MEETING

STATE OF CALIFORNIA

OFFICE OF ENVIRONMENTAL HEALTH HAZARD ASSESSMENT

PROPOSITION 65

DEVELOPMENTAL AND REPRODUCTIVE TOXICANT

IDENTIFICATION COMMITTEE

JOE SERNA JR.

CAL/EPA HEADQUARTERS BUILDING

1001 I STREET

COASTAL HEARING ROOM

SACRAMENTO, CALIFORNIA

MONDAY, FEBRUARY 25, 2013

10:07 A.M.

JAMES F. PETERS, CSR, RPR
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A P P E A R A N C E S

COMMITTEE MEMBERS:

Ellen B. Gold, Ph.D., Chairperson

Laurence Baskin, M.D.

Hillary Klonoff-Cohen, Ph.D.

Ulrike Luderer, M.D., Ph.D., M.P.H.

Aydin Nazmi, Ph.D.

Meredith Rocca, Ph.D., D.A.B.T.

STAFF:

Dr. George Alexeeff, Director

Mr. Allan Hirsch, Chief Deputy Director

Ms. Carol Monahan-Cummings, Chief Counsel

Dr. Marlissa Campbell, Staff Toxicologist

Dr. Jim Donald, Chief, Reproductive Toxicology and Epidemiology Section

Dr. Allegra Kim, Staff Toxicologist

Ms. Cynthia Oshita, Proposition 65 Implementation

Dr. Martha Sandy, Chief, Reproductive and Cancer Hazard Assessment Branch

Dr. Lauren Zeise, Deputy Director, Scientific Affairs

ALSO PRESENT:

Dr. Sarah Janssen, Natural Resources Defense Council

Mr. Steve Risotto, American Chemistry Council

I N D E X

P R O C E E D I N G S

DIRECTOR ALEXEEFF: Good morning, everyone. Let's do ahead and get started with today's meeting. This is the meeting of the Developmental and Reproductive Toxicant Identification Committee.

I'm George Alexeeff. I'm the Director of the Office of Environmental Health Hazard Assessment. And I serve as, in this role, as Secretary to this Committee.

So I'd like to -- what I'd like to do is I'll just introduce the members, and then I'll ask them to give a little bit more introduction about themselves, but I'll just -- to my left is Dr. Ellen Gold. And to the left of her is Dr. Meredith Rocca. And to the left of her is Dr. Ulrike Luderer. And then on my far left is Dr. Laurence Baskin. And then to my right is Dr. Hillary Klonoff-Cohen, and next to her is Dr. Aydin Nazmi.

And we have three members not present here today Dr. Isaac Pessah, Dr. Tracey Woodruff, and Dr. Catherine VandeVoort. So why don't I just start with Dr. Gold. We'll just go in the same order that I introduced the members just to give a little background about themselves.

CHAIRPERSON GOLD: God morning. I'm Ellen Gold. And I'm Professor and Chair of the Department of Public Health Sciences at UC Davis and also Chief of the Division of Epidemiology in that Department. And I've been

interested in lifestyle and environmental factors as they relate to reproductive health reproductive epidemiology and women's health.

COMMITTEE MEMBER ROCCA: Good morning. I'm Meredith Rocca. I'm the Director of Non-Clinical Safety Evaluation at Janssen Alzheimer's Immunotherapy, which is a pharmaceutical company. I have been doing reproductive and developmental toxicology assessments on pharmaceuticals for many years.

COMMITTEE MEMBER LUDERER: Good morning. I'm Ulrike Luderer. I'm Associate Professor in the Division of Occupational and Environmental Medicine at UC Irvine. I'm also the Director of the Environmental Toxicology Graduate Program. And my research interests are in ovarian toxicology, and also developmental toxicology of the ovary understanding factors that modulate sensitivity to ovarian toxicity. And I'm also an occupational and environmental medicine physician.

COMMITTEE MEMBER BASKIN: Hello. Larry Baskin. I'm a Professor of Urology and Pediatrics at University of California San Francisco. I'm a pediatric urologist who practices clinical pediatric urology. And my laboratory interest has been on congenital anomalies and preventing them, specifically looking at hypospadias on undescended testes and our focus has been on endocrine disruptors.

COMMITTEE MEMBER KLONOFF-COHEN: I'm Hillary Klonoff-Cohen. I'm a Professor in the Department of Family Preventive Medicine at the University of California, San Diego. And I'm interested in reproductive and pediatric epidemiology, as well as oncology.

COMMITTEE MEMBER NAZMI: Good morning. My name is Aydin Nazmi. I'm an epidemiologist and a faculty member at California Polytechnic State University in San Luis Obispo. I'm also the Director of the STRIDE Center for Obesity Research.

DIRECTOR ALEXEEFF: Okay. Thank you, everyone. A few housekeeping issues. If there is a need to evacuate or a fire drill, the exits you can see them lit up and you can exit out down the stairs. And if you need to evacuate the building we go to the park across the street.

Also, the restrooms are out the back door there, and then to the far left. So the next thing I'd like to do is administer the oath of office for all the members. So I'll ask them all to stand, and then just to repeat after me. And when I say, "I" and then there's a blank, you add your own name. All right. We're all set.

Okay, so, I --

COMMITTEE MEMBERS: I --

DIRECTOR ALEXEEFF: Oops, I'll speak into the microphone here.

Do solemnly swear or affirm --
COMMITTEE MEMBERS: -- do solemnly swear or affirm --
DIRECTOR ALEXEEFF: -- that I will support and defend the Constitution of the United States --
COMMITTEE MEMBERS: -- that I will support and defend the Constitution of the United States --
DIRECTOR ALEXEEFF: -- and the Constitution of the State of California --
COMMITTEE MEMBERS: And the Constitution of State of California --
DIRECTOR ALEXEEFF: -- against all enemies, foreign and domestic --
COMMITTEE MEMBERS: -- against all enemies foreign and domestic --
DIRECTOR ALEXEEFF: -- that I will bear true faith and allegiance to the Constitution of the United States --
COMMITTEE MEMBERS: -- that I will bear true faith and allegiance to the Constitution of the United States --
DIRECTOR ALEXEEFF: -- and the Constitution of the State of California --
COMMITTEE MEMBERS: -- and the Constitution of the State of California --

DIRECTOR ALEXEEFF: -- that I take this obligation freely --

COMMITTEE MEMBERS: -- that I take this obligation freely --

DIRECTOR ALEXEEFF: -- without any mental reservation or purpose of evasion --

COMMITTEE MEMBERS: -- without any mental reservation or purpose of evasion --

DIRECTOR ALEXEEFF: -- and that I will well and faithfully discharge the duties upon which I am about to enter.

COMMITTEE MEMBERS: -- and that I will and faithfully discharge the duties upon which I am about to enter.

DIRECTOR ALEXEEFF: All right. Thank you very much.

One more thing I'd like just to mention on housekeeping, is this meeting is being webcast. So if, you know, the Committee members will remember to speak directly into the microphone. And then when we have any questions or comments from the audience, please use the microphone, so everyone can hear your question.

Okay. Just a couple more things before I turn it over to the Chair here. Okay. I just have a couple introductory comments.

First of all, over the last several years, OEHHA and the DART Committee and stakeholders have debated the subject of time limits for public comments without coming to a lasting consensus on a balanced approach. And the tentative agenda contained a note advising that public comments would be limited three to five minutes per person.

This generated concern from the public and the legislature that five minutes is not adequate time to discuss the scientific issues that should be considered by the Committee when making a listing decision. It may also be more efficient to allow two or more parties to combine their time for presentation.

So OEHHA takes these concerns seriously, and wants to provide adequate time for public comments, while also ensuring that the Committee has sufficient time for its deliberations.

So we've received a request for additional time, that is 20 minutes, for the presentation by the American Chemistry Council today, which the Chair granted. Also, for this meeting, the three to five minute limit has been dropped. Stakeholders have raised other concerns about the process as well.

And since this is a new Committee, this is a good opportunity to evaluate thoughtfully any changes we might

want to make on the process. OEHHA plans to consider changes and will welcome suggestions from the Committee and the public concerning the most productive process for conducting the meetings of the Committee, and it may be a good agenda item for the next meeting. And we'll work with the Chair on how best to proceed.

So those are my introductory comments for today.

I will now turn it over to Dr. Gold.

CHAIRPERSON GOLD: Thank you. Well, first of all, I want to welcome the new Committee members to the first meeting the DART IC with its new membership in the year 2013. Can you hear me all right?

It's too far away. Okay.

So I feel strongly that the Committee's business should be made as public and transparent as possible, and we will work to that end. And so for this reason, I declined a request for a private meeting with interested parties concerning the procedures of this Committee, and, in particular, with reference to the amount of time for the public comments, the time limit of three to five minutes.

