviously, is the most sensitive endpoint. All I'm saying is it's a WOE. This question is about weight of evidence and the mechanism for immune suppression is consistent with the mechanism for hepatotoxicity. It's consistent with the mechanisms for neurotoxicity. So that's all I'm saying.

It's a consistency issue for WOE, and that's what this sort of approach uses. It's not saying I'm going to switch immune function for neurotox, and particularly, even developmental neurotox; you can get those data. But it's just saying it's adding more confirmation, more evidence to that pathway that you have.

So I'm not saying replace that, I'm just saying -- and I'm definitely not saying that you should use reduction of glutathione in immunocytes. All I'm saying is it's consistent with a mode of action of activation by CYP 2e1, conjugation by glutathione. Glutathione depletion and lipid peroxidation, cellular toxicity that results in this particular effects in these multiple target organs. That's all I'm saying.

DR. KENNETH PORTIER: Dr. Marty.

DR. MELANIE MARTY: I just have one additional comment. So I understand, being in a regulatory agency myself, why do your dose responses based on frank effect levels?

I think, you know, sort of the trend is to pull back a little bit and look at upstream events. So you have a couple of studies that you could do, dose response, quantitatively, on, I believe, Zhang et al (2013) decreased neurotransmitter levels in parts of the brain in 1-BP exposed animals.

There was another study that looked at decreased expression of brain-derived neurotrophic factor, which I found really interesting because that is very important for the development of the brain. And also decreased neuroglobin, which is an important antioxidant in the brain, in Ghoul (ph) et al (2015).

So must moving -- maybe you can't do it for this report, but just think about using a little more upstream event and then compare the point of departures from the frank effect level versus the point of departure based on a more upstream event and just see where you are.

I realize that you might have to use different uncertainty factors or something else like that, but I think it's important to get moving in that direction now.

DR. KENNETH PORTIER: Dr. Blando.

DR. JAMES BLANDO: My question might be a little out of order, but it was something that Dr. Schlenk had said about the different enzymes. Yesterday, we had some public testimony about differences in rodent lungs versus their relationship to humans. And not being a toxicologist, I'm trying to follow the conversation and hear these different, I guess, isoforms of these different enzymes. And I was just wondering if the toxicologist on the Committee, for those of us that are not toxicologists, explain a little bit about that particular point and some of these differences that you see in these animal models versus human populations in the relationship.

If somebody could explicitly explain that, that would be great.

DR. KENNETH PORTIER: Dr. Schlenk.

DR. DANIEL SCHLENK: Sure. I'll take a whack at it. Rodents have -- so small molecules, particularly things like benzene, styrene, halogenated alkanes are great substrates, particularly to major P450s. One is CYP 2e1, which we've been talking about. The other one, I think, is 2f1 in human and f2, I think, in mice, I believe. And the issue is, I think it was brought up by the public commenters yesterday is that rodents tend to have very high levels of these. Particularly in the lung. But they also have high levels of 2e1.

I'm not sure about 2f1 in the liver, but 2e1 is screaming in rodent liver, which makes a lot of those materials a lot more susceptible, if they are bio-activated by that P450, which is -- I once had a friend of mine ask me are there good P450s and bad 450s? And it's like I that a bad one or is that a good one?

And it's like well, you know, we wouldn’t have them if they're all bad, right? I mean, they're there for detoxifying primarily, but there are these cases with these particular compounds where they do get bio-activated. In fact, that's what got me into toxicology, quite honestly. The fact that you have this battle going on.

So generally speaking, you have these species-specific effects and expression differences that are present with these two isoforms, primarily. There's other ones too. But as it pertains to this particular compound, those are the two primary isoforms that are responsible for the activation. So the species dependent differences could very likely be dependent on that. It's a hypothesis for sure that seems to be consistent with the expression of those enzymes.

Does that help?

DR. JAMES BLANDO: Somewhat. Well, I guess what I was wondering is, is that sufficient to explain an observation you might have in an animal model that you might not have in a human population? I'm trying to make the link. What's the meaningfulness?

You know, is it just academic that, yeah, you can measure these different isoforms and --

DR. DANIEL SCHLENK: No. I think

qualitatively, you can actually say, you know, hypothetically, but you have a scientific basis for -- again, if your molecular initiating event is the starting point upstream, the ultimate upstream event that Dr. Marty was talking about, if that's the starting point, then you look to see where that starting point, you know, when do you have the most susceptibility and where do you have the most susceptibility? So where would be tissue dependent and when would be developmentally, if you're looking at stages. So if these enzymes aren't responsible for the negative pathway of these compounds, where are they are what species and what tissue?

So that's basically, you know, hopefully that's a clear way to look at that.

DR. KENNETH PORTIER: Dr. Marty, you want to add to this?

DR. MELANIE MARTY: Yeah. I would just like to chime in that it's not just the activation, but also the detoxification and the balance of the two that's critical when you're looking at these kinds of things. So there is the ontogeny of the CYP enzymes. There also ontogeny of the glutathione transfer of enzymes and the balance of those is going to play a key role.

DR. DANIEL SCHLENK: I would also add, just glutathione levels in general, we assume that they're linear throughout development and they're not.

DR. MELANIE MARTY: It's not.

DR. DANIEL SCHLENK: We've done the studies in zebra fish and show that they go all over the place, depending on where you're at in development. So again, it's -- and quite honestly, it points back to that to that sensitive window hypothesis that you guys are using for the acute exposure that actually can be used for a chronic endpoint because you do definitely have these windows of when you have high -- for example, high CYP 2e1, perhaps, and low glutathione. If you've got high CYP 2e1 and low glutathione and it happens to hit at that particular point, all it takes in the acute exposure at that particular point before you can get toxicity.

I totally agree with what Dr. Marty is saying.

DR. KENNETH PORTIER: Dr. Hossain?

DR. HOSSAIN: Hi. I just want to add one more thing. So oxidative stress alters 1-BP. So I think maybe neuro permission could be another point to look at. That maybe cause the oxidative stress and then neuro permission then neuro degeneration and then the outcome that comes from abnormal neuro functions.

DR. DANIEL SCHLENK: And just to add, the brain is very susceptible to oxidative stress. There is not a lot of glutathione, typically, in the brain.

DR. KENNETH PORTIER: So Dan, following up on Dr. Blando's question, I'm not quite sure I heard the answer to the question. So lung cancer in the mouse was the endpoint that they used for the cancer, right. And the concern is that the enzymes in the mouse are different and more than in the human. So what does that mean when we're trying to translate the mouse health endpoint of lung cancer to the human health endpoint or human adverse health endpoint?

I mean, that's the link we're trying to make here.

DR. DANIEL SCHLENK: Sure. And I think humans do have 2e1 in the lung, it's just not as much as you see in the rodent. It's there. It's in very small amounts, but it's there. So it's present but it may explain why you don’t see lung cancer in humans, epidemiologically. I mean, I'm just saying that

that's a possibility.

But it doesn’t mean it's not there. It doesn’t mean there's a potential for activation by those enzymes. They're definitely there, they're just not -- it's a sensitivity issue, which is why we use rodents anyway, right?

I mean, you want to find something at much lower levels before you actually see things in humans. I mean, in that sense, it's a nice sensitivity issue for an effect. Can you translate that directly into humans? Mechanistically, yes. But again, it depends on quantitative components at that point, which get a little bit messier, I would say.

DR. KENNETH PORTIER: I'm thinking that's good for hazard, but now we're talking point of departure and if they are very sensitive, much more sensitive, don’t you end up with a point of departure based on the animal model that's a lot more sensitive than we would be in humans? And I think that was the --

DR. DANIEL SCHLENK: Correct.

DR. KENNETH PORTIER: At least I thought that was the public commenter's point that you might be getting a very low point of departure that's abnormally low for humans based on that mechanism that you're looking at.

DR. DANIEL SCHLENK: Yeah. And I would argue that if you follow the precautionary principle, that's exactly what you want.

DR. KENNETH PORTIER: I think Dr. Marty was next.

DR. MELANIE MARTY: Yeah. I would also -- you know, I really don't buy the argument that it's irrelevant for humans, either qualitatively or quantitatively. I'll go back to what I said yesterday about cite concordance. There's not even good cite concordance between mice and rats for carcinogens, much less mice and rats in humans.

So, you know, the whole object of risk assessment is to make sure you're protecting the public, so you use the most sensitive cites when you have multi-cite carcinogens like 1-bromopropane, and you don't necessarily anticipate that you will therefore see the most cancers in the lung and humans. That is not what you're necessarily going to see. So I just think it's not an issue.

DR. KENNETH PORTIER: Dr. Meliker.

DR. JAYMIE MELIKER: I mean, maybe we need to back up a little bit and think about what is the purpose of the risk assessment, right. Like, is it to find, to be very conservative so that, you know, following a precautionary principle type thing or is it more to try to assess as best we can, you know, what risk there would be in humans.

To me, it's the latter. And along those lines, I think that if there is some evidence that rats are more sensitive, then I think that should be included. Like, that should be factored into the assessment process.

DR. KENNETH PORTIER: Dr. Thayer.

DR. KRISTINA THAYER: I just wanted to echo comments of Dr. Marty. I agree with her. I sort of think that if you're going to sort of take that path, it has to be more than hypothetical. It has to be more empirical-based if you're actually going to sort of make that change that can influence policy.

DR. DANIEL SCHLENK: And I totally agree. I'm not saying -- again, it's qualitative. It’s totally WOE. That's when I said when you get to the quantitative aspects, it gets a lot more messier. So you go with the data that's more quantitative. But you can use it in a WOE approach if somebody comes up and says well, yeah, this isn't this way and you can say well, yeah, that's because of this. Again, it's qualitative argument. That's basically all it is.

That's all I'm saying.

DR. KENNETH PORTIER: Excuse me. I realize that a full PBPK model that links mice to rats, to humans. And I've only seen that done once. It takes into account that changing of endpoints, because the model itself begins to show you where the real physiological effects occur. So I understand that point, but it gets a little hard for me here because we have that conservativeness in the rat, in the mouse and then we're translating that to a quantitative measure in the humans.

DR. KENNETH PORTIER: Dr. Marty. I would say we don't know where the humans are in terms of sensitivity. We don't have epidemiologic studies in cancer in workers exposed to 1-bromopropane. So I don't think we say, sitting here, based on CYP 2e1. Oh, the mouse is obviously much more sensitive. You can't say that. We don't have the information.

DR. KENNETH PORTIER: That was good. That was a good discussion. Any more comments from the Panel?

Yes, Dr. Gilbert?

DR. KATHLEEN GILBERT: This is purely for my information, I just wanted to ask the EPA, why did you -- I mean, you obviously two really strong endpoints. Why did you include the other ones as well? Is it one of those things where you need to have as many as possible or?

DR. TALA HENRY: I was actually going to comment on this. I think this was a really -- not the latter part so much, but the earlier part of this conversation was extremely useful for me because I think if anything, it points out our lack of clarity or transparency.

If you go back and you look at Section 3.2, that's where we lay out all the available tox information. Maybe 3.3 needs to be better titled or something, but that was the WOE we used to select the critical effects that we based the risk characterization on. So again, to many of the comments we heard about a better design of how we lay out our data review, so 3.2 is everything available; 3.3, we picked these, which I was glad to hear, everyone agreed. The developmental and the neurotox is what we did a calculation for the risk characterization upon.