And in addition, I also, on February 21st, received a letter from Gary Roberts on behalf of the SC Johnson and Company, which lists a number of reasons why public comments should not be limited to five minutes at

the March 18th meeting, next month's meeting, and a copy of this letter is available at that back of the room. So I will not be providing a written response to that letter, but we, as you have heard, have modified the time limits for today's meeting.

And if Mr. Roberts or others wish to raise the issue further during the public comment period, that would be the appropriate time to do that.

We also received, as you heard, a request from the American Chemistry Council for additional time for its presentation. And after I discussed this with Dr. Alexeeff, we agreed to provide the additional time as you heard. So the additional time is for 20 minutes. And any other commenters will also be allotted 20 minutes. So overall, we have allocated an hour for public comment portion for the chemical we're taking up today, xylene, but if a number of people wish to speak, we should be able to accommodate them by extending the time.

Okay. So without further ado, I think we turn now to our counsel.

(Thereupon an overhead presentation was presented as follows.)

CHIEF COUNSEL MONAHAN-CUMMINGS: Good morning. Can you hear me okay?

More or less.

Okay. Good morning. I just also wanted to welcome the new members of the Panel and also those of you that have been on the Panel for a while. And I am Carol Monahan-Cummings. I'm the Chief Counsel for the Office of Environmental Health Hazard Assessment. And I've been with the Office for about 10 years. And I've been the counsel for this Committee for 10 years also. In that capacity, I do provide legal consultation for Committee members regarding their work on the Committee. And you're welcome to contact me anytime, if you have questions about -- of a legal nature.

Speaking of legal things, I wanted to go over a couple laws that apply to this Committee in particular. And so we'll start off with the Bagley-Keene Open Meeting Act.

Can we go to the next slide.

Thank you.

The purpose of the Bagley-Keene Open Meeting Act -- and I sent you some materials in advance, so that you could look at them. I'm required to give you the actual text of the law, and so you should have that. And I also gave you a pamphlet from the Attorney General's office that explains the law in more detail. So I'm not going to go line by line in that, but I just wanted to highlight a few things. And we also discussed briefly

with the new members in our welcome phone calls the general provisions of the Act.

So the ones I wanted to highlight is that the purpose of the law is to allow the public to be informed about the proceedings of public agencies. The purpose of the law is not to make the meetings efficient. So really it's to make sure that the public knows what you're doing, and that -- it wants to ensure that the State's actions, and that includes through this Committee, and deliberations be open to the public.

And that kind of references the information that Dr. Gold mentioned too, about having open and transparent processes.

And the other purpose that I wanted to highlight is to ensure that the public has input into decision making. And you'll notice on our agenda today that we have three -- I think it's three -- opportunities for public comments. We're going to have comments after this orientation material that we're presenting. We'll have comments after the presentation of the information on xylene, and we'll have another public comment at the end of the meeting just to allow the public to make any other additional comments they think are necessary.

Next slide.

So the essential requirements of the Bagley-Keene

Open Meeting Act are that the public must be provided with reasonable notice about the location, time, and content of our meetings. The general requirement is that the notice of the meeting and the content of the meeting needs to be published at least 10 days prior to the meeting. And our agendas are generally published at least a month prior to the meeting, but minimum requirement is ten days.

You are required, as a Committee, to meet and discuss your decisions together in a public location. And communications between members concerning issues that are being considered by this Committee should only occur at a public meeting. And that doesn't mean that you can't talk to each other when you run into each other at a technical meeting, or if you happen to work together on projects. You can certainly do that, but what we're trying to avoid is deliberations or discussions about the issues that are in front of the Committee, or could be in front of the Committee.

And then communications or discussions with third parties or other Committee members need to be disclosed at the meeting. And you can see an example of that from Dr. Gold's comments. She disclosed that there was a request from a third party for a meeting that she received a letter from a third party, and she also received a request through the -- I think it was a verbal request for the ACC

to have additional time to speak today.

And so that's essentially what you need to do if there's a communication. You're certainly welcome to talk to members of the public, including the press, or other interested individuals, but it's best to go ahead and disclose that at the meeting.

Next slide.

Okay. And for purposes of the Open Meeting Act, there's a number of definitions of what a meeting is. It includes any congregation of the majority of the members of the Committee, that in this case would be five, to hear, discuss, or deliberate on an issue that's within the jurisdiction of the Committee.

So, for example, if you had all gotten together before this meeting and talked about xylene, and kind of reached some -- you know, had a discussion or reached some kind of a conclusion before the meeting, that is a violation of the Act.

That can include email exchanges between individuals on the Committee and telephone calls or communications through a third party. So generally, the issues that come up here are when you receive an email, for example, from one of our staff that goes to all of you, and then you hit "reply all", and you discuss something that's going to be coming in front of the

Committee. So you want to avoid the "reply all" function on your email.

And you can't do kind of a serial meeting, where say Dr. Baskin talks to Dr. Luderer who talks to Dr. Rocca who talks to Dr. Gold, those are still considered meetings.

One thing that a meeting does not include are if a -- even if a quorum or a majority of the Committee members happen to attend a conference or other scientific meeting, and they all happen to be there, you can certainly do that and attend the meeting, but again you shouldn't discuss the issues that will be coming before this Committee.

Next slide.

So the remedies for a violation of the Open Meeting Act is that -- the primary one is that there's the -- whatever action the Committee took based on that violation has no legal effect. And so you essentially have to do the whole thing over, and do it in public. And so given the time that's involved in attending one of these meetings and the work that's done, we're wanting to avoid that outcome.

Okay. So next slide.

I'm going to change the subject a little bit here and talk about a couple of other issues that can affect

this committee. One is the Public Records Act, and the second one is litigation holds. And I'll go into those separately.

First one, the Public Records Act is applicable to all actions by a public entity, and that includes members of this Committee. And so I just want to let you know that virtually all your hard copy and electronic records that relate to this Committee are open to the public upon request. And if we get a request for that information, we'll advise you of that and you're required to collect it and provide it to us. And that includes if you've, for some reason, are using your private email accounts or private computers or whatever, you still have to collect the information off of those that might be related to your work on the Committee.

And then lastly, there is an issue that comes up from time to time when our office or the Committee or both are subject to litigation. Every once in a while, you all get sued and so do we. And right now the Carcinogen Identification Committee, each of the members are defendants in action that was brought by the Sierra Club. So it does happen from time to time. This Committee has not been named in litigation at this point.

But I do want to let you know that when I believe that litigation is imminent or certainly after it's filed,

that I will send you information, usually via email, and ask you to -- explain to you what items that you may have that are covered, and you are required to maintain those, not delete them, not destroy them during the time that the litigation hold is in place. And that can be a long time.

In the Sierra Club case, it's been over six years. And so you might want to get a box and pile all your stuff in there and keep adding it in.

And again, the only way that it expires or changes is if I notify you in writing that it has been lifted. And again, it can include items that are saved on your home computer and hand-held devices, to the extent that they are relevant to the potential or actual litigation.

Okay. I said that was the last, and it's not.

Next slide

You are all currently in compliance with the requirements to complete a Statement of Potential Financial Conflicts under the Fair Political Practices Act, and -- also known as completing your Form 700. That's required within 30 days after you're appointed, and then annually thereafter.

So I appreciate you disclosing that information. In the event that anything comes up during the next year before you have to complete it again, you're welcome to

give me a call, ask any questions you have about whether or not something is a conflict, or how to maintain records, and I'm be happy to answer those questions. Does anybody have questions on that piece of the information?

Do we need more coffee?

(Laughter.)

CHIEF COUNSEL MONAHAN-CUMMINGS: Okay. Now. I get to talk again. So this one is -- let's see, what does it come up as?

(Thereupon an overhead presentation was presented as follows.)

CHIEF COUNSEL MONAHAN-CUMMINGS: Okay. This piece is going to be a discussion about -- just to give you some context about Proposition 65 and how your Committee fits within the law.

The Safe Drinking Water and Toxic Enforcement Act of 1986 was passed as a voter initiative with two-thirds of the vote in California voting in favor of it, so it was a very popular initiative.

One of the things that it was specifically designed to do is avoid the application of governmental discretion to the extent possible. So you'll find, and we've found, that there are a number of limitations on what our office can do in regard to listing chemicals. Much of it, the law is mandatory.

And -- next slide.

The part of the law that you're probably most interested in is the Proposition 65 listings. The law only focuses on carcinogens and reproductive toxicants. It doesn't apply to like neurological chemicals unless they also cause cancer or reproductive toxicity. You know, irritants or things like that that are also issues, but they are not under Prop 65.

So I also believe that there's an intentional overlap in the law that we'll kind of point out as we go along. But essentially, what we're looking at is the whole universe of chemicals and then finding those that we believe are carcinogens or reproductive toxicants.

Next slide.

So there's four listing mechanisms under the law. The one of most interest to you probably is the identification of chemicals by our Carcinogen Identification Committee or this Committee. And there's a slightly different criteria for each one of the listing processes.

For your group, the criteria is specifically established in the statute. And it is you have to find a chemical that is clearly shown by scientifically valid testing, according to generally accepted principles, to cause developmental or reproductive effects.