So again, it's all in there. I think we could strive to make that a little clearer. And then just around some of this discussion that happened, I'm certain on these issue endpoints, you know, things about the concordance and some of these, many of our guidances -- or strange endpoints that happens, seemingly happen only in specific kinds of rodents or whatever. Many of our guidances, where we do know about these things, they speak to those on how we should handle those.

DR. KENNETH PORTIER: If I learned anything working with NTP is that a rat is not a rat is a not a rat. You know, it depends on the strain and it just adds uncertainty and complexity on top of complexity. We have one more question in this section. We're at 11:30. I think we have time to finish this before lunch so that we can come back after lunch and do the risk characterization discussion. So Question 4-4.

DR. KATHERINE ANITOLE: Question 4.4. Typically, EPA uses the benchmark dose modeling software (BMDS) with a BMR of 10 percent and the models are restricted to multistage models or the broader suite of dichotomous models in BMDS and a single best model is chosen for the POD.

EPA/OPPT used an alternative approach to calculate the cancer POD versus the standard approach of choosing best fit model. Briefly, EPA/OPPT used a model averaging approach considering multiple benchmark dose models to calculate the POD at a benchmark response (BMR) level of 0.1 percent.

Please comment on the assumptions, strengths and weaknesses of the model averaging approach for determining the POD in the cancer assessment.

DR. KENNETH PORTIER: Okay. Dr. Pennell is the lead on this discussion.

DR. MICHAEL PENNELL: Thank you. So starting with the assumptions. So the key assumption here in the model averaging approach is that an appropriate model space has been chosen upon which you do the averaging. So what the EPA did is they chose the three model suite used in the Wheeler and Bailer paper that they cited. So this includes the log-probit model, the Weibull model, and the multi-stage of highest allowable order, according to the number of dose groups. And they did this because it represents a flexible class of models and in their simulation study, Wheeler and Bailer found that using these three models actually often perform better than using a larger class of seven models in terms of bias of the benchmark dose estimate and coverage rate of the one-sided confidence interval from which you get the benchmark dose lowered down.

Okay. Now, one point to make about this choice of this three-model suite, as recommended in the paper by Wheeler and Bailer, one should exclude models that don't match the mechanistic assumptions of the toxin. So when we're talking about a carcinogen, you know, your usual assumption is that you have linearity at the low doses, right.

So this would automatically, you know, exclude the log-probit model from this suite because this model falls in what's known as a tolerance distribution or comes from a tolerance distribution class and models, where there is inherently a lower threshold. Actually, the Weibull model does fall within in this class too, but as long as the alpha parameter is reasonably close to one you get linearity at the low doses.

Okay. Now, moving onto advantages. So

the advantages of model averaging approach is that it is a valid method for addressing model uncertainty. It has been shown, through the simulation studies that I mentioned earlier to outperform a selection of the best fit model, in terms of bias and coverage of one-sided confidence interval for the benchmark dose. And I mean, by "best fit model," the single best model with the lowest IAC or something like that. And another advantage of the approach is that it actually exhibits very good performance, when the true model is not included as long as the model suite that you're using for the averaging is broad enough and contains some flexible models like that three-model suite that they were considering.

So then the weaknesses. So it goes back to the assumption. So the results are sensitive to the model space. So if you include inappropriate models, you can experience bias in your benchmark dose estimates. Even if the models that -- your inappropriate models actually poorly fit the data because sometimes the weight given to them is not small enough to offset the huge difference in the benchmark dose estimate or "risk estimate" is actually more appropriate. The risks estimates you get from that model.

So with this said, the inclusion of the log-probit model does concern me because as you see in the appendix, P3, the benchmark dose estimates from this model actually differ quite a bit from the Weibull and multi-stage models.

Okay. So my summary comments then. So in many cases, model averaging is an effective method for addressing model uncertainty. And as I mentioned earlier, it does have some advantages over more traditional approaches like just choosing the single best fit model.

However, when you need to restrict the model space due to mechanistic assumptions of a toxin, it isn’t particularly useful because it may just be averaging across two different models. And in my opinion, actually, the approach should've been applied to the non-cancer endpoints and actually, very curious as to why it wasn’t because there, you know, pretty much everything is open for a possible dose response there because you don’t really know -- no mechanistic assumptions are usually applied there.

So here's my personal recommendation: it’s to remove the log-probit model from the model suite and only consider models which adequately fit the data and are linear at the low doses. Again, going back to the Weibull model, this is only linear at the lose doses. If you have an alpha parameter, which is close to 1, which it was in each of the situations. So it was 1.2 in one data set, and actually, it hit the boundary value of 1 and the other two cancer data sets, in which case it was equivalent to a one-year multi-stage model.

Also, that one data set where the Weibull model had an alpha different from 1 and it was actually different from the linear multi-stage. This was the only dataset in which you were able to obtain a multi-stage model which had an order higher than linear. The other two datasets you hit the boundary value of zero for the higher order polynomial terms. So in fact, if were to take out the log-probit model from the averaging, then you really only have one dataset in which the model averaging would be feasible.

Now, a couple final comments about implementation, notation/reporting issues. First off, in the appendix, the degree labeling for the multi-stage model are misleading because in only one of the instances, where the coefficient is beyond the linear term, non-zero. All right. So essentially, two of three cases it was really just a linear multi-stage model, it was not a third order multi-stage.

Okay. And getting to the last point, and it just kind of stressed me out because I noticed this last night when I was checking over this again, when parameters hit the boundary values -- so like, for instance, when you get zero for the polynomial terms and the multi-stage model, then really, the model reduces to a simpler form. And the AIC and BIC shouldn't be penalized for those additional terms. So for instance, a particular example in the appendix. So the female lung tumor dataset, only the linear and the beta-1 coefficient could be estimated.

So there, the model should only be penalized for two terms. Like, the background incidents and the linear terms, but instead of 4, which, you know, third order model it would have 4.

So for this dataset, what happens though is the penalties are appropriate. They are, in fact, appropriate in the table that appears to be based on the BMDS results. So that's table P-62 for this particular dataset. Okay. So there, it only penalized for two parameters. But if you go to the table labeled "Summary of Model Averaging Fit Statistics," it applies the four-parameter penalty. And unfortunately, I think you probably used those AICs and BICs for the weights for the modeling averaging. So that would need to be corrected.

Okay. Those are all my comments.

DR. KENNETH PORTIER: Thank you. Dr. Georgopoulos?

DR. PANOS GEORGOPOULOS: Okay. After hearing Dr. Pennell's comments, this is why I defer to my biostatistician when I have a question like this.

Again, the use of model averaging procedure is something that, you know, takes place in many fields when you want to characterize uncertainty and include model uncertainty in the overall calculation. But as it was mentioned before, the criterion there is for the models to be mechanistic and reflect the same measures because if you go over models that have completely different assumptions, you are basically averaging apples and oranges together.

So I had not noticed the issue with log-probit model, but definitely, you have to have models that represent or reflect the same kind of underlying process. The issue here is that the justification and how it is presented if this regulatory assessment, and since it deviates usual EPA practice because the justification in the document is based on the standard because extrapolation to a .1 response level is sensitive to model selection and model averaging technique was used.

So does it appear to do this whenever you have a BMR of .1 percent? If you are using 1 or 5 percent BMR, you will use -- you will not use the model evidence approach. That's not what -- it has to be more clear. And I think there was something mentioned yesterday that NIOS used the model.

So I would feel -- I would personally accept justification based on the harmonization of procedure between agencies. I know the work harmonization is far more popular in Europe where they have many different agencies and they try to reconcile things so you see it in every report on this. And it makes sense to me. But the bottom line is I second the comments of Dr. Pennell, but I also think the justification of the selection and what it means should be there.

One thing that I also wanted to point

out since they were mentioning of it, and it happens when I see some of these studies. When I see tables with 12 -- with parameters listed with 12 digits, like a parameter estimate being .0006136953057, and it was said in a comment somewhere that the parameters appear to be equal, but they are not really because in digits that were not shown. I don't know. The data is so sparse, the whole procedure is so approximate that I would have some standards in, you know, how many, how you show the parameters, show the criteria for the parameters to be equivalent to practically the same.

I just don't feel comfortable with seeing values of anything with 12 digits after the decimal point because it creates a completely false sense of accuracy in the calculations. That's at least my feeling. But I was covered by the response before my comments.

DR. KENNETH PORTIER: And what you're referring to is the output from the program they used and they just copied it and put it in there and it's a valid point. My comments I gave to Dr. Pennell yesterday afternoon. So everything I wrote was incorporated in what he presented. The only kind of caveat I have on the weaknesses, you have to be very careful with this methodology because it looks robust, but if the data provides a very flat response surface, you can get estimates that go way out that have a lot of uncertainty. And if you're not paying attention, which I think you were here, you can get some really unreasonable estimates. Just because it is computationally intensive, modern method, doesn't mean it can give you junk if you're not paying attention.

Any additional comments on this? Again, this is why you have biostatisticians. They pay attention to the details. Dr. Pennell?

DR. MICHAEL PENNELL: Actually, you had some additional that I didn't actually hit on if you want to mention them.

DR. KENNETH PORTIER: Well, let me look through them here. Okay. You know, one of the things I did mention, I think it's described as a weighted average. And it's a lot more complicated than that. So just watching your language, you know, because this is -- it's really a complicated computational intensive resampling methodology, somewhat like a bootstrap, but not exactly a bootstrap.

So I don't want you to kind of give them the idea that I'm fitting five models and then

I'm just averaging across the five responses. One of the other benefits of the methodology that I didn't hear Dr. Pennell mention is that it does improve the stability of the estimates. So that small changes in the data don't result in huge changes in the estimates that come out of it. So you have some benefit there that you're not as tied to that dataset, you know. That everything comes from one or two datasets that are incorporated in there.

And then the other point in mentioned is that the results aren't that different from the standard DMDL fits that you get using the standard package and picking the best fit model. So you're not, while it's computationally intensive and all this other stuff, EPA is not deviating that much from their standard methodology when they go to model averaging. It might sound complicated, but they're not that far.

I will point out that a recent other IRIS panel I was on, it was interesting. There were four statisticians on that panel. It was a big panel. And yet when we looked at the data, we recommended that they model average because they had shown fits to a bunch of models and then picked the smallest one and we're sitting there thinking, yeah, but a better estimate would've been a composite through some kind of model averaging methodology. And I was kind of glad to see that you were doing this because I think that's going to be more the standard methodology moving forward, rather than what's been done in the past.

I think that's everything that I had. Anybody else?

Comments. Oh, Dr. Marty. I'm sorry.

DR. MELANIE MARTY: Just a really quick comment. So I am definitely not a biostatistician, so I'm not going to even walk into what you guys just said, other than to say I would've appreciated seeing the results of the standard BMDS model, 10 percent response rate, linear extrapolation so that you wouldn't have had a coronary when I looked at the results. Because if it's really close, then good, let's see that.

DR. KENNETH PORTIER: That brings up another disadvantage of the methodology. It's new and it's not that easy to describe. You have to go back to the stat paper and read the stat paper and understand it. So there's going to -- there's a learning curve occurring, but I think it's technologically an improvement on the standard methodology. But I don't think you would've seen a biologically significant difference in the estimates, but it's a good point. In an interim, it might be good to show the standard BMDL result and then show the model averaging result. I don't think you're going to see much difference.