So you'll hear comments about that from time to time about whether or not something has been clearly shown to cause those effects.

Next slide.

Oops. I'm sorry. If we could go back for a second.

I'm sorry. I shouldn't have said go back.

I'll just a couple of things

DR. CAMPBELL: We've got an amateur on the --

CHIEF COUNSEL MONAHAN-CUMMINGS: That's okay.

DR. CAMPBELL: I don't know. That didn't work. How do I go back?

CHIEF COUNSEL MONAHAN-CUMMINGS: That's all right. Now, we're going forward.

While we're trying to get -- there we go.

So in terms of your Committee, there are a couple things to keep in mind. The definition of a chemical that is subject to Prop 65 that I just read to you is not a legal standard. Some people want to equate it with a standard that might be used in a legal proceeding, such as beyond a reasonable doubt, or clear and convincing evidence, things like that.

But you are not a jury, and you weren't -- you weren't put on this Committee for the purpose of making legal decisions. Your expertise is in the science, and

you're making scientific conclusions about chemicals, so you don't have to worry about that.

Related to that, the Committee, some years ago, adopted some guidance in how they can approach looking at chemicals and whether or not they meet the criteria in the law. You have copies of those in your materials. And one of the things you might want to look at, since they were adopted some years ago, is maybe updating that document to take into account some of the newer science and the newer approaches to looking at some of these issues.

Next slide, please.

The second way that chemicals get listed is via findings by Authoritative Bodies. And this Committee is involved in that listing process, because you identify which bodies are considered authoritative, in terms of identifying reproductive toxicants or developmental toxicants.

So currently, the Committee has identified the National Toxicology Program as to the final reports by the Center for -- Center for -- well, it's called the CERHR.

Help me.

DR. DONALD: It's the Center for Evaluation of Risks to Human Reproduction.

CHIEF COUNSEL MONAHAN-CUMMINGS: See, I'm not a scientist. I can't remember these things.

There's also NIOSH, the U.S. EPA, U.S. FDA and then the International Agency for Research on Cancer, specifically transplacental carcinogenicity.

Again, your group has the ability to take off any of these authorities, if you decide that they aren't authoritative any more, and you also have the opportunity to add any other agencies that you do think are authoritative.

And in the event you want to do that, we can schedule a meeting, get some materials together for you, and we could discuss that, but we need to do it in a public forum.

Next slide, please.

There's a couple of mandatory listing procedures that don't relate to this Committee and have different criteria. Oh, I should mention under the Authoritative Bodies listing criteria, that was actually -- the regulation was actually developed with the input of this Committee in how we would evaluate the reports, and from these different Authoritative Bodies. And again, you can help us to update those regulations, if you think those should be updated. They were adopted in the -- I think the early eighties or late eighties or early nineties.

Okay. So under the formal labeling requirements, that listing mechanism is mandatory, and it's based on

whether or not -- generally, it applies to chemicals that are identified by the package inserts or on the label as reproductive toxicants, or developmental toxicants. And most of the time that has to do with the FDA requirements for prescription drugs.

Next slide.

And the last listing mechanism, which has ended up in the last few years being the most controversial are warnings that are required -- occupational warnings under the California Labor Code and the federal OSHA requirements for identifying chemicals where employees need to be warned about their exposures. When the law was adopted, the intent was that if a person, in the course of their employment, was required to be provided a warning, then certainly the people of the State of California should also know about that, and be provided a similar warning.

This particular listing mechanism has been the subject of recent litigation, which I'll talk about when we talk about the litigation update. And there's also been some changes to the federal hazard communication standard language that also affects this listing mechanism. And we do plan to adopt regulations in the future that can clarify our approach to those, but they haven't been proposed at this time.

Next slide.

Okay. So once we use these four processes for identifying chemicals, they're added to the Prop 65 list. And currently, there's about 800 chemicals on that list that have been identified over the last 25 years or so. And the outcome of being on the list is there's a possibility that a warning is required for certain exposures to the chemicals, and there's a discharge prohibition under the law, where businesses are not allowed to discharge listed chemicals into sources of drinking water.

Next slide.

So more specifically for your Committee, as I mentioned previously, there's -- your primary duty is to determine whether a chemical has been clearly shown, through scientifically valid testing according to generally accepted principles, to cause reproductive toxicity. That's a quote directly from the statute. And it is essentially the only requirement that we have in the regulation that's related to these listings.

You also identify authoritative scientific bodies that we can use to administratively list chemicals. You assist OEHHA with a chemical prioritization process, so that we can bring the chemicals of most concern and most interest to the Committee, first.

In terms of listing chemicals, you can and should use animal or human data for listing. There was early litigation that made that clear. And you can assist us with regulations and change your guidance to the extent you believe that it needs to be changed.

Next slide.

We also ask you to review a document, such as risk assessments that we use to establish safe harbor levels. I think this Committee has already received at least one of those sets of materials for a chemical that is already listed. And we're asking you to review the risk assessment for that document as part of our regulatory process.

And then lastly, the last thing that you are required to assist us with is a somewhat obscure part of the law that requires us to -- or you to identify chemicals that have not been adequately tested for the potential to cause reproductive toxicity.

Generally, we just poll the Department of Pesticide Regulation and U.S. EPA to identify those chemicals. And then we let you know. We'll do that towards the end of this meeting.

Next slide.

In terms of your options on listing decisions today and at any other meeting, you can either find that

the chemical meets the standard for listing, you can find that the chemical doesn't meet the standard for listing, or you can defer your decision to a later meeting.

Sometimes you may need more time to think about it or you need additional information that a new study has come up and you haven't had time to look at it. So it's entirely possible and fine for you to defer your decision to another time.

All right. I've talked enough. Do you have any questions on what I covered?

No.

I'll get back to you again. But, at this time, I want to turn this over to Dr. Jim Donald. And he's going to cover some of the more specifics about the materials that you received for the meeting today.

(Thereupon an overhead presentation was presented as follows.)

DIRECTOR ALEXEEFF: Carol, I'll just interject right in here. I just thought I should just introduce the staff here. Dr. Jim Donald is on the far left there. And next to him is Dr. Lauren Zeise. And next to Dr. Zeise is Dr. Martha Sandy. And then you see over there behind the recorder that we have, Dr. Marlissa Campbell and Dr. Allegra Kim who will be later on giving the presentation for xylene.

So just so you know in case there's any question that comes up that they'll be answering.

Thank you.

Jim.

DR. DONALD: Good morning. I'll try not to reiterate too much of what Carol said, but there will be some overlap.

Could I have the next slide, please

This is an overview of the entire process beginning when we select chemicals through our prioritization process through to the decision by this Committee.

Our prioritization process is based on a focused literature review, and application of certain criteria of which change over time as we work through certain sets of chemicals.

In that process, there's opportunity for public input, both written input when we release the materials we prepared, and verbal input at a meeting where we consult with the Committee and solicit your recommendations about which chemicals should come before you.

OEHHA makes that decision. And when we have selected chemicals, we conduct, what we call, a data call-in, basically a notification that we're going to begin working on the chemical. And, at that point,

there's also an opportunity for the public to submit data or other information to us that they think should be included in the materials.

We develop the hazard identification materials, and I will discuss those in more detail in a moment, and release those for public comment at the same time as they're sent to you for review. The public has a 60-day period to prepare comments and submit them to us. And we provide those comments in their entirety to the Committee, with the expectation that the Committee will review all of the material they receive, including the public comments.

And then at the public meeting, such as today's meeting with the Committee, deliberates on and makes a decision on the listing of the chemical or a decision to defer that to a future date. There is also, as you've heard, the opportunity for additional public comment.

Next slide, please.

Okay. So the purpose of the hazard identification materials obviously is to support the Committee's deliberations. In the materials, we do cover -- provide some general information on the chemical's identity, the occurrence of the chemical in the environment and the uses to which it's put. But obviously, the main focus of the materials is on the potential for the chemical to cause male reproductive

toxicity, female reproductive toxicity, or developmental toxicity.

Next slide, please.

So the content of the material is primarily whatever information we can identify through extensive literature searches on effects of the chemicals in -- of the chemical in question in humans evaluated usually through epidemiologic studies, occasionally through experimental studies or case reports.

Experimental studies in animal models. And any other data we can identify that we think is relevant to the consideration you're going to give to the chemical. And that would certainly include mechanistic data, if they're available, data on pharmacokinetics, metabolism, histopathology, and so forth.

Next slide, please.

The format of the hazard identification materials is fairly consistent, but not rigid. They generally consist of a summary and review of the information that we have identified by OEHHA staff. In addition to that, we will generally provide you with all of the scientific publications that are included in the review to the extent that we can.

One exception to that may be situations where, for example, for pesticide studies made -- regulatory

studies may have been submitted to the Department of Pesticide Regulation, and there are certain considerations of confidentiality that do not permit us to provide you with the entire study reports.