Dr. Pennell?

DR. MICHAEL PENNELL: I have a couple of additional comments. So if you choose to stick with the current methodology and, one thing to point out in the case where the Weibull and the multi-stage model are equivalent because you hit the boundary value for the alpha parameter for the Weibull, don't include those two models in the averaging because then you're overweighting, essentially, the same model and that's problematic and that's actually pointed out in the Wheeler and Bailer paper.

And another thing, this is related to a footnote that Dr. Georgopoulos alluded to, in two of the three datasets, the Weibull and multi-stage models were exactly equivalent. It wasn't an issue of reporting of significant digits there. They were equivalent.

DR. KENNETH PORTIER: Comments from EPA?

MR. CHRIS BRINKERHOFF: This is Chris Brinkerhoff from EPA. One comment I think is important to be clear is that at the stage of dose response -- so we do hazard of the end dose response. The stage of dose response, we have not then yet presumed linearity for modeling the data. We're using metric dose modeling.

The linearity part of the discussion applies to the extrapolation later from that point of departure. And I point that out because that seemed to be a key point in the analysis and I wanted to make sure that that was not misunderstood or might not change the perspective.

Was that clear?

DR. KENNETH PORTIER: Dr. Pennell?

DR. MICHAEL PENNELL: No, I understand that's the standard approach is to do the low dose linear extrapolation, but again, mechanistically, assuming when you have model, like a probit model or a log probit which has an S shape, right, inherently, that is contrary to what's the common practice for low dose extrapolation.

So shouldn't actually fitting a model that's consistent with what you're actually when you're doing your extrapolation that is more consistent with sort of the usual assumptions of the dose response in that range?

It seems to me like it is.

DR. CHRIS BRINKERHOFF: The challenge there is that we're looking at the animal data at this point, which is not in our lose dose range. When we're applying to humans, then we're often extrapolating to low doses. So we're not presuming it to be linear. Actually, in this case, it turned out to be quite linear, looking at the data.

DR. KENNETH PORTIER: So what's happening is they're not letting what's happening the in extreme low dose drive the functional form of the response model in the higher dose levels where the actual data resides. So you're allowing that flexibility. But I don't think that's going to change the result all that much from what Dr. Pennell is saying. He's just eliminating one model because it maybe has too much extreme low dose curvature, is what you're saying, right?

In the model, you're excluding the

multi -- which one was it, the multi-stage?

DR. MICHAEL PENNELL: The log probit.

DR. KENNETH PORTIER: Log probit, yeah.

DR. MICHAEL PENNELL: Again, it's more of the sort of the philosophy behind the models. Like, for instance, of you go to like, the Piegorsch and Bailer text book, "Statistics and Toxicology Environmental Biology," they describe those models like the probit and logistic models. Are those models where you're assuming that, you know, the organisms inherently have some sort of threshold tolerance for a chemical that must be exceeded in order to observe an adverse response.

DR. KENNETH PORTIER: And I think in those models there's parameterization for that, right. You're fitting that model with a threshold parameterization? Is that one of the parameters in the model that --

DR. MICHAEL PENNELL: No. So if you think about it -- so it falls from this sort of latent variable construction where you have this sort of -- a latent variable is the organisms inherent tolerance, right. And so for like, the probit model, so the tolerance distribution is characterized by a normal distribution, right?

And so once that tolerance exceeds a threshold which is, you know, some people call it zero. Some people call it like some sort of function of dose, that's when you get like a 1 for a binary outcome, right, as opposed to a zero.

So you have like this latent, sort of continuous variable describing tolerance underlying this binary variable.

DR. KENNETH PORTIER: So what we're going to do here, Dr. Pennell will talk about this and we'll make sure that the write-up is kind of clear because I do understand where EPA is coming at with this modeling at that level. We'll get the language right for you.

Any additional comments?

(No response.)

I see 11:56. I think we'll take our normal lunchbreak and we'll be back at 1:00 for the last section. For those of you on the webcast, we're going to shut the webcast down and bring it back up again at 1:00. That will avoid it shutting itself down around 2:00.

Thank you.

(Whereupon, at 11:56 a.m., a luncheon recess was taken.

AFTERNOON SESSION

(1:05 p.m.)

DR. KENNETH PORTIER: Okay. I think we're ready to get started here. At this point, I'll look to the panel to see if there were any additional comments from this morning's discussion that you want to have on the record. Dr. Pennell?

DR. MICHAEL PENNELL: Yes. I'd like to make one more point I thought about over lunch about the model averaging and the use of the log-probit model.

If you look at the results from the BMDS output for the log-probit model, that model appears to be very unstable for all the data sets. So for two of the three cancer data sets, you're unable to estimate a benchmark dose lower bound. The one data set where you are, the ratio of the BMD to BMDL is of the order of ten to the tenth.

So now in the model averaging approach, you're not using those BMDLs. You're not averaging those specifically. You're averaging the risk estimates from the models, but that should be some indication that this probably isn't a good model for these data sets.

DR. KENNETH PORTIER: Anyone else? Any additional comments?

Yes, Dr. Gilbert?

DR. KATHLEEN GILBERT: I don't know anything about modeling, but it sounds like you're making really good points. And I was just curious to hear what the EPA had to say in regard to those.

DR. KATHERINE ANITOLE: Yeah, our modeler's currently not in the room. However, and honestly, I don't know anything about modeling. Half of what you said, I was like woo. Toxicologist.

But I did want to reiterate and several people acknowledged we did this hand-in-glove, actually, with NIOSH. In fact, they took the lead on this. So certainly we'll get with them as well based on your feedback.

But Chris, can you -- Dr. Pennell pointed out he looked at the data over lunch and with the log-probit model all of the data sets were unstable, which I can't explain what that means.

So and then Dr. Gilbert just wanted to inquire as to if you had some insights or something to add to clarify why we went ahead with the various inclusions or not. And I just reiterated that we did this very much together with NIOSH.

DR. KENNETH PORTIER: Yes. So the log probit only was estimated for one of the three end points and that last one, as Dr. Pennell pointed out, the difference between the BMD and the lower bound was ten to the six.

DR. MICHAEL PENNELL: Ten to the tenth.

DR. KENNETH PORTIER: Ten to the tenth.

DR. MICHAEL PENNELL: Rather.

DR. KENNETH PORTIER: I'm sorry. So it's really an indication that that model was not well fit to the data. And yet, it's part of the model averaging, so its probabilities kind of get averaged in. And we kind of both agree that that kind of fits an indication that it's, you know, not a stable estimate that the estimates to fit the model are probably very uncertain, not just kind of uncertain.

And, you know, most of us would probably exclude that and refit without and we wonder what your thinking is on that kind of a scenario, and realizing that, now like you said, you did this in conjunction with NIOSH, so you probably have to go back to those people and argue through some of that discussion as well.

DR. CHRIS BRINKERHOFF: This is Chris with the EPA. I don't have much to add other than we really appreciate that looking into details on what was done there.

DR. KENNETH PORTIER: Dr. Pennell?

DR. MICHAEL PENNELL: Just one more question about that. So the model averaging, was that done using a software provided by NIOSH? And if so, you probably should alert them to the miscalculations in the AIC as I mentioned earlier and they need to make sure that's updated in the software.

DR. CHRIS BRINKERHOFF: So this is, again, Chris. Let me be clear on what you're asking. The calculations for the model averaging were done by a piece of software developed by -- in the Wheeler and Bailer paper. That is on the EPA website for download.

Are you saying that's where there is an issue?

DR. MICHAEL PENNELL: Yes. So it didn't account for the boundary issue when parameters were hitting their boundary, so there actually weren't really parameters anymore, unknown parameters that are constant. So those shouldn't be included in the penalty. And actually, Dr. Portier, I don't have the reference, I can find it, said that in one of their papers they mentioned that if that happens, you shouldn't be penalizing for those parameters.

DR. KENNETH PORTIER: So I think what we've pointed out was there is a consistency between what's on the printout from that output and what's in one of your tables. So I think we said the printout had it right and the table had it wrong or the other way around. I forget which one it is but there's an inconsistency in the report between one and the other, right?

So somehow taking the output and transferring it into the report, the AIC got miscalculated.

DR. MICHAEL PENNELL: I'm pointing it out because probably it's a greater issue. It's not just the report. It's a software issue probably that needs to be fixed so this mistake isn't made in the future.

DR. CHRIS BRINKERHOFF: It'll be in our report.

DR. KENNETH PORTIER: At this point, I think we're going to move on to the risk characterization questions. We have four additional questions in this area and we'll start with 5-1.

DR. KATHERINE ANITOLE: Question 5-1, EPA/OPPT interpreted the end point of decreases in live litter size following exposure to 1-BP before and during gestation as a surrogate for frank developmental effects relevant to humans per EPA's guidelines for developmental toxicity risk assessment.

EPA/OPPT used this endpoint to calculate a point of departure, to assess non-cancer risks associated with acute inhalation exposures to 1-BP. Please comment on the assumptions, strengths and weaknesses of the MOE approaches used to estimate the non-cancer risks to workers and occupational non-users following acute inhalation exposures to 1-BP including the MOEs presented in the document.

Please comment on the assumption, strengths and weaknesses of the MOE approaches used to estimate risks to consumers following acute inhalation exposures, including non-users, for example, bystanders who may be children or women of childbearing age.

Specifically, please comment on the decision to limit the analysis to acute exposures without residual concerns between events and what data could critically inform modifying this approach for consumers.

Please comment on the selection of uncertainty values and deriving the benchmark MOE for acute inhalation exposures.

DR. KENNETH PORTIER: So, Dr. Marty, it looks like there's four questions here, not one.

DR. MELANIE MARTY: Yes, it was a little hard to answer those. But and actually, I have to say a lot of this we've already discussed in some, way, shape or form, so I'll try to be as brief as possible.

Overall, using the point of departure for developmental toxicity is appropriate for the acute exposure scenarios, both the occupational and the consumer residential. And, in fact, it's standard risk assessment practice.

And then comparing the estimated exposures, the acute exposures to the developmental point of departure to look at what is margin of exposure is also appropriate and is a standard risk assessment procedure.

Many of us are more familiar with generating reference concentrations and really the approaches are parallel. In the one case, the uncertainty factor is applied directly to a point of departure from an animal study or a human study to develop a reference concentration, which we believe is save exposure level. In the other case, this case, the MOE case, we're using those uncertainty factors to benchmark what a margin of exposure should be in order to protect the public.

The assumptions are the same in both approaches, namely that the animal evidence is relevant to people and we had a discussion about that already, and that the uncertainty factors account for toxicokinetic and toxicodynamic differences among a species and between people and the other database deficiencies.

So the EPA as a measure chose to use a developmental tox, and I think that's completely appropriate. There were actually multiple endpoints related to developmental toxicity and reproductive toxicity with points of departure pretty close to the one that was for decreased live litter size, including decreased brain weight, 50 ppm, the decreased seminal vesicle weight, which was a repro endpoint, about 38 ppm. So these are all consistent.

Let's see. I think they even note that for the live litter size, it's really a reflection of the constellation of both male and female repro effects, and I might add also developmental effects direct to the fetus that contribute to this and that they all occur within a short window of exposure between ovulation and implantation.

And going back to the whole point of using developmental tox, nobody really ever knows when the windows of susceptibility are because of the design of the studies. It would be like really hard to figure that out and take a lot of animals.

So, you know, you have to consider that it could be happening in a woman who's pregnant at the time of exposure. And there's really no indication that reproductive and developmental toxicity seen in the animals from 1-BP exposure would not be relevant to humans, so it's appropriate.

I did note earlier that one of the BMDS analyses for F1 male pups in the WIL study had a lower BMDL, so EPA should explain why they didn't choose that.

Now, in terms of margin of -- I mean, excuse me, uncertainty factors, which actually are the margin of exposure in the MOE approach, so EPA used the typical defaults of 10 for interspecies extrapolation and 10 for intraspecies variability to determine a margin, a benchmark margin of exposure of 100.

And honestly, you could actually argue for a larger one, particularly for intraspecies variability. Toxicokinetic studies indicate metabolism is relatively complicated and involves both oxidation by the CYP P450 as well as flavin containing monooxygenases possibly in conjugation with glutathione. There's genetic polymorphisms in the GST enzymes, which can strongly influence response to toxicants.

Recently Kelly PA looked at benzene and we ended up with an intraspecies uncertainty factor of 60 based on gene-gene interactions for toxicogenomics, both the CYP enzymes as well as the detoxifying enzymes. So, you know, it's really a lot more complicated than people think.

The variation in the CYP enzymes exist.

They exist by age. And these are particularly important for infants and toddlers where there is the larger differences relative to adults. So in California we now use an intraspecies uncertainty factor of 30 as the default to help account for the variability, which is fairly wide amongst people in terms of genetics, age, gender, disease status and so forth.

Remember that these studies are done in genetically homogenous rodents and then we take those results and we extrapolate them to a very broad genetically heterogeneous human population, and not just genetics but epigenetics, lifestyle, other exposures, et cetera. So a benchmark MOE up to 300 is justifiable in my opinion.

So for the consumer exposure, the same comments apply. EPA considered only acute exposure and I, you know, made the comment earlier that do-it-yourselfers might actually use this stuff for whatever project they're doing on multiple uses per day, multiple days per week. And so, you know, maybe you might end up somewhere between acute and chronic, but you could still use a developmental endpoint as your point of departure, even if you had an exposure scenario that was up to a couple of weeks.

Okay. And then I also mentioned earlier the bystander, that the kid might actually be in the same room as the parent using the material, so that's something I think that needs a little bit more thinking.

Okay. That's -- who's next?

DR. KENNETH PORTIER: Okay. Dr. Gilbert?

DR. KATHLEEN GILBERT: I thought that was a really thorough evaluation. I really don't have much substantive to add to that. I think the choice of the acute for the consumer is obviously a logical choice and I just want to reiterate that if you look at the Etsy website, it certainly gives you the idea that people are using some of these products more than once a day. So I don't know if there's any way to factor that into the calculations, but I do think that's a reasonable assumption.

But other than that, I really don't have anything.

DR. KENNETH PORTIER: Dr. Meliker?

DR. JAYMIE MELIKER: All right. I have a little bit.

So as I mentioned earlier, I thought it made sense to use litter size, but I thought it would be nice to also show something else. I wasn't sure in going back through the table from earlier whether or not you had acute exposure like HEC estimates for other endpoints, be they neurologic or reproductive, like fertility. I just couldn't tell. You know, in that earlier table it specifically says HEC acute for these pups but it doesn't say any HEC acutes for anything else, so maybe that's why you chose this. I don't know. But I thought it might be nice to have another outcome with it just to give it a little more strength to see, you know, give you more confidence.

The description of the MOE approach, you know, it's new to me, so I went back and forth when I was looking at it. I thought I followed it now but it definitely was confusing and I think it would be nice to have an example that you carry through and to have all the parameters that are required in that table together because right now, you know, you're pulling parameters from other places when you're calculating those risks.

And the next part was acute exposures without residual concerns between events. I was okay with all these decisions. I mean, there was residual concerns between events. There are relevant exposure mixtures. I mean, there's definitely other things that you could do. I just, I didn't have ideas on how you could model them or how you could include them, so I was okay. And I was comfortable with the uncertainty factors that you selected.

DR. KENNETH PORTIER: Thank you. Anyone want to add anything to that?

DR. JAYMIE MELIKER: I didn't hear any conversation on weaknesses. You know, what are the -- Dr. Marty, what are the weaknesses here?

DR. MELANIE MARTY: Well, as a risk assessor, you know, we tend to understand that there's a lot of uncertainty in any risk assessment. And basically for the reasons I gave why you really should consider uncertainty factors even larger than the ones that are used for intraspecies. So, you know, that goes both directions. There's, you know, you never have the data that you want to have, particularly for an industrial chemical where there are no requirements to be tested.

So, you know, the weaknesses are really all the same for almost all risk assessments where you have limited data on the toxicology side, and as Dr. Kissel pointed out, limited data on the exposure side. So, you know, there always is uncertainty. And I think I, you know, just kind of know that, so I never ever mention it.

So I guess I can say all the uncertainties that you heard about on the exposure piece are wrapped into the risk characterization piece. Ditto, all the uncertainties you heard on the toxicology side are also wrapped into that hazard characterization.

DR. KENNETH PORTIER: Okay. EPA, I don't see any additional comments on this one. I think they kind of buy your story. Okay. Let's go ahead and move on to 5-2.

DR. KATHERINE ANITOLE: 5-2, please comment on the assumptions, strengths and weaknesses of the MOE approaches used to estimate the non-cancer risks to workers and occupational non-users following chronic inhalation exposures to 1-BP including the MOEs presented in the document.

Please comment on the selection of uncertainty factor values and deriving the benchmark MOE for chronic inhalation exposures.

DR. KENNETH PORTIER: Dr. Marty?

DR. MELANIE MARTY: So this is going to sound really similar to the last response. But, you know, EPA appropriately, in my view, chose the lowest points of departure in associated HECs for each of the endpoints from among the data sets, of minimal dose response with the possible exception of the one I mentioned earlier. EPA could have considered hematological and immune also. I don't know what the BMDS modeling results would have been for those and whether those PODs would have been lower. I don't think so, though, just glancing at the data.

And then, you know, again, you could argue that the intraspecies uncertainty factors could actually be larger than 10. I was happy to see that the MOEs were calculated for high-end exposures as well as average exposures because, essentially, you really want to protect people from the compound. And if you basically of you use a median and you're like throwing half the people overboard.

And then also given that neurotox has been observed in the occupational setting, this is a really important endpoint to consider for the chronic exposure. I think that was totally appropriate.

Again, I mentioned earlier that the Ichihara 2004 found -- they measured eight-hour TWA exposures in individual workers and found a range of sub ppm to about 49 ppm with a geometric mean around three, and so it might be useful to look at those and compare them to the human equivalent concentrations that were utilized.

So I think the MOEs presented in the documented, they presented them based both on monitoring and modeling and they're mostly pretty small compared to the benchmark MOEs. So this really does indicate that there is a significant risk for non-cancer health effects for almost all of the endpoints in the exposure scenarios with a few exceptions. And I think that's a very important finding and I agree with EPA on their conclusion.

DR. KENNETH PORTIER: Dr. Blando?

DR. JAMES BLANDO: So I'm just going to kind of read from what I've written, but I have some things to add.

So the uncertainty factors, at least my read on the document, seem to follow a lot of the previous assessment that have been done and seem to me, anyway, to follow the developmental assessment guidelines presented by the U.S. EPA and the Science Policy Council Handbook on risk characterization.

However, I did have some additional questions about the uncertainty factors that were used. In particular, I noted that there were two documents, which I happened to find online from EPA, which I have cited here in my document, about uncertainty factors and had discussion about their appropriate selection and application. Let's see, where -- I'm losing track here.

As a peer review, some questions remained about the selection of only a total uncertainty factor of 100 to form the basis of the MOE for the developmental and reproductive endpoints selected.

My question is regarding the potential use of additional uncertainty factor of 10 for the impacts that may affect offspring or pregnancy, such as, as suggested by EPA's comments and documents on the pesticide program's consideration of additional uncertainty factor and tolerance assessment in the Food Quality Protection Act, which I've cited here, which suggest that when merited, an additional uncertainty factor can be considered insensitive subpopulations.

Additional consideration may be merited in this particular case because of reproductive and development endpoints and because data exists beyond just animal studies but in human populations of potential similar reproductive effects.

And just to clarify, I presented some of this information in the 2009 cited presentation that I gave at NJDEP and also the MMWR written by Jeanmarie Perrone who was our clinical toxicologist who saw the first vapor degreasing case at U-Penn, back in 2008. I provide these citations regarding a clinical case report of a worker receiving medical treatment.

So rather than reading this, I'm just going to describe it. So in these particular cases in the MMWR that we cited, we didn't realize at the time in 2008 that this was really interesting and really important. And with the page per word limits in MMWR, we ended up not including it in that particular paper. But we since have presented these results.

One of the cases in that report was somebody who was receiving a workup from a urologist and we happen to actually have data on sperm counts and motility before he was poisoned and after he was poisoned. And if you actually look at the time trend of this reproductive data, you will find that his sperm counts went from 45 million per mL and 65 percent motility, immediately after the poisoning event went down to 3 million per mL and 15 percent motility, which our urologist was telling us was a little bit low to begin with but really, really low after the poisoning case.

And I can -- I have to check with our ethics officer about the HIPAA and IRB issues about releasing this data, but I can certainly provide that to you, provided our ethics person tells me I can do that.

So in this particular case, we found it interesting sometime later, because after looking at the animal studies that were starting to come out, we recognized that reproductive endpoints seemed to be of interest and we had neglected to include that in the MMW report.

So I find that kind of interesting, animal studies, human studies. Albeit, it’s anecdotal because it’s one clinical case report, true. But found that to be interesting.

If you really dig into the Ichihara paper from 2005, which is a summary of both 2-BP and 1-BP, you will note that the reproductive effects of 2-Bromopropane are pretty well known, which is a similar isomer to what we're talking about here. And Ichihara in particular observed azoospermia, oligospermia and amenorrhea in factor workers in his study, so we're using 2-bromopropane.

So here we have animal studies suggesting reproductive effects. We have an anecdotal clinical case report evaluated by our clinical toxicologist and urologist showing this change in this individual's sperm counts over time. We have Ichihara showing pretty convincingly, in my opinion, that 2-bromopropane is related to these reproductive effects.

But it's also interesting to note that when Ichihara summarizes some of the NIOSH health hazard evaluations, and in particular the health hazard evaluations conducted by Rae in 2002, he noted and speculated that there were some folks using 1-bromopropane in the spray adhesive industry that also reported and documented cases of infertility and reproductive problems for folks working those spray adhesive applications who were using 1-Bromopropane.

So with all of this taken together as a peer reviewer, you know, I have to be honest. I sat back and wondered about the uncertainty factors. I read your EPA documents from the pesticide regulation program on the Food Quality Protection Act suggesting that maybe for sensitive subpopulation it might be worth it to consider additional uncertainty factors. And I thought I would pose that today as something potentially to consider just because of the combination of animal and human concordance or potential concordance.

DR. KENNETH PORTIER: Thank you. Dr. Hossain?