But in circumstances like that, we will make the entire reports available to you to review, if you wish, if you come into this building to do it.

In some circumstances, there may be other reviews that have been prepared by other bodies that we think are comprehensive enough to serve your purpose. In that case, we may provide you with those reports and only summarize information that was not covered by the other body. An example of that is when we brought bisphenol A before this committee, we included the European Union risk assessment on bisphenol A as part of the materials.

Next slide.

The intent of the materials is not to tell you what decision you ought to make. But bearing in mind your charge to observe generally accepted principles, we try and provide the information in a way that is most -- we think will be most useful to you.

One issue that frequently comes up as an example is the relationship between maternal toxicity and developmental outcome. As recognized in your own guidelines, that generally requires particular attention

on a case-by-case basis.

That issue has been -- positions on that issue have been taken by a number of other bodies. So, for example, U.S. EPA has a longstanding position that adverse developmental effects that are produced only at doses that cause minimal maternal toxicity, as they define minimal maternal toxicity, are still considered to represent developmental toxicity and should not be discounted as being secondary to maternal toxicity.

Much more recently, the concisely named United Nations Economic Commission for Europe Globally Harmonized System of Classification and Labeling of Chemicals has stated developmental effects which occur even in the presence of maternal toxicity are considered to be evidence of developmental toxicity, unless it can be unequivocally demonstrated on a case-by-case basis that the developmental effects are secondary to maternal toxicity.

So again, we do not try an influence how you interpret the data, but we do try to present the data in a way we think will make it most easy for you to interpret.

Next slide, please.

So then to briefly summarize, as I've said, the purpose of the hazard identification materials is to aid you in determining whether a chemical has been -- and I'm

sure you're already tired of hearing this phrase -- clearly shown, through scientifically valid testing according to generally accepted principles, to cause reproductive toxicity.

So to that end, you receive hazard identification materials that contain information compiled and prepared by OEHHA, and all public comments submitted on that information for you to -- and we believe you should give those due consideration.

And, as Carol already mentioned, if there's information that you believe has not been provided to you, pertinent information, or there is some further clarification or summation of information that you think would be beneficial, then OEHHA staff can prepare -- obtain or prepare that for you.

Next slide, please.

And, at this point, I'd be happy to take any questions you have.

DIRECTOR ALEXEEFF: This is George Alexeeff.

I'll just add a little bit more. So the actual materials that we prepared for today's meeting on xylene, you know, that's one example of materials that we put together. But, you know, if you felt -- or if you feel that other types of information would be helpful for us to provide to you in your process, like on a future chemical,

let us know, and we can prepare things that way.

So the whole point is for us to get you the information that you need. And we're trying to -- just to be clear, even when we prepare a document, it may not be similar to other documents you've reviewed for other committees, like U.S. EPA where the Committee -- where the document you review actually has a conclusion and says, you know, this is what we're concluding, and this is the level, and this is the -- instead, we're just trying to gather the materials for you to draw a conclusion, if that makes sense.

And as Dr. Donald mentioned, when you think of -- when we think of the materials, we think of the information that we've compiled, the information that the public has presented as well, and anything else that might come up, so it's the whole body of evidence there.

CHAIRPERSON GOLD: Okay. Thank you for those presentations. At this point in the agenda, we have time allotted for public comments on the foregoing, on what we've already discussed, so I don't know we've received notice of --

We have. Okay.

So we have one person who wishes to speak, Dr. Sarah Janssen. Maybe you could introduce yourself.

DR. JANSSEN: Good morning. My name is Dr. Sarah

Janssen. I'm a reproductive biologist by training, and also a physician boarded in occupational and environmental medicine. My comments are made on behalf of the Natural Resources Defense Council, NRDC, where I serve as a senior scientist in the Health and Environment Program.

First of all, I want to congratulate all of you on your appointments and wish you the best during the next year. I'm really pleased to see all of you here today. And actually, I'm -- it's a little bit nerdy, but I'm kind of excited about what, you know, you might be able to accomplish in the next year. I think there's a really deep and diverse expertise here on the Committee. And I hope that you will use your expertise to do something that was mentioned early in the orientation, which is to update the guidance on how the criteria are used for the listing process.

That guidance is probably approaching 20 years old, and many of you are in the laboratory or doing studies on humans that could probably benefit updating that document. Specifically, there's been, in my time watching the DART proceedings, some confusion, and a little bit of frustration over the policy of not including postnatal developmental outcomes as part of listing decisions. And I think that is not supported by our current understanding of science. It's probably not

supported legally in the statute. And so I think it would be worth this Committee revisiting that. So I would encourage you to do that.

And secondly, on the issue of time, that was an issue that NRDC and other stakeholders brought up historically, because our organizations have been at a disadvantage when public comment time periods were being done.

Where, you know, we saw that we were limited to three to five minutes, where other organizations were ceding time to one another and giving 20 to 30 minute presentations. So I understand the request for today, and, you know, I appreciate your commitment to transparency. I just would encourage you guys to revisit this and think about, you know, how we can make this equal for both sides who have a stake in the decisions that this Committee is making.

Thanks for your attention.

CHAIRPERSON GOLD: Thank you for your comments.

DIRECTOR ALEXEEFF: I just wanted to clarify, and hopefully this will not make it more confusing, because Dr. Sarah Janssen mentioned this issue of postnatal outcomes -- I think that's the term that you used.

And so just to clarify that, clearly, if -- I think the intent of the proposition was to consider

outcomes in humans. So the idea is, you know, first, the term birth defects and such in the discussion of the proposition on the ballot and such.

So the idea is to look at outcomes in humans, but, of course, animal evidence is sufficient for that. You don't need human evidence.

But in terms of postnatal outcomes, as Dr. Janssen mentioned, actually, if -- clearly, if there's a prenatal exposure and there is a postnatal outcome, that is clearly within the jurisdiction of this Committee, because the actual expression of the exposure could occur postnatally easily.

The question becomes more complicated, I think, when different species are exposed at different times of their lifecycle, either prenatally or neonatally, and the question is how does that infer upon the human experience and such? I think that's something that possibly could be discussed by the Committee at some point.

CHAIRPERSON GOLD: Thank you.

Yes, Dr. Donald.

DR. DONALD: If I could perhaps expand on that a little bit.

I'm not sure if the Committee was aware that only prenatal exposure is considered relevant to Proposition 65. That's an interpretation of the intent of the

statute. The statute refers only to reproductive toxicity. But in practice, we present information to you that pertains to exposures that are analogous to human prenatal exposures, and we consider information on overlapping pre- and postnatal exposure relevant to the proposition, to the extent that effects manifested at any point in the lifespan of the animal can be attributed entirely or predominantly to exposures during the prenatal period.

As George also mentioned, we also consider -- take into account whether postnatal development in an animal model, such as the rat, that early postnatal exposure that's analogous to late prenatal exposure in humans is also considered relevant to the intent of the proposition.

Are there any questions on that?

COMMITTEE MEMBER LUDERER: Yeah. I do have a question. So a study that did, for example, only neonatal exposure in the rodent model would be potentially considered to be applicable, or we would not be able to consider that? I'm a little unclear.

DR. DONALD: That's rather case by case. For example, if very early postnatal exposure in a rodent model caused a neurobehavioral effect that was what we considered the period of exposure analogous to post --

early -- excuse me, late prenatal exposure or the same stage of development of the human nervous system that occurred during late prenatal exposure, we would certainly consider that a relevant effect under Prop 65.

COMMITTEE MEMBER LUDERER: One more clarification. So other -- so from a developmental biology standpoint, we know that many organ systems continue to develop after birth in experimental animals, as well as humans, you know -- and that there are critical windows of exposure for some things. For example, I think of mammary cancer and peripubal exposures can be very important, but those would not be?

DR. DONALD: Well, again, it's very much case by case. And, you know, as the State's qualified expert, you get to make that call. But, yes, we -- our position would be that you should use all of the relevant information about comparable periods of exposure in determining whether or not an effect that was caused by exposure to the chemical could be attributed to a period of exposure that would occur prenatally in humans.

COMMITTEE MEMBER LUDERER: Thank you.

CHAIRPERSON GOLD: Okay. Thank you.

So the next item on the agenda is this staff presentation of xylene to consider its reproductive toxicity.

(Thereupon an overhead presentation was presented as follows.)

DR. DONALD: Okay. So just to briefly introduce Dr. Marlissa Campbell is going to make a summary presentation on the evidence for developmental and reproductive toxicity of xylene in animal models. Then Dr. Allegra Kim is going to present the human data and a very brief synthesis of those two lines of data.

DR. CAMPBELL: Thank you. Good morning. Am I live here?

Let me see if I can work all the equipment at the same time.

Xylene is a colorless liquid that occurs naturally in petroleum. It consists of a benzene ring with two attached methyl groups, which can vary in position to form the ortho-, meta-, or para-isomers. The mixture of isomers is commonly referred to as technical or mixed xylene or as xylol or just as unspecified as xylene.

Commercially available xylene typically contains about 40 to 65 percent m-xylene, and up to 20 percent each of o-xylene and p-xylene.

Xylene is relatively insoluble in water, with solubility ranging from 100 to 200 ppm at 25 degrees centigrade, depending on the exact isomer or the mixture, which is why although exposure through drinking water is

possible, there are no drinking water toxicity studies in animals.

The general population is expected to be exposed primarily to mixed xylenes rather than to any of the individual isomers. Exposure can occur via inhalation of indoor air, particularly in the workplace, inhalation of automobile exhaust, cigarette smoking, inhalation or dermal absorption of xylene-containing solvents or by ingestion of contaminated drinking water. Xylene and its metabolites have been detected in samples of human urine, blood, and expired air.

Although xylene can enter the environment from natural processes, such as forest fires or petroleum seeps, most xylene in the atmosphere originates from human activity.

Xylene is well absorbed by both the oral and inhalation routes of exposure. Absorption efficiencies have been estimated at 90 percent for the oral route and 60 to 65 percent for xylene in each of its isomers by inhalation. Efficiency of absorption by the dermal route depends upon exposure conditions, but is generally estimated at less than one percent.

Experiments with oral administration of radiolabeled m-xylene to rats have indicated that it's rapidly absorbed with peak plasma concentrations reached

within about 20 minutes.

The mean absorption half-time in female rats was significantly shorter than for males. There was also a difference in elimination half-time between female and male rats, suggesting a gender-dependent difference in xylene pharmacokinetics for these animals.

Whole-animal autoradiography of pregnant mice following inhalation of xylene also showed rapid absorption distribution and elimination from tissues other than fat.

Volatile radioactivity was identified in the placenta and the fetuses almost immediately, and up to one hour post-inhalation of xylene. Fetal levels were much lower than those found in the maternal tissues, but it did get into them.

Just a quick review of non-reproductive and developmental effects of xylene. Acute exposure to xylene has neurological effects similar to those seen with other organic solvents. Roughly, there's an odor threshold of about one ppm in air and a taste threshold of about one ppm in water.

In a range of about 1 to 100 ppm, people report nausea, headache, irritation of mucous membranes. At higher concentrations than 100 ppm, start getting reports of sedation, disorientation, and ataxia.

At concentrations of several thousand ppm, you start seeing severe lung irritation leading to pulmonary inflammation, edema, and hemorrhage. And deaths that occur are attributed to respiratory depression rather than to lung damage, per se.

Technical xylene and each of the three isomers have essentially the same effects, and experimental animal shows similar effects to humans and roughly a similar range of concentrations.

Repeated dose studies in animals have shown permanent hearing loss with short-term inhalation of a high concentration or longer-term inhalation of a somewhat lower concentration.

Impairment. There's also impairment on neurobehavioral tests, such as rotarod performance, spontaneous motor activity and radial maze performance. And these types of effects have been seen in several studies of rats exposed to 100 ppm m-xylene, in particular.

Although, not seen in all studies, decreased body weight appears to be a general effect of repeat-exposure studies, with effects on body weight and rats and mice observed following oral doses of xylene in the range of 500 to 800 milligrams per kilogram per day.

Data on cancer have not been considered

sufficient by OEHHA, U.S. EPA, or IARC in order to determine the potential carcinogenicity of xylene.

Looking first at male reproductive toxicity. There were only three studies that provided information relevant to male reproductive toxicity following xylene exposure by inhalation. Only one of these studies reported male reproductive effects with xylene exposures, specifically reduced weights of the testis accessory male reproductive organs, as well as decreased epididymal sperm counts. This particular study also reported lower plasma testosterone levels, and lower prostate acid phosphatase activity with treatment.

Confidence in these data, however, is severely limited by methodological issues, such as the lack of quantitative exposure information. They just put the animals in the chamber and pumped in xylene until they became ataxic, and then did their tests, and never quantified that.

The neurological effect does indicate that the animals were exposed to a biologically significant concentration, but we don't know what it was.

There's one study that looked at the male reproductive effects of xylene in rats treated by the intraperitoneal injection. These -- the xylene-exposed animals that were also subjected to housing at

temperatures between 24 and 30 degrees centigrade showed an increase in the frequency of abnormal sperm, which was not seen in xylene-treated animals that were kept at a temperature between 20 and 24 degrees centigrade.

Moving on to female reproductive toxicity. Just to start, there was only one reproductive toxicity study of xylene -- a full reproductive toxicity study that was conducted in animals, and that was a one-generation study that was conducted by the inhalation route in rats. The male and female rats were exposed to xylene for 131 days prior to mating, and then throughout the mating period. The pregnant females were exposed throughout gestation and lactation. And this was the only study that evaluated endpoints of female reproductive toxicity, such as mating index and fertility.

No studies evaluated the effects of xylene on the estrous cycle.

Another study exposed pregnant rats on gestation day nine or gestation days nine and ten to 692 ppm xylene, and then looked at ovarian and uterine blood flow as well as secretion and peripheral blood levels of progesterone and 17 beta-estradiol.

All the remaining information on the potential female reproductive toxicity of xylene comes from standard developmental toxicity studies. While most of these

studies used rats as their test species, one included experiments with mice and rabbits, as well as comparing the effects of individual xylene isomers with technical xylene. These particular studies -- these developmental toxicity studies are included here because they collected data on measures such as implantation frequency, resorption frequencies and numbers of live and dead fetuses or newborns, which could result from either toxicity to the female reproductive toxicity -- to the female reproductive system or to the developing organism itself. Since -- in the absence of information that indicates it's either one or the other, then we considered these outcomes as evidence relevant to both female and to developmental toxicity.

And just to look at the general results. Out of all the 13 animal studies that provided information relevant to female reproductive toxicity, very few showed any evidence of xylene-induced female reproductive toxicity. That single one generation reproductive toxicity study found no effects of xylene on pregnancy or fertility indices.

The study, which measured hormone levels, found significant effects on peripheral blood levels of progesterone and 17 beta-estradiol secretion following 48 hours of exposure. There were no effects on ovarian or

uterine blood flow.

The one developmental toxicity study that included experiments with rats, rabbits, and mice and found evidence of increased embryo-fetal mortality in rats -- rabbits and rats with inhalation exposure to technical xylene, in addition to one or more of its isomers.

Mice did -- oh, What?

Sorry. I'm trying to go back.

Is there one missing?

DR. KIM: Can you go back one more?

DR. CAMPBELL: No. This is the right one. I'm still talking about females. Okay. Never mind. Sorry for the confusion.

Where was I?

Okay. The mice did not show these effects. An additional rat study also reported increased post-implantation loss and resorbed fetuses.

And a third study, which used mice and -- with exposure to xylene via the oral gavage route of exposure also reported increased resorption frequency with oral exposure to xylene.

Interpretation of the findings from these studies is complicated in some, but not every case, by co-occurring maternal mortality that was in excess of the

10 percent suggested by the U.S. EPA risk assessment guidelines as rendering developmental effects difficult to evaluate.

Okay. Now moving on to developmental toxicity in animals. Fifteen studies were identified as having information on the developmental toxicity of technical or mixed xylene or its individual isomers in animals. Most of these were conducted by the inhalation route of exposure in rats, but there are also data on mice and rabbits, as well as one study -- one study using the oral route and another using the dermal route of exposure.

Because there are overlapping endpoints between developmental toxicity and female reproductive toxicity, many of these studies have information relevant to both. And we've already talked about them a little bit.

A few additional studies did not provide data on endpoints relevant to female reproductive toxicity. So they were not included in that section, but we will see them here.

The one-generation study also appears, because it has relevant information to the effects of gestational exposure on development, such as pup viability, viability at birth and birth weight. Other studies evaluated term fetuses are newborn pups following exposures, either throughout gestation or targeted specifically to the

organic genesis stage of prenatal development.

Just for ease of presentation, we tend to divide the endpoints of developmental toxicity into four major manifestations following what's described in the U.S. EPA risk assessment guidelines for developmental toxicity. And that would be death at the developing organism, which as I've said before also has implications for female reproductive toxicity, alterations in growth, structural abnormality, and functional deficits. But it is important to remember that these manifestations are not necessarily independent of one another.

With specific regards to xylene, three of 15 studies reported significant effects of xylene on embryo fetal viability. The strongest effects were seen in the study that reported experiments conducted in three species with technical xylene or individual isomers.

As I mentioned before, rabbits showed significant embryo fetal mortality with various forms of xylene at concentrations of 115 and 231 ppm. Interpretation of the data for technical and p-xylene at the higher concentration is complicated by excessive maternal mortality. However, offspring viability was also decreased with p- or m-xylene at the lower concentration of 115 ppm, which was not in association with excessive maternal mortality.

In the rat experiment conducted as part of that same study, the frequency of dead or resorbed fetuses was increased at the high concentration of 784 ppm with only one out of the 20 dams dying at that concentration. No effects on viability were found in mice.