DR. MUHAMMAD HOSSAIN: My comments are incorporated in previous comments, so based on the dose response assessment, EPA appropriately chose the lowest PODs for the non-cancer endpoints. Beside the non-cancer endpoints, EPA should also strongly consider neurological endpoints as worker exposed to 1-BP experienced with severe neuropathy, muscular weakness, headache, gait disturbances and cognitive deficits. Furthermore, residual neurological symptoms such as disruption of cognitive function has been reported in individual who are highly exposed to BP-1.

However, the mechanism by which this occurs is not clear. Another point, since ocular symptom has been observed, following acute exposure to 1-BP, it should be considered for non-cancer endpoint if the symptoms persist. And just one uncertainty factor is that variability in the duration of (inaudible) and the number of exposure events for human -- number of humans for human exposure.

DR. KENNETH PORTIER: Thank you. Dr. Thayer?

DR. KRISTINA THAYER: Hi. I really don't have much to add either. I think I would just also sort of echo maybe consideration of something more along the lines of a 300 uncertainty factor.

DR. KENNETH PORTIER: Anyone else on the panel? Dr. Marty, you want to add?

DR. MELANIE MARTY: Yeah. I was just going to remind people that that -- for the chronic exposure, because it was based on a three-week study, they did use an additional uncertainty factor of 10 to extrapolate from subchronic exposure scenario in the animals to chronic exposure in people. Just keep that in mind.

DR. KENNETH PORTIER: Dr. Blando?

DR. JAMES BLANDO: I've got to find my card. Just one other point I was going to make, and this was kind of already mentioned previously.

There was some discussion yesterday -- I think it was yesterday about possibly instead of using an eight-hour time weighted average to using something more along the lines of a twelve-hour, and I just wanted to make the note that if you did do that -- and I know I said this yesterday that because it's not a compliance activity that you'd be engaged in, I think the extended shift guidance from OSHA would not apply here and you might want to consider using a crude, fully integrated time weighted average, rather than an eight-hour time weighted average, if you made the decision to change the scenario to a 12-hour extended shift from two eight-hour shifts in the computation of your MOE.

So I'll just reiterate that if you made you that decision you might want to consider that.

DR. KENNETH PORTIER: Dr. Meliker?

DR. JAYMIE MELIKER: So I know I'm beating the horse on the human data and trying to use the human data. I'm just trying to understand.

So you have an HEC from the animal

model of 25 ppm for your neuro endpoint and then you have an uncertainty factor of 1000 on top of that, right? So you're basically saying you're going to see effects at 0.025 ppm, right? No? I've got someone yes, someone no.

DR. KENNETH PORTIER: I think what they're saying, in certain sensitive subpopulations that's feasible. I mean, that's what the uncertainty factor is all about, right?

DR. JAYMIE MELIKER: Right.

DR. KENNETH PORTIER: Dr. Henry? Oh, Dr. Marty.

DR. MELANIE MARTY: Can I chime in here? So what you're trying to get at is to make sure you're below a level that's going to produce an effect. So you're not saying that 1000 full below that is going to produce an effect. You're saying 1000 full below that is not going to produce an effect, hence the -- you know, it's a nuance difference, but it's important.

DR. JAYMIE MELIKER: Right. But you're saying it needs to be even lower to produce an effect, right? So you're -- right.

DR. KENNETH PORTIER: I think they're arguing for another 10-fold reduction for other reasons, right? I mean, or threefold reduction.

DR. MELANIE MARTY: I'm arguing that EPA should look at that carefully. And there's actually another reason to look at not just a general variability in human response, but it's a development -- it's a neurological toxin. And to my knowledge, there has not been a developmental neurotox, functional observational barrier, for example, assessment on this chemical. So we actually don't have very much information on potential developmental neurotoxicity.

DR. KENNETH PORTIER: Dr. Gilbert.

DR. KATHLEEN GILBERT: Well, the WIL study did look at F1 and F2 and they looked at neuro. So and that was following development exposure. Is that not sufficient?

DR. MELANIE MARTY: It's not sufficient.

DR. KENNETH PORTIER: Dr. Meliker, did you finish with your --

DR. JAYMIE MELIKER: Well, I --

DR. KENNETH PORTIER: I see query on your face.

DR. JAYMIE MELIKER: It seems very low to me. It seems like, you know, we're saying that there is potentially risk and very like sub-1 ppm levels, right? And I mean, I'm just looking through the human data and, you know, it's -- there's nothing that low, even close, so.

DR. KENNETH PORTIER: But I think the argument in the human data is that's in a healthy population and now we're starting to extrapolate to pregnant women, children from animal data. I mean, that's -- yeah, but those of us who have seen these things see that quite a bit, that, oh yeah, 100-fold reduction is not unusual.

I have kind of a related question. I'm not quite sure in my mind how this works. But it still comes up in my mind that some of this data, especially in the occupational setting, was captured in extreme high situations, those two NIOSH.

So how does that work with the uncertainty factor in that some of the human data was seen in -- what would you say -- unusual scenarios? Does that factor into this at all?

I'm looking at Dr. Marty here.

DR. MELANIE MARTY: Yeah. Sorry. I'm

not sure I'm exactly interpreting what you're asking correctly. But when I look at it, especially the Ichihara paper, so and I mentioned the concentration range to which people were exposed where they were finding effects, it's quite a broad range.

And as I -- I've got to remember this paper correctly. I think it was more of a cross-sectional design across the industry, so it makes it really hard to say anything about causality, but we already know from other studies that it's a neurotoxicant.

So, you know, the geometric mean in that case was about 3 ppm and the range went up to about 50 ppm of exposures across the facilities that Ichihara looked at. So and that was an effect level, so I think that that argues actually to be pretty careful about the uncertainty factors and kind of liberal with them.

DR. KENNETH PORTIER: Thank you. That did answer my question. I had forgotten that.

Dr. Blando?

DR. JAMES BLANDO: I'm just going to add in relation to the human and animal data, at least the way I tend to think of it, just my opinion, is that I think the animal data tells us something about the potential. And, you know, the animal data's obviously much more controlled than anything you would have in an actual human setting.

You also may have, depending on the animal study, lifetime exposures. A lot of human settings -- and our individual cases, I wasn't going to wait until the guy was 70 years old to then follow up and say, hey, what happened over your lifetime? So you have those issues.

For example, it was reported to me for various reasons that one of our cases has since developed a tumor. I don't know what kind of tumor it was but that back in 2008, that was before he had developed anything. So, you know, you can look at that individual anecdotal case and say, well, you know, he doesn't have cancer, so it can't cause cancer, so the animal data doesn't mean anything, and I would argue that, no, that's not the case because just the nature of collecting this data in human populations.

Honestly, our individual case, he would have never known that his sperm counts weren't low if he wasn't trying to have a child at the time. If he wasn't trying to have a child at the time, he probably would have never sought medical care to realize that there were issues. So I think those real-life complications tend to really play here when you're looking at the human data in individual patients and that kind of thing, so I just wanted to emphasize that.

DR. KENNETH PORTIER: Okay. Any additional comments? EPA, any clarifying questions?

DR. MELANIE MARTY: I think you guys handled it well.

DR. KENNETH PORTIER: I see support on this one, too. So let's go on to Question 5-3.

DR. KATHERINE ANITOLE: 5-3: please comment on the assumptions, strengths and weaknesses of the approach used to estimate added lifetime cancer risks to workers which EPA/OPPT derived from an inhalation unit risk based on lung tumors in female mice for estimating incremental or added individual lifetime cancer risk.

DR. KENNETH PORTIER: Dr. Thayer?

DR. KRISTINA THAYER: I feel like my comments are going to be really short because we have covered so many aspects of this without sort of the dimension of the uncertainty factors that we had to cover in the previous question.

So we've talked about sort of assumptions, strength and weaknesses of the exposure assessment, the dose modeling, sort of the lung tumors. And so I would -- I agree with using the most sensitive tumor response and lung tumor response in the female mice as the basis of this.

I would also -- I don't think we need to sort of recapitulate all the discussion about the assumptions used in the models. That's already been on record. But I would just encourage EPA to consider those and then update appropriately.

I think the only other thing is maybe, you know, this is sort of looking at lifetime cancer risk and so not -- this issue about sort of co-residence near dry cleaning application, some of those general population exposures that might be more than acute, maybe there's not much that can be done, but I would sort of -- try to sort of see if whether that belongs in sort of non-acute exposure scenarios and whether that could be worked in. Or if not because you don't have the data to sort of at least explicitly acknowledge why not.

DR. KENNETH PORTIER: Dr. Blando?

DR. JAMES BLANDO: So the two comments that I have I think have really essentially been answered and I really have to defer to our toxicology and statistical modeling folks for this. But since I'm listed as I have to say something, so I'll say something.

So as a non-toxicologist and non-statistician, this is the following thought I have, and I think it was just -- it's already been mentioned and addressed and I clearly have to defer to others for this. But I just happened to notice that the three tumor types that were identified in this risk assessment with lung adenoma and carcinoma occurring at the lowest model human equivalent BMCL, if I have that right, however this specific observation was for females only in one animal species.

Similarly, the other two tumors types were also each among one sex and within one animal species. And I'm sure that when you're running these toxicity studies, you know, the most conclusive thing is to have multiple species and multiple genders and have it in everybody. And I presume that that probably rarely happens.

But the question had, which I had, which hi think has already been answered, is the fact that overall the aggregate of these three tumor types was among mice and rats and among males and females is definitely a strength in the observation, which I felt very convinced by that. But the fact that no individual tumor occurred in more than one species, in more than one gender, I wondered if that would imply that perhaps the BMCL should be averaged over the tumor types summarized in Table 3-3, page 112, rather than being based only on the lung adenomas and carcinomas.

So, again, I clearly -- I don't have the expertise to really answer that. It's just the question I had as the non-toxicologist, non-statistical person on the committee. And I think it's been answered, but I'll just throw that out there for consideration.

DR. KENNETH PORTIER: Thank you. And I'm sure Dr. Marty's going to address that.

DR. MELANIE MARTY: Yeah. I mean, the standard practice in risk assessment is to use the most sensitive site in the most sensitive gender in the most sensitive species for estimating cancer risk to humans. And, again, it's because we don't know where we are on the continuum of sensitivity, so that is -- that's the reason why they didn't average the BMCLs to approach that.

And actually, you know, those are -- it's not uncommon to see gender-specific tumors at all in the rodent studies. At least you had them in both species, rats and mice, so and you actually had three tumor types that were statistically significant and then you had additional tumor types that approached statistical significance between exposed and control in the NTP study, so that's other indications that it's, you know, the stuff is carcinogenic.

In terms of adding to what has already been said, I don't think I have very much to add other than it is a, you know, that they appropriately did not try to quantitate risk from acute exposures, but all the unit risk factors are based on long-term animal models, and it's really hard to wrap your head around when you have an acute exposure to a carcinogen how to estimate cancer risk, so that was done appropriately.

And then I did have one sort of picky thing, but Table 4-3 indicates that the cancer risk --

let's see -- it's described as possible cancer effects in the lung from chronic exposure. Could you drop in the lung from that? Just say possible cancer risk? Again, that goes back to the side concordance issue.

DR. KENNETH PORTIER: Dr. Pennell?

DR. MICHAEL PENNELL: I'd like to make one comment about the averaging thing. I think that another problem there is how we would choose how to weight the studies if you averaged across, because something like using fixed statistics in the model is no longer relevant because these are different data sets. May be something interesting, but I think it would be a very hard task.

The only additional comment I have is I think there should be some explanation as to why an additive risk -- or added risk was used instead of extra risk, which is more common.

DR. TALA HENRY: I'll give you one real quick: harmonization with NIOSH. We generally do it the other way at EPA, but in this case we came together and I'm told it really makes no difference.

DR. KENNETH PORTIER: That was Dr. Henry. And I was going to say, I think you did mention that in the report.

Dr. Pennell and then I think Dr. Meliker's got his sign up, but I'm not sure he wants to comment. Okay. So Dr. Pennell and then back to Dr. Marty.

DR. MICHAEL PENNELL: If some data supporting that, that it's sort of the similarity between add an asterisk could be added to the document, that would certainly help.

DR. MELANIE MARTY: Melanie Marty. I just wanted to add that sometimes when you have multiple tumor sites, you actually can come up with an inhalation unit risk factor or cancer slope factor that adds those separate risks so that rather than averaging them you're actually adding them. And, you know, that's a procedure that we have done a couple times. In this case, it was sort of academic because the lung was much more sensitive in the other.

DR. KENNETH PORTIER: Any other comments from the panel? I'm just reading to make sure we answered the question here. The EPA? Any comments? No? Let's move on to Question 5-4.

DR. KATHERINE ANITOLE: Question 5-4, please comment on whether the risk characterization has adequately described the assumptions, uncertainties and data limitations and the methodology used to assess risks from 1-BP. Please comment on whether this information and risk conclusions are presented in a logical, transparent manner and provide suggestions that could increase clarity in the risk characterization.

DR. KENNETH PORTIER: You really opened yourself to some comments here. Dr. Davies.

DR. HOLLY DAVIES: I think we've covered a lot of the first part of the question in all of the other comments we've made on assumption strengths, weaknesses over the last two days, so I'm going to focus on the second part.

One of the big questions I have is who's the audience? It seems like it's really kind of all over the place and sometimes things are -- very complicated things are not explained at all and then very simple things are explained to a great detail that we all know.

So and you have multiple audiences, I understand, and when I write things like this, I'm often writing to the legislator because we don't have authority and we have to ask for authority, whereas you already have authority. You're kind of -- you're writing both for the risk management within your agency that you have the authority to do but also for other people to look at. And you -- we talked about risk communications.

You want kind of the simple layperson explanations but also, you know, you do want -- I want to be able to quickly look and see, oh, you know, it's an MOE approach, means you want those details also.

And some of this comes from the repetitiveness, so the conclusions, the risk conclusions are in the back, the very end, and then it's like they're copied almost but not quite then in the executive summary. And so some of those issues of how much repetitive do we need and those two parts might have different audiences.

I think in the summary, in the executive summary, it'd be nice to have more of an explanation of the risk assessment approach for people who only read the executive summary and haven't, you know, read the whole thing when they get to the explanation of the risk.

Also, the -- we talked about the questions earlier, beginning of yesterday, questions in Section 1. And so you asked those questions but you don't answer them. Your conclusions don't match up and it would be nice if those matched up. These are the questions we're asking and here's we found risk. You can change one or the other, but it would be nice for those to match up.

I think this is, you know, the -- you talked about the benchmark cancer risk level not being in the assessment but in the risk management. I think that should be determined in the risk assessment, because that's where we're determining is there a risk that needs to be mitigated and risk management should be we have a risk, how should we address it. This doesn't matter for this one because all of them had the added cancer risks were so much -- were so high.

And then I have other comments about clarity in this part and others that I'll include.

DR. KENNETH PORTIER: Thank you. Dr. Marty.

DR. MELANIE MARTY: Yeah. I don't really have any additional comments beyond what you already heard. It was kind of hard to jump from one place to the other to hear all these things. So just a little work on reorganizing, I think, will be helpful.

DR. KENNETH PORTIER: Dr. Pennell?

DR. MICHAEL PENNELL: Okay. So I think there's some few instances here where in this section of the document where I think you could provide some more support for some of those statement -- your statements or consider revising them. A couple of them relate to sort of the exposure uncertainty that was mentioned yesterday.

For instance, top of page 147, you addressed the issue of the assumption of one dry cleaning machine per facility. You mentioned this as an uncertainty. It would be nice if some comments were made about how representative this may be of the population of, you know, dry cleaners, you know, some sort of -- I mean, some sort of population. I guess, maybe not in the entire U.S., but if you have something regional, you know, something we could extrapolate to.

Similarly, on the bottom of page 147, there's the assumption of spot cleaner use comes from a single dry cleaner in Massachusetts. How representative is the single dry cleaner? Do you think of, you know, other dry cleaning establishments?

Okay. Then on the top of page 151, so

the EPA acknowledges the presence of model uncertainty in estimating PODs but then there is a statement there that I don't agree with. There's a statement that says the effect is likely minimal as long as the model fits the data well within the range of the data.

So I strongly suggest to revise or remove this statement. For instance, so big reason is this. The fit of a lot of their models for the non-cancer endpoints were virtually indistinguishable. So we're talking about AICs within a factor of -- within two units, okay. And that's a general rule of thumb and it comes from reference by Burnham and Anderson.

Actually, this particular criterion actually for models being indistinguishable was actually referenced in the IRIS document for Libby Amphibole asbestos, okay. So it wouldn't be the first time that this has been used.

Now, think about -- we have four data points, essentially, in a lot of these data sets, right? Now, because I'm saying that the model fit is indistinguishable doesn't mean the curves are overlaid, right? There's multiple different ways you could drive a smooth line through those four data points. And because of that, the BMDLs can be quite different, even when you have AICs, which are essentially the same.

So for instance, this is just one example. So Table P13 in the Appendix, we have renal pelvic mineralization. That fit model was the probit model, had an AIC of 130.24 and produced a BMDL of 174. But this fit was actually within two AIC of all the models that were fit and most of which within the logistic model had BMDLs that were half the BMDL for the probit model.

So for instance, one particular example, the quantilinear model was within 0.1 AIC of the model you chose and had a similar BMD to BMDL ratio. It was 1.4. The model you chose, the probit was 1.2. BMDL was 79.3, right, which is less than half of the BMDL from the model you chose.

So that's the statement that goodness of fit minimizes concerns of model uncertainty. It is really not true, and so I would consider revising that particularly because the data are kind of sparse.

Then finally on page 152, when addressing model uncertainty and calculations, IUR is stated as sensitivity analysis comparing reasonable alternative models found similar PODs. Just define what you mean by similar.

DR. KENNETH PORTIER: Thank you. Dr. Thayer?

DR. KRISTINA THAYER: Okay. Not too much to add, but maybe sort of when talking about sort of the uncertainties of the exposure, speaking to some of the general population scenarios that were beyond the scope of this.

DR. KENNETH PORTIER: Any other comments from the panel? Dr. Georgopoulos?

DR. PANOS GEORGOPOULOS: I would just tell you some brief comments regarding the clarity. And not only the uncertainty but it would be essentially what things come with certain conclusions out of these assessments.

Let me first tell you when I read the executive summary which I do first, I thought, oh, this must be very clever executives that it's intended for. I mean, it's more of a technical summary. I mean, it requires quite knowledge of the concepts. It doesn't, you know, knowing some of the administratives that sometimes we have to prepare reports for at the state level and so on. This would be, you know, put aside after a couple of pages. Some things need to be

-- I think this is a very good technical summary, but not an effective executive summary for this to communicate risk.

And the reason I'm saying this why -- sorry, risk communication is not my expertise and we have risk communication experts that very timely they tell me about the KISS principle, keep it simple stupid, because otherwise it's not going to have an effect.

The reason I'm mentioning this is the first time I've been in many risk assessments for different agencies, but it's the first time that it's a risk assessment for a chemical that is marketed as a green chemical, as a consumer-safe product that has no adverse effect. Basically somebody can go on YouTube and find nice videos. I mean, they're not -- obviously it's not marketed widely, but you find YouTube videos where the guy soaks this red shirt essentially in this stuff at least in a way that is like, you know, you can put it on your table, you can put it -- it's a very safe thing.

And, you know, you look at the website from which you can buy it and there are multiple websites. There is, you know, appears no harmful ingredients in it. And seems we're talking about something with potential, you know, developmental effects that worries me more than constant the context of the users.

I think it's a first measure in communicating risk and subject with mitigation is to just make sure that, you know, there are appropriate labeling or this information that this is not good thing for, you know, for kids to take and play. It's not as harmful and benign and green and wonderful as it is communicated. That's my concern.

Then relative to this, I would urge you to make sure that the word "consumers" is replaced by something like general pop -- you know, segments of general population. And when we have an executive summary, for example, there is only one paragraph in the final conclusions. It talks about no consideration in the -- there are no consideration in the fight for consumers.

This cannot -- you know, when I think of consumers, I don't think of a child playing in a residence or in a school that has carpets that may be cleaned by this. So the word consumer should be used in the context that most people understand it and the fact that actually children may be exposed or, you know, sensitive members of general population like pregnant women and could be exposed and have these effects, that should be in the first of the final conclusions rather than the word conclusions. That is at least my feeling and that would help clarify and communicate the risks for 1-bromopropane much better.

Since this is the last comment, I don't know if we have time, but I would like to congratulate EPA for a very difficult task that for it, you know, I think you performed something very great with very limited data available with many knowledge gaps. Still, it's a very solid product and you should be commended for it.

DR. KENNETH PORTIER: Dr. Meliker?

DR. JAYMIE MELIKER: Yeah, I have an, I guess, outside-the-box suggestion. I mean, you heard a lot this morning, yesterday, about probabilistic modeling within the exposure realm. But I wonder about taking that into the risk realm as well. Like right now we're just modeling it deterministically. This is our point value and we've talked about what the range of uncertainty should be and in the end you have to pick a value.

And I'm just wondering about as a way to include this question or address this question of uncertainty and how to address it quantitatively whether to do that probabilistically or not, and if that's, I don't know, maybe in the horizon. I don't know, but just a suggestion.

DR. KENNETH PORTIER: Any additional comments?

I did remind the panel that after the questions we'd go around, if they had any additional thoughts on things you didn't ask questions on. So you have your opportunity then.

You know, I did think of something. Again, under this increasing clarity in the risk characterization and thinking about the fit for purpose and who's going to read this document.

Yesterday we talked about the concept of scenarios and I just want to kind of keep coming back in that there are a number of places here where we've combined settings that I felt, especially on the exposure side, that I felt should be separated out into separate scenarios and then the risk carried all the way through, not so much because it's going to change the conclusions of the report, but it's going to help the risk manager begin to understand where we can do something to decrease risk.

And while I don’t see it on the health effects side, on the exposure side, I’d really like to see some of the number of scenarios increased a little bit. You know, for example, you combined the third generation and the fourth generation machines on the exposure side and that risk is kind of combined coming forward.

So I don’t know what the full effect would be, but I think in terms of communicating where the risk is and where we might go to mitigate risk, some of that scenario change might help, especially when carried all the way through into the conclusions.

Any additional comments?

EPA, any clarifying questions on this?

Dr. Marty, did you have a last comment you'd like to make on this?

Like I said, we're going to kind of come back once more around.

DR. MELANIE MARTY: That's okay.