An additional rat inhalation study looked at individual xylene isomers and found significant decreases in embryo fetal viability at 692 ppm for all three isomers with excessive maternal mortally reported only for m-xylene.

A third study, which exposed mice to xylene via gavage, reported increase resorption frequency with oral exposure at a dose of 3.1 milligrams per kilogram per day xylene. And this level was also associated with over 30 percent maternal mortality.

This table just shows a compilation of the data pertaining to growth endpoints, which in this case is specifically fetal or birth weights. Four of the studies that had data on weights found no effects on fetal or birth weight, even a the highest concentration or dose used in the study. Seven other studies did show effects on weight with some combinations of dose, isomer, species, and/or sex of the offspring.

The first one noticed the Hass and Jakobsen 1993 found that a subset of the litters that went to term for

treated male pups were actually significantly increased over controls. The other experiments that they did, they found no effects.

The Biodynamics 1983 study found a significant decrease in fetal weights with exposure to 500 ppm xylene, but that was only for female rat fetuses and not in every experiment. It was only in the experiments in which both male and female parents were treated, as opposed to some of the other experiments in which only the dam was treated at the same concentration, and that part was negative.

Looking at the Saillenfait 2003 found the lowest effective concentration was 500 ppm of o-xylene, but technical xylene as well as m- and p-xylene were also associated with reduced fetal weights at the higher concentration they used of 1000 ppm.

Ungvary et al. 1980 also tested all three isomers and found reduced fetal weights with o-xylene at 346 ppm and for m- and p-xylene at the higher concentration of 692 ppm.

Ungvary and Tatrai found technical xylene at 115 ppm was associated with a significant decrease in the mean weight of female rabbit fetuses. None of the individual xylene isomers affected fetal weights in either mice or rabbits.

The only oral study was Marks et al. 1982. And

that one found that doses of 2.06 milligrams per kilogram per day and higher were associated with decreased fetal weights in mice.

None of the studies -- the inhalation studies of xylene or its isomers reported significant increases in the frequency of external or internal soft tissue malformations or anomalies. So all we have to represent this category would be skeletal anomalies, primarily -- well, it's not always really clear the terminology that they use, but a lot of it is skeletal retardation or failure of ossification. So point being, it's not unrelated to growth.

Of the studies which did evaluate fetuses for skeletal anomalies, most of them did report effects under -- at least under some conditions.

And just to move on to some of the specifics. The Saillenfait et al. 2003 reported increased skeletal variations at 2,000 ppm of o-xylene, p-xylene or m-xylene, but not with the technical mixture.

Hass and Jakobsen 1993 was the only study to report a specific effect, and that was delayed ossification of the os maxilliare at the test concentration of 200 ppm xylene.

Ungvary and Tatrai found increased frequency of skeletal retardation in rats at concentrations of 58 ppm

and higher with the increased minor anomalies, specifically wavy ribs at 784 ppm. This study also looked at mice, which showed evidence of skeletal retardation at 231 ppm. The rabbits that were also evaluated in this study showed no skeletal effects of treatment.

Ungvary et al. observed skeletal retardation in rats with exposure to p-xylene at 35 ppm. The higher concentration of 692 ppm p-xylene was also associated with findings of extra ribs. This study also looked at o-xylene and found skeletal retardation at 692 ppm.

The one oral mouse study, that was the Marks et al. 1982 found no skeletal effects, but did report a treatment-related increase in the combined malformation frequency. So this would be a combination of skeletal soft tissue anomalies at the lowest effective dose of 2.06 milligrams per kilogram per day, and with an apparent dose-response relationship. The most common individual findings that they reported were cleft palate bilateral open eye, exencephaly, and fused or missing vertebral arches and ribs.

Four animal studies looked specifically at developmental neurotoxicity following prenatal exposure to xylene. Three of these studies came from the same group, that would be the Hass and co-workers '93, '95, and 1997. And they exposed pregnant rats to technical xylene by

inhalation at concentrations of zero and either 200 or 500 ppm for six hours a day on each of gestation days four through 20 or 7 through 20 depending on the specific study.

The fourth study, the Rosen et al. 1986 used p-xylene and exposed pregnant rats to concentrations of zero, 807, or 1,615 ppm xylene for six hours a day on each of gestation days seven through 16.

One of the Hass studies found reduced rotarod times for female rat pups prenatally exposed to technical xylene at 200 ppm. For males, the rotarod time was significantly reduced only on the second of three test days. The authors concluded that the poor rotarod performance could be an indicator of impaired motor ability in the xylene-treated animals.

Yet, another study by the same group found no impairment -- no significant impairment of rotarod performance with exposure to 500 ppm, but they did find a significant delay in acquisition of the air-righting reflex. Other developmental landmarks were unaffected which led them to suggest that there was some kind of specific damage to the neural processes required for air righting, such as vestibular function rather than a more generalized developmental delay.

No effects of treatment were seen on an open

field test, but they did see changes in the Morris Water Maze test. In particular, the female -- the exposed female offspring showed a significant increase in swimming time, but no difference in swimming speed relative to controls.

A follow-up study using the Morris Water Maze performance also reported increased latencies in exposed female offspring when tested at the postnatal ages of 16, 28, and 55 weeks.

Again, they thought this latency broke out as being due to increased swim path lengths, suggesting a lag in learning the maze rather than problems with motor coordination of swimming.

The final behavioral study, which used only p-xylene, reported no effects of exposure on locomotor activity or the acoustic startle response test.

And that's the end of the animal data. I don't know if we want to take questions now or move on to the human data and do questions at the end.

CHAIRPERSON GOLD: If the panel has any questions of clarification at this time or the Committee.

Hearing or seeing none, why don't we go on then to Dr. Kim.

DR. CAMPBELL: I have to set up her slides.

(Thereupon an overhead presentation was

presented as follows.)

DR. KIM: Okay. Thanks. Good morning.

I'm going to be talking about the epidemiological data. So I will start as Marla -- as Dr. Campbell did with the male reproductive toxicity.

There were three epidemiologic studies that looked at male reproductive toxicity. Two studies examined associations between male reproductive outcomes and exposures to xylene and other organic solvents. I will first briefly -- very briefly outline these, plus another study of paternal exposure in relation to pregnancy outcome and then summarize the results.

One study was a cross-sectional study conducted in China by Xiao and colleagues. Xiao et al. measured benzene, toluene, and xylene or BTX in blood and semen. Semen was also analyzed for outcomes which were semen parameters and indicators of effects accessory sex gland function.

A retrospective cohort study was conducted in Finland by Sallmén et al. The authors were interested in whether paternal exposure to xylene and five other organic solvents, styrene, toluene, xylene -- sorry, not xylene, but tetrachloroethylene, trichloroethylene, and 1,1,1-trichloroethane is associated with delayed conception, a measure of decreased fecundability as

indicated by time to pregnancy, or TTP, among their wives.

In this study, fecundability is the probability of clinically recognized pregnancy during a menstrual cycle.

The cohort for the study comprised cases and controls from a previous study of birth outcomes. Each man's occupational exposure to solvents the year the pregnancy was assessed based on self-reported occupation, job description, and solvent or other chemical usage and biomonitoring data from the previous study.

TTP, or time to pregnancy, and related information were collected by questionnaires mailed to the wives eight to 18 years after the pregnancies ended. Data were analyzed using discrete proportional hazards regression with fecundability density ratio, or FDR, as the outcome. The FDR is analogous to an incidence density ratio and is defined as the fecundability of the exposed divided by the fecundability of the unexposed. An FDR less than one indicates reduced probability of conception

In addition to the two studies of male-specific outcomes, a third study, this one by Taskinen et al., which is the same group of authors in Finland, that authored the last study I'd outlined, the study examined paternal exposure to xylene and potential effects on pregnancy outcomes. The study by Sallmén et al. drew its

cohort from this nested case-control study Taskinen et al.

The authors of this study conducted this study to investigate the effects of paternal exposure to xylene and five other organic solvents, which I've already described, a pregnancy outcomes of wives of workers who had been biomonitored for solvent exposure.

Again, exposure classification was based mainly on job descriptions and reported solvent use in the 80 days preceding the pregnancy. Questionnaires were mailed to both spouses to obtain detailed data on occupational exposures during the year of conception, earlier employment, chronic diseases, smoking, and alcohol consumption. Wives were also asked for information on pregnancy history, heavily lifting, and febrile disease.

A case was either a woman who had a spontaneous abortion treated in a hospital or outpatient clinic, or a child with a malformation registered in the Finnish register of congenital malformations. Controls were age-matched to cases.

Here, I'll highlight the relevant findings of the three studies I've just outlined. For all of these studies, the authors reported that those exposed to xylene were usually exposed to other solvents as well, making it difficult to distinguish effects of xylene from those of other solvents.