DR. KENNETH PORTIER: She says she's going to wait for that. Okay. So with that, we've gone through, I think as far as I can tell, we've gone through all of EPA's questions. One of the things I like to do at these panels is sometimes in the discussions or in reading the materials, questions arise to the Panel that EPA hasn't asked. And while we're not going to spend the next five hours going around that, typically, interesting issues we can bring up and suggest that EPA might want to question themselves on that.

So what I'm going to do is I'm just going to go systematically around the room and see if there's anything that kind of came up that you would've wished EPA had asked a question about or that you wished they had answered your question in the document or in this presentation. Or if like, Dr. Georgopoulos -- George -- I can't quite get it right here -- said -- and I'll start by saying, I think actually, everything is in this document. I think it needs some organization, but you've answered all your questions in here and we've provided you some marginal comments. Like you said, I think this is a good document in the sense that everything's there, you just need to work on the story. That's my feeling.

We'll start with Dr. Thayer because she had put her card up, so I'll start with Dr. Thayer.

DR. KRISTINA THAYER: I think maybe just sort of process comment for moving forward on the next ones and then sort of a question. So in terms of the process for sort of how you get feedback when you still at the problem formulation phase. One of the approaches that we found to be helpful is to engage a group of technical experts at the front end, so these questions about sort of is the scope of the valuation appropriate? You get that kind of feedback early on. And then we go out for sort of a public presentation and we talk about here's a proposed scope, our concept, sort of a high level. And then we get feedback on that. And that helps with the transparency. I think it helps with the credibility of the valuation because you've got those content experts available to you and we sort of use them, not only to give us feedback on the scope, but also to be on hand as we're implanting the assessment.

So then you can sort of quickly address some of those trick issues that you always come across when you get into the study. So just a suggestion in terms of -- and we haven't really actually found that it's slowed us down because it's sharpened -- by the time you roll out with your scope, you feel more confident about you're not missing things.

And then I think sort of maybe the questions that gets at some of the risk communication is do you envision that when you roll this out that there might be some sort of fact sheet or some sort of suggestions to reduce exposures?

DR. TALA HENRY: Yeah. In fact, there is one now. I was just thinking about our fact sheet when Dr. Georgopoulos was speaking. We have one currently on our website. So typically, we do a fact sheet, which is much, much more public facing and much, much simpler.

And when we do have situations like this and with a couple of our previous assessments where, you know, the risks are there and they're not even close to marginal. We provide at least a little bit of advice about what the general should do about limiting exposure. I mean, that's really all we can say at that moment.

DR. KENNETH PORTIER: It's interesting, at the American Cancer Society when we ask researchers to send proposals, we ask for two abstracts; one is the technical abstract and then the other one is something someone at the 6th grade could understand.

Now, the word "cancer" itself moves any document up to a 9th grade level. So it's very difficult for them to write it. I've looked at those things, and researchers don’t know how to write at the 9th grade level. They're writing at the 16th grade level. So I understand the complexity with that.

Dr. Blando, any comments?

DR. JAMES BLANDO: I would just say that I'm sure it must be particularly fatiguing to sit here for two days and have people throw darts at you. So I really commend you on your efforts. I'm sure it has been a tremendous effort that was done on a nice quality product.

I would just reemphasize a point that's been stated a couple times here today that I think when you do move to the risk management phase, I think the fact that this particular chemical has been marketed as a "green" chemical, and it's the larger issue of what does it mean to be green. And I think that's just something that is a really significant issue, and I'm thinking about it from a public health communication standpoint, I think that's particularly important.

And the only other thing I would say

that kind of struck me today was that the consumer use survey was based on data, the only available data that exists from 1987. You know, it's probably a good time to maybe update that if that were possible. That seems like something that would be important to do. But just with the risk communication, I think that's extremely important. We can have all the engineering controls designed by engineers, but if people don’t recognize the hazards, that can very problematic.

Buy anyway, thank you.

DR. KENNETH PORTIER: Dr. Hossain.

DR. MUHAMMAD HOSSAIN: I'm just glad that EPA looked at lots of non-cancer endpoints. So since 1-BP entered into the body through the lung, so is there any data -- any adverse effect on the lungs, for example, asthma after chronic exposure?

DR. SHARON OXENDINE: Sorry. I was reading notes.

DR. KENNETH PORTIER: Re-ask the question.

DR. MUHAMMAD HOSSAIN: So EPA looked at several nontoxic -- sorry, non-cancer endpoints following exposure to 1-BP, since 1-BP entered into the body through the lung; so is there any data on the respiratory outcomes after long-term exposure, maybe people who can suffer from chronic asthma, those kind of things?

DR. KENNETH PORTIER: Or emphysema.

DR. SHARON OXENDINE: I think that's a really good question. Unfortunately, we have not come across those studies. And what we found with the rodent studies is that for the lung, in particular, inflammation was observed in the rat and not the mouse. So the question is still out on that one.

DR. KENNETH PORTIER: Dr. Marty.

DR. MELANIE MARTY: I just wanted to go back to something that we had been talking about and that is the general population risks. And to reiterate that while that's important, you got lots here to go and move forward on. So we don’t want you to hold the thing out for a year while you're figuring that out.

Just in messing around last night, looking at the NTP 2013 report on page 12 under Fate, occurrence, and exposure, they have a couple of sentences in there that sort of jumped out. "EPA has estimated 1-bromoropane concentrations in ambient air at a distance of 100 meters from average adhesive use, mild facilities, via air dispersion modeling to be .138 mL per cubic meter and 1.38 for high adhesive use facilities." And they cite Wolfe et al (2003), and then they go on to say what the EPA's estimate of the actual dose in milligrams per kilogram a day based on what those air concentrations. So it got me to thinking, well, you know, instead of like, trying to figure out how many people are exposed in the general public to these kinds of different emissions. Just to do like, a cite-specific risk estimate.

So if that were the case, what would the risk be at the receptor point. And that could help you describe, at least, some of the potential risk to the general public and it would be fast.

DR. KENNETH PORTIER: Dr. Pennell?

DR. MICHAEL PENNELL: Yeah. So I actually have a lot of comments about your analysis of the non-cancer endpoints. That wasn't really asked for in the charge question, so I'll proceed with those now.

The first one has to do with my comment I just made a little bit ago, and it has to do with comparing the fit of the model, okay, to the non-cancer endpoints. So it appears, pretty much throughout that the model with the lowest AIC was chosen, but in a lot of the cases, the differences in AIC were miniscule. Definitely within that two-unit rule of thumb that I mentioned earlier. So this is really a situation where something modeling averaging would be a good approach when you have models that, you know, appear to split the data very similar, right. You can, average across those fit statistics. And actually, since they're so close, it'll be just a simple average, probably, right. So that's something to consider there.

Another thing is that, and I know this wasn’t really used as a criterion in the end to determine what was the best fit model, but it was mentioned that P values of the Goodness of Fit test were compared across the models and actually, within the benchmark dose guide, technical guidance provided by the EPA, discourages doing that. I mean, one issue with that is that it's really hard to compare those results across models because, you know, it's based on looking at groups of the model within groups that are defined by risks estimated by the models. And those groups will differ from model-to-model. So it's not really a good way to compare a fit.

So there are a few statements that really need to be clarified; like, for instance, what is considered a large spread of the MCLs? What's a high BMD, BMDL ratio? Just clarify that.

And also, similarly, there's some comments in there about BMDS giving warnings. Like on page 360, there's a warning about the BMDL calculation. If you could elaborate on that problem, that would be good. And then some of the analysis I felt like needed a little bit more description.

For instance, analysis of fetal pup weight, right. How is the litter effect accounted for there in that analysis?

Also, this is sort of a big issue, or at least in my opinion, and hopefully I'm not misunderstanding things. It's well known that the litter size affects the pup weight. So is the litter size accounted for in this analysis? Because if it's not, then what you could get is an effective dose on pup weight which is not causal, right. It's really through the effect on, or in part, due to the effect on the size of the litter. There have been several papers about that.

Also, the cases where there is poor fit

model and you defaulted to using sort of the very traditional approach of LOELs/NOELs. I think it would be useful to actually provide the plots there to show for the model with the best AIC, how bad was the fit, right? Just don't provide the plots for when the models fit well.

And also, I assume that some sort of multiple comparisons procedures was used to do the comparisons of the dose groups to the zero control. That should be mentioned as well. And I have some just quick editorial comments. One thing that made it difficult to navigate that appendix is that the structure of the summary statistics tables changes like halfway through.

So in some instances, the doses are in the rows and some are in some of the columns. It disoriented me a little bit. And then one error is on page 331, the multi-stage model actually provides the best fit to the -- I'm going to say this wrong centrilobular hepatocytes data in the rats.

DR. KENNETH PORTIER: Thank you. Dr. Quiros.

DR. LESLIAM QUIROS-ALCALA: Again, similar comments. Trying to improve the clarity in order to improve the transparency, especially when you're trying to report studies in data that support what you're trying to do. Again, the systematic review. Again, the importance of really including something in the general population, especially because studies have shown that also populations living nearby tend to be low-income communities, as well as minority communities that are already suffering disproportionate exposures to other environmental agents. So that's another reason why it's really important.

And also, cross-checking the values reported and references because there are oftentimes where I check the reference and I couldn't find the statement -- I couldn't find what was supporting the statement that was being indicated or values may have been transposed. And I think Dr. Marty also noticed this, where like the 90th percentile value was higher than the median. So just cross-checking those.

And again, we know this took a lot of work. It's easy for us to sit here and just, you know, provide feedback and say what's wrong with it, but we know a lot of hard work went into it. So thank you.

DR. KENNETH PORTIER: Dr. Schlenk.

DR. DANIEL SCHLENK: Well, actually, I may be the only one in the room. I thought it was really good. Having read many of these before for other purposes, what you guys have done, I thought it was a pretty good job in terms of what you laid out and what you had go through to do it.

Again, the only thing I'd add, I think, a little bit more figurative sort of explanations which might help with a management component off of that. And I included that in the comment. Good job, actually.

DR. KENNETH PORTIER: So Dan, that's an example of a dose response? You're saying the more dose we get, the less response we're going to giving EPA or less critical?

DR. DANIEL SCHLENK: Yeah, exactly.

DR. KENNETH PORTIER: Dr. Meliker.

DR. JAYMIE MELIKER: No, I would agree. I mean, I read it. I thought it was a pretty strong document. I think we've highlighted some areas to work on. The thing that keeps bothering me in the back of mind is the regrettable substitution problem. And I don't know how we include that or address that in any way.

I mean, we haven't talked about that. This is just as one contaminant at a time, which was used to replace, I think, methylene chloride, which was banned previously. So how we tackle that as part of this whole problem is still, in the back of mind, which we haven't addressed at all. But other than that, I think, you know, hopefully we were helpful to you.

DR. KENNETH PORTIER: Dr. Kissel.

DR. JOHN KISSEL: I have a somewhat similar thought. This process is going forward and this is Chemical 5 or 6, I'm not sure, of 80 that are targeted. I think it would be nice to include, somehow, kind of a summary matrix or a table of what's been so far and maybe some comparative. You know, the outputs may not be the same for each chemical, in terms of how the risk is presented, and that might be a clue that there is a lack of uniformity in this process. And uniformity is apparently part of the reason why there is a standing CSAC.

So it might be useful to try to think how you would present a summary table for all the compounds that have been done so far and attach it as an appendix with every one that comes out. And if you can't do that, if you can't think, well, what actually is the similar endpoint we could put in a table, at least make a list of here's the ones we've done so far and here's an electronic link to where that document is so that somebody's who's looking at this can say, I see where this fits into the big picture.

DR. KENNETH PORTIER: Dr. Gilbert.

DR. KATHLEEN GILBERT:

I also just wanted to say I also thought it was a really awesome document and I was really impressed. And I know we have been throwing darts for the last two days, and I guess that was kind of our job. So I don’t envy you the task of deciding which of those really need to be addressed so that you can still, in a timely fashion, create a stronger document. That must be tough for you.

All I want to say is it's obvious to me, at least, that the risk is there and I would hate to see too much delay in moving onto the risk management part of the process.

DR. KENNETH PORTIER: Dr. Georgopoulos.

DR. PANOS GEORGOPOULOS: Thank you, again. Since I already used my chance to congratulate the EPA for a very good job, I mean, it's nothing wrong in doing it again. It was an impressive document. But there are certainly knowledge gaps and the science moves forward and along with getting more knowledge about this particular chemical, others in the pipeline.

So I want to echo what John said, I think it's nice to have a framework that will apply to the majority of these chemicals and see how, for some of the things that are coming up will be less information and some will be more. But it would be nice if the framework is casted in a lifecycle analysis type of thing, looking at the manufacturing of the chemical, transportation, distribution, different uses, both occupational and residential and institutional settings, and finally, disposal. What happens in the end?

So I know, I mean, there will be many boxes that will remain empty, but if you have that framework, it is the checklist concept that is becoming very popular in many professions. You know, if you have that checklist then at least you think about it, and maybe this information. So it would be very good to see this. I mean, you know, eventually, there will be pharmacokinetic modeling.

Eventually there will ambient release data and there will be other things. So more information will be there for 1-bromopropane. This information may already exist for other chemicals in TSCA, but looking in a framework that puts lifecycle analysis and then population lifecycle analysis with occupational workers and then sensitive populations, pregnant women, developing children and so on, and identifying potential risks. What we know, of course, for this population, in a clear manner will help, I think the process to move forward and make this communication easier. I've said enough. Congratulations again and keep up with the good work.

DR. KENNETH PORTIER: Dr. Davies.

DR. HOLLY DAVIES: I also want to say that the document was well done, well-supported, believable. My comments kind of go beyond your current charge in some ways. I did want to mention the Federal Trade Commission has guidelines on green marketing. They're green guides that come out and say what's legal and what's not legal for marketing. So we have another federal agency that deals with that. I mean, it's important for risk communication, but there's another agency that has that as their primary charge.

What we need is more forward looking assessments to avoid the regrettable substitutes. We shouldn’t have to wait until the dry cleaners switch, you know PERC is banned then everyone switches to 1-bromopropane to then do a risk assessment to show that they shouldn't have done that. It would be nice if we could look at uses -- and again, this is too much for now, but in the future, it would be nice if we move towards looking at possible uses that we could say would be a regrettable substitute and picking safer substitutes in a logical way, like using the alternative assessment guidelines.

DR. JAMES BLANDO: May I say something?

DR. KENNETH PORTIER: Sure. Dr. Blando.

DR. JAMES BLANDO: Just in following up with Dr. Davies just said, I'm sure you've already done this, but it's important for you to talk to your air quality program because as far as I understand, the PERC ban is still set to go in place in four years. So you have an opportunity to hopefully prevent a regrettable substitution. Because if you don’t do anything and the air quality program moves ahead with that PERC ban, most dry cleaners are not going to be converted to higher generation machines by then. So you'll end up with that regrettable substitution it's just repeating itself.

Anyway, I just wanted to emphasize that point.

DR. KENNETH PORTIER: Or worse than that, they will move their generation up, thinking they'll reduce their risk that way and they still haven’t reduced it enough to get below the MOE that we've looked at.

I wanted to reiterate what Dr. Thayer says. EPA now has a Chemical Safety Advisory Board. You have permanent members here. You notice that they get engaged in this stuff. While it's nice for us to look at these near final products, at the end of the cycle, I would encourage EPA to bring to the panel some of the stuff that's maybe a little further from completion where we can provide some insight on the evidence support or structure for some of this stuff.

I think I speak for the permanent panel that they'd look for that opportunity. Now, we don’t want to have extra meetings, but you can always add a half-day to a two-day meeting like this where we could come in and look at a broad suite of things that are on your TSCA platter coming up that you might want some insight on.

I think, as Chair, I would make that offer. I think we'd like to be able to do that. And my understanding is if the TSCA -- maybe this is off record. If the thought TSCA legislation that's moving forward actually has an advisory board in there, you will think to structure that as well when EPA gets the opportunity actually design a chartered legislatively mandated Board, you can kind of build that into the early evaluation, as well as the late evaluation component.

Statisticians always know, and you've heard us say this before, our biggest benefit is coming in early at the design phase than doing a saving grace at the end. So we'd rather be at the beginning.

Dr. Thayer?

DR. KRISTINA THAYER: I just have one comment on that. And I know you obviously sort of work amongst yourself and I you partner with NIOSH. When I was mentioning about sort of external, I meant sort of non-federal. It just sort of gives that extra layer. For whatever reason, it's appreciated. I didn't mean to diminish the federal work that's gone into this.

DR. KENNETH PORTIER: And I think with that, I'll turn it over to EPA for some final comments and then we'll go to the DFO for closing remarks. Before I do that, I want to tell the Panel, we're going to take about a 10-minute break and then we'll meet in our meeting room to discuss the timeline and plans for the reporting. So don't run off to the plane; we have a few more. I promise it won't take long. I have to say this because they're gone. We close the meeting, if I don’t say that, they disappear. So don’t disappear. Don Wood is over there. He's not going to let you get in a taxi -- Don is over here -- before we have that meeting. EPA.

DR. TALA HENRY: Okay. Well, it's kind of in response, a little bit to that last round up because many of you are on this commission/committee, if you will, I think it's worthwhile to just give you a little bit broader view of some of the things we have done or do do because they go exactly to some of your points.

So I'll just go through some. I already took some notes. So Kristina gave this talk about earlier consultation, potentially, at the problem formulation stage. So certainly, we mentioned that we have a public comment period there. What we have learned from our several past risk assessments, as we get done with the risk assessment and then we go into the risk management thinking. And we do need to know some more specifics of this or that. So we have, for example, after our TCE risk assessment, we had an expert workshop around a lot of questions about how you could employ risk mitigation measures and so forth. Well, already, on 1-BP, we were thinking about that sooner. So again, this won't be completely final before that so, we've moved that whole process up. So certainly, that's a lesson learned us along the way as well.

This risk communication thing, as I had mentioned, we do, in fact, have much, much simpler fact sheets. Maybe that should go out when we distribute the documents to you all well. It could almost be in the intro section or something like that or Appendix No. 1 or something to that effect. That's a great idea.

The screen chemistry issue, certainly, whether somebody is labeling something or not is not exactly our purview, as Dr. Davies pointed out, but nonetheless, if we're moving up this expert consultation in some way, that's probably, especially in a public venue, somewhere where that attention can be put and say, you know, this may have been called this or that or whatever. And maybe it's not.

The thing about EPA's estimation of concentrations in air, as well as Dr. Blando's comment about our Air program. Again, we worked pretty closely with them. And some of you may know that the agency, I'll speak on behalf of the agency at this point, has a petition under the Clean Air Act to list 1-BP as a hazardous air pollution. We're still deliberating over that. But nonetheless, we're well aware and we will hopefully address not only this TSCA stuff but that whole issue of general population and air as 1-EPA, as we like to call it now.

So stay tuned. I mean, there's internal schedules and so forth as well, but we're both aware. The regrettable substitution issue, we're also very well aware. Again, we have completed TCE, 1-BP was the replacement for TCE and the PERC is already out there. So we're aware of exactly how to juggle it all or to put everything through in parallel, is a little beyond us at the moment, but one of our next batches of chemicals that we were going to address are additional halogenic solvents for this very reason because of the regrettable substitution issue and because lessons learned, hopefully we could be more efficient when we do those assessments as well.

I think I really like the idea of keeping that running list. Again, we kind of had that internal argument about how to best communicate our word, our findings. And if you look at these documents as you just have, there's hundreds of MOEs, sometimes in there. So that certainly isn’t the most efficient way, but what is that common denominator that we can communicate around. It would be really good. And currently, we do have everything on the one website, which I think you got a link to. And granted, it starts to become a very, very long page. So certainly, there's room for improvement there.

Just one other comment on the lifecycle. Again, this was one of our earlier assessments where we sort of went into kind of of a narrowing approach right away. I think if you looked at any of our flame retardant conceptual models, you'll see that those really do include the full lifecycle manufacturing if it occurs in the United States on down. So we really do consider the full lifecycle because it is under the purview of TSCA.

So I look forward to a little bit more completeness on that end in the future. I think there is waste disposal in at least one of those flame retardant conceptual models.

MR. GREG MACEK: Recycling.

DR. TALA HENRY: Recycling. Right. So anyway, again, we're still growing and still improving we very, very much appreciate all your feedback. I think we got some really valuable input here and we very much appreciate all your time and effort. Thanks.

DR. STAN BARONE: Just to add to Tala's remarks, thank you, Tala. The comment that was raised about the utility in the charge to the existing standing panel, does include looking at the sort of continuum of our assessment program, as well issues, cross-cutting issues. So that is part of the charge to this FACA Committee. And as we go along and as more issues and specific peer review products are brought to the committee, that will be part of the ask to you all about, you know, looking across this subject matter, what can you provide us advice on?

So that is definitely in the back of my mind as the new acting office director, of what we'll be coming to you with in future charges. So thank you very much for bringing that up. And consistent with language in the new TSCA, I think, as well.

Thank you very much for your robust conversation and the input to the agency. And hopefully we'll have a timely report. Plug.

DR. KENNETH PORTIER: Of course. So I see the time is 2:34. And I'm going to call the meeting to an end and turn it over to our DFO for some final comments.

MR. STEVEN KNOTT: Okay. Thanks, Dr. Portier. So just in closing, I want to add my appreciation. Thank you, Dr. Portier, for chairing at this week's meeting. And also thank you to the members of the CSAC. For our first meeting, this was an excellent meeting. I was lying awake, wondering if you were going to get through 16 questions in two day and we're ending early. So I think that says a lot about how focused the discussions were and how efficiently we moved through the charge. And got a lot of excellent feedback in the process, so thank you very much.

And I'd also like to thank OPPT, the presenters for this meeting. They had excellent, clear presentations and also being available to assist with clarifications as we move through the past few days. I really appreciate everyone's efforts along those lines.

Thank you also to our public commenters. We really appreciate getting the public comments and the feedback for the Committee. And really, for our public participants, including those who have been listening in on the webcast. We appreciate everyone's interest in the Committee's activities. And I also don't want to miss thanking my colleagues on the SAP CSAC staff for all of their work in assisting with organizing, coordinating to make this meeting possible.

So thank you very much. The only other thing I'll add is just a reminder, within the next 90 days, the Committee will be completing the report. It will be made available in approximately 90 days. That will be posted on our website and also in the public docket. I think that's really about the last administrative item. So with that I will close the first meeting of the CSAC. Thank you.

(Whereupon, the meeting was adjourned.)