In the Xiao study, the Sample included 24 exposed men working in shoemaking, spray painting, or paint manufacturing, and 37 managers who were considered unexposed. Blood xylene was statistically significantly associated with decreased seminal gamma-glutamyltransferase activity, which the author said was an indicator of poorer prostate function.

They did report statistics, but it wasn't really clear what the statistics meant. It's worth noting that semen benzene was also associated with gamma-GT activity. And the analysis does not appear to adjust for exposure to other solvents such as benzene. I'd like to also note that benzene is listed on the Proposition 65 list for development toxicity and male reproductive toxicity.

The 1998 study of fecundability by Sallmén et al. included 282 couples with 70 men in the low and intermediate xylene exposure category and 51 in the high and frequent exposure category. The FDRs for xylene were 0.75 with a 95 percent confidence interval of 0.52 to 1.09 for low or intermediate exposure, and 0.91 with a confidence interval of 0.61 to 1.36 for higher or frequent exposure. And as you can see, they were not statistically significant.

These estimates were adjusted for menstrual cycle length and regularity, older age at menarche, frequency of

intercourse, maternal age, maternal exposure to organic solvents and missing information.

In the third study on the slide, the Taskinen 1989 study of spontaneous abortion and malformations, there were 120 spontaneous abortion cases and 251 controls. The adjusted odds ratio for spontaneous abortion and likely paternal exposure to xylene was 1.6 with confidence interval of 0.8 to 3.2 when likely paternal exposure to other organic solvents and dusts, maternal exposure to solvents, maternal heavy lifting, and history of previous spontaneous abortion were taken into consideration.

In the malformations part of the Taskinen study, there were 25 cases and 96 controls. And the unadjusted odds ratio for xylene and malformations was 1.6 and also was not statistically significant. No adjusted analyses were reported for malformations in this paper.

Next.

I will move on to female reproductive toxicity. Here, I just want to reiterate that outcomes such as spontaneous abortion may be mediated through toxicity to the reproductive system of the mother or they may be manifestations of direct toxicity to the conceptus only. That is, the effect may be directly on the female reproductive system, on the conceptus, or both.

I will describe the studies that looked at spontaneous abortion later under developmental toxicity.

And so for here I'll just move on to the two studies with female reproductive outcomes.

A retrospective study of time to pregnancy and maternal solvent exposure was conducted by Sallmén and colleagues in Finland. Similar to the male repro study by the same group, this cohort was made up of cases and controls from earlier studies of spontaneous abortion and congenital malformations. Exposure classification was based on work description and reported solvent use.

Information about time to pregnancy, contraceptive use, menstrual cycles, lifestyle, and other potentially related factors was collected from the subjects by mailed questionnaires.

Sallmén et al. used discrete proportional hazards regression to estimate the fecundability density ratios of clinically recognized pregnancies for exposed versus unexposed women, which is the same as in 1998 study of time to pregnancy and maternal -- paternal exposure, excuse me.

Another study in China conducted by Cho and colleagues examined petrochemical industry exposures to benzene, toluene, styrene, and xylene based on classification of workshops and women's self-reports of

chemicals handled and the possible relationship with menstrual patterns.

Okay. This slide highlights the findings of the two female reproductive studies. Again, for both studies, most women exposed to xylene were also exposed to other solvents.

First Sallmén et al. Of their cohort of 197 women, 31 were assessed as having had low exposure, and 10 as having high exposure. The fecundability density ratios for xylene were 1.41 with a confidence interval of 0.91 to 2.2 for low exposure, and 0.93 for high exposure compared to no xylene exposure, and adjusted for other solvents, recent contraceptive use, and age at menarche.

In the Cho et al. study the odds ratio for oligomenorrhea and xylene was 1.63 with a confidence interval of 1.04 to 2.53 adjusted for age, body mass index, enrollment cohort, passive smoking, and exposure to chemicals other than aromatic solvents. Oligomenorrhea was defined as an average cycle length greater than 35 days -- that's okay. In this study, no women were exposed to xylene alone.

So now, I'll move on to developmental toxicity, and here are the outcomes that were studied were congenital malformations, spontaneous abortion, birth weight, and there was one study on cord blood T-cells. As

we've said, some of these outcomes could indicate female reproductive toxicity.

So I'll start with congenital malformations. The recent case-control study by Lupo et al. examined the association between maternal exposure to environmental BTEX, that is benzene, toluene, ethylbenzene, and xylene, and spina bifida and anencephaly in offspring. Benzene was a primary pollutant of interest in this study.

Data on birth outcomes were obtained from the Texas Birth Defects Registry. Cases were live births stillbirths, and electively terminated fetuses with spina bifida, or anencephaly. Closed neural tube defects and chromosomal anomalies or syndromes were excluded.

Controls were a stratified random cycle -- excuse me, sample of unaffected live births selected four to a case and frequency matched by year. This was the only xylene study to focus on a single class of defects. The other malformation studies included all reported malformations.

There's a nested case-control study of paternal exposure and birth outcomes by Taskinen et al., which I've already briefly described in the context of male reproductive toxicity.

Next slide.

The same researchers, Taskinen et al. conducted

another case-control study of the possible risks of maternal laboratory work on birth outcomes, including malformations, spontaneous abortion, and reduced birth weight, so you'll be hearing about this study again.

Exposure assessment was based on job descriptions and reported solvent use in those jobs. Malformations were ascertained from the Finnish register of congenital malformations. The women provided information on occupational exposures, potential confounders, and child's sex and birth weight by mailed questionnaire. For each malformation case four controls were selected from women who had no spontaneous abortion and had given birth to a child with no registered malformation, and matched to cases by age and year.

Axelsson et al. studied the relationship between laboratory work, particularly exposure to solvents and pregnancy outcomes among a cohort of female laboratory employees at a University in Sweden. Information on occupational exposure to solvents, pregnancy outcomes, and potential confounders was collected by mailed questionnaires. Information on malformations was also obtained from birth and malformation registries and hospital data.

The prevalence of malformations among births to women exposed to solvents was similar to that among

unexposed women. And although xylene was specifically named in the questionnaire, no specific results for xylene were reported. The study is therefore not included on the results table that follows.

Okay. Again, exposures to multiple solvents was highlighted by the authors of all three of these studies. The study of neural tube defects by Lupo et al. included 533 spina bifida cases, and 303 anencephaly cases, and 3,695 controls. Estimates of annual ambient BTEX concentrations for each mother's census tract were obtained from a U.S. EPA modeling system, ASPEN, which uses emissions data, meteorological conditions, and other information. Five exposure levels were compared for each type of neural tube defect.

After adjusting for year of birth, maternal race and ethnicity, and parity, xylene exposure at each of the second through fifth exposure levels compared to the lowest, or first, was consistently associated with non-significant increases in risk for both spina bifida and anencephaly.

However, due to very highly correlated levels of BTEX, multiple pollutant models were not assessed. The only significant associations noted -- the only statistically significant associations noted were for benzene and spina bifida.

The Taskinen 1989 study included 25 malformation cases and 96 controls. The unadjusted odds ratio for paternal xylene exposure and malformations was 1.6, but with a confidence ratio of -- confidence interval of 0.4 to 5.7 was not statistically significant. No adjusted analyses were reported for malformations in this study.

The 1994 paper reported by Taskinen at al. included 36 malformation cases and 105 controls, and reported no associations between maternal occupational exposures to xylene and malformations.

Moving on to spontaneous abortion. The next four studies -- there were six studies, but the next four studies, including the three on this slide, have already been described in the context of male reproductive toxicity and/or malformations.

So, first, is the Taskinen at al. 1989 study, which examined paternal exposure. Then the remaining studies of spontaneous abortion examined maternal exposures. The Taskinen 1994 case-control study and Axelsson cohort study were both described in the context of malformations.

The next three studies I'll describe focused on spontaneous abortion specifically.

So, first, I have Lindbohm et al. This case-control study is another study by the same

researchers in Finland, and it examined the effects of maternal occupational exposure to different types of solvents on risk of spontaneous abortion. Data on women who are biomonitored from xylene and five other organic solvents were linked with hospital, clinic, and registry data to identify pregnancies and spontaneous abortions.

A case was a women who had a spontaneous abortion. For each case, the authors tried to select three age-matched controls from women who had neither a spontaneous abortion or a child with a malformation.

Detailed data on first trimester occupational exposure and other potential risk factors for spontaneous abortion were collected via mailed questionnaires. Likelihood and level of exposure was based mainly on each woman's occupation, work description, and reported use of solvents, and biological exposure measurements when available, which was not common.

A case control study in Santa Clara County by Windham et al. examined the risks of spontaneous abortion associated with solvent exposure defined on different levels, including occupational and specific solvent exposure. Cases were women who had spontaneous abortion by 20 weeks of gestation, for which a pathology specimen was submitted to one of 11 hospital laboratories in Santa Clara county.

Controls were live births frequency matched to cases, 2 to 1. Respondents were asked for detailed information about jobs and occupational exposures to 10 specific solvents, solvent-containing products, and other solvents and degreasers during the first trimester. Women were also asked about non-occupational use of eight solvent-containing products and any other solvent.

Swan et al. conducted a retrospective cohort study to examine occupational exposures in semiconductor manufacturing. The authors used company records to identify 506 current and 385 former female employees who became pregnant while working at one of 14 semiconductor companies. Job activities at conception and first trimester exposures to specific agents were used to classify exposures. Exposure scores were grouped into four levels ranging from zero for no exposure to three for highest exposure.

So the Taskinen study -- in the Taskinen study the odds ratios and confidence interval for spontaneous abortion and likely paternal exposure adjusted for potential paternal exposure to xylene, likely paternal exposure to other organic solvents and dusts, maternal exposures to solvents, maternal heavy lifting, and history of SAB, or spontaneous abortion, were all greater than one, but not statistically significant.

For lower rare exposure, the odds ratio was 1.2. There were seven cases and 13 referents. For intermediate exposure, the odds ratio was 1.7, and there were 11 cases and 19 referents or controls. And for high or frequent exposure, the odds ratio was 1.6 with 19 cases and 29 referents or controls.

In the Taskinen et al. study from 1994, there were 206 cases of spontaneous abortion and 329 controls. And they examined maternal exposure to xylene and laboratory work. First trimester exposure greater than three days per week or more frequent than three days per week was associated with an odds ratio of 3.1, and a 95 percent confidence interval of 1.3 to 7.5 adjusted for employment, smoking, alcohol use, parity, previous miscarriages, failed birth control, and fever during pregnancy, but it was not adjusted for other solvents or exposure to other solvents.

The Axelsson cohort included 556 pregnancies, including 194 exposed. And there were 20 spontaneous abortions. The authors found no association between maternal exposure to xylene in laboratory work and spontaneous abortion.

In the Lindbohm et al. study, they had 73 spontaneous abortion cases and 167 controls. Of these, five cases and seven controls were exposed to xylene. The

odds ratio for first trimester occupational exposure to xylene and the spontaneous abortion was 1.3 adjusted for previous spontaneous abortion, parity, smoking, use of alcohol, and exposure to other solvents, and it was not statistically significant.

Next slide.

In the Windham study, there were 626 cases and 1,300 matched controls, but few subjects, that is nine cases and 12 controls, actually reported exposure to xylene. The unadjusted odds ratio for xylene and spontaneous abortion was 1.6, and was not statistically significant. There were no adjusted odds ratios for xylene reported in the study.

In the Swan semiconductor study, xylene was one of seven agents identified as strongly associated with spontaneous abortion. Compared with unexposed workers, women at the second and third exposure levels were at increased risk of spontaneous abortion with relative risks of 2.31 with a confidence interval of 1.39 to 3.58 for all women, adjusted for smoking, age, education, income, ethnicity, pregnancy history, pregnancy start year, and stress. Relative risks were somewhat higher for women working in masking, including photolithography and etching and lower for women working with dopants and thin film.

However, due to simultaneous exposures to xylene,

n-butyl acetate, and ethylene-based glycol ethers, which are also associated with spontaneous abortion, Swan and colleagues state that the associations observed for xylene may reflect EGE exposure.

Okay. Moving on to birth weight. For birth weight there were three epidemiologic studies, two of which I've already outlined. There was a Taskinen 1994 Finnish occupational case control study, which also examined spontaneous and malformation. And there was also the Axelsson 1984 study of female laboratory workers in Sweden, which also examined spontaneous abortion and malformations.

Xylene was specifically named in the questionnaire, but again no specific results for xylene and birth weight were reported, so the study is not included on the results table that follows.

Ghosh et al. used air pollution data from the California Air Resources Board, or CARB, for Los Angeles County in 1995 to 2006 to study the effects of BTEX in air pollution on term low birth weight. Exposure was assessed throughout the pregnancies. Only the 27 percent of women who resided less than five miles from at least one of four CARB air toxic stations -- monitoring stations were included in the study. This was still more than 400,000 women.

Next.

So here I'll highlight the outcomes. Taskinen reported a significant association between increased birth weight and exposure to xylene at most two days a week. However, they did not report data or statistics for this finding.

Ghosh et al. found that term low birth weight associated with increase in third trimester exposure to m- and p-xylenes and o-xylene. The odds ratio for third trimester exposure to m- and p-xylene was 1.03 with a 95 percent confidence interval of 1.01 to 1.06. The odds ratio for o-xylene was also 1.03, and the confidence interval was 1.01 to 1.05 adjusted for maternal age, race, and ethnicity, education, parity, gestational age, and the square of gestational age. Exposures to xylenes in the last month of pregnancy were also associated with term low birth weight.

However, in this study, the BTEX compounds were strongly inter-correlated with correlation coefficients between 0.79 and 0.92. And for this reason, the authors state that the results for xylenes must be interpreted with caution. Higher exposure to other air toxics including carbon monoxide, nitric oxide, nitrogen dioxide, and nitrogen oxides, and particulate matter in the third trimester and entire pregnancy also increased the odds of

term low birth weight.

The last study I will describe examined the relationship between cytokine secretion profile of umbilical cord blood T-cells and exposure to volatile organic compounds, or VOCs.

This was a cross-sectional study that drew its sample from an ongoing study of maternal exposure to VOCs and immune status at birth. The authors randomly selected 85 healthy full-term neonates whose mothers did not suffer autoimmune diseases or infectious disorders during pregnancy.

Cord blood samples were taken at delivery and T-cell function was analyzed. The authors assessed possible sources of VOC exposure including painting, flooring, and smoking in the home, and family atopy history by administering a questionnaire to parents. VOCs were collected by continuous passive sampling in children's homes for four weeks after birth.

Elevated m- and p-xylene was significantly associated with increase in cytokine producing cord blood T-cells in unadjusted analyses. Specifically, the median numbers of Interferon-gamma T-cells and interleukin-4-producing T-cells were higher when m- and p-xylene levels were above the 75th percentile. However, in multivariate analyses xylenes were not associated with

cord blood cytokine producing T-cells.

There were -- no significant associations were observed for o-xylene in analyses. And in this study, the authors acknowledged that the clinical relevance of their findings wasn't clear.

So, I just want to wrap up a little and summarize what I've just talked about. The epidemiologic studies all faced problems with multiple exposures to organic solvents and other compounds.

For male reproductive toxicity, there were three studies, one finding of decreased semen gamma-glutamyltransferase activity. For female reproductive toxicity, there was one finding out of two studies. One finding of increased risk of oligomenorrhea. And in this case, I wasn't including embryo fetal viability. That's in developmental toxicity.

So under developmental toxicity, there were four studies reporting results on malformations, and they found no effects -- no statistically significant effects.

For spontaneous abortion, there was one finding of -- there was a finding of increased risk in two of six studies. For birth weight, one study found an increase of birth weight in women exposed, at most, two days per week to xylene, and another study found an increased risk of low birth weight, and that was an air pollution study.

And finally, there was no effect found in a study umbilical cord blood T-cells.

And -- sorry. Just to refresh your memory on the animal evidence, we had -- for male reproductive toxicity, we had one of three inhalation studies reporting effects, but that study was limited by the lack of quantitative dosing. There was one I.P. injection study, and that found increased risk of abnormal sperm only or increases -- excuse me, increases in abnormal sperm, but only in treated animals kept between 24 and 30 degrees centigrade.

For female reproductive toxicity, there was one inhalation study that found decreased progesterone and 17 beta-estradiol. There was also a decrease in embryo-fetal viability in two of 12 inhalation studies and one oral study. And then the interpretation of these is complicated by excessive maternal mortality.

For developmental toxicity, there was decreased embryo-fetal viability, as stated above, decreased birth or fetal weight in seven of 11 studies, increased minor skeletal or total anomalies in six of eight studies, and evidence of neurobehavioral effects in three of four studies.

And are there any questions?

CHAIRPERSON GOLD: So thank you to Drs. Campbell

and Kim. I think in the interests of giving the recorder a break and that it's approaching noon and lunch time, that maybe we can hold questions by the Panel until after lunch, unless somebody has something really, really burning right now.

So I would suggest that we reconvene at 12:45. Does that sound -- is that feasible?

CHIEF COUNSEL MONAHAN-CUMMINGS: If the members can just remember if you have lunch together to talk about the weather or something.

(Laughter.)

CHAIRPERSON GOLD: Okay. So thank you, everyone. And we will come back at 12:45.

(Off record: 11:54 AM)

(Thereupon a lunch break was taken.)

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

(On record: 12:49 PM)

DIRECTOR ALEXEEFF: Well, good afternoon, everybody. We're going to call the meeting back to order now.

CHAIRPERSON GOLD: Okay. Good afternoon. So before we start the Panel discussion of xylene, I would ask, first, if the Panel members have any specific questions of clarification for Drs. Kim and Campbell?

No questions?

Okay. So just one brief announcement. I did ask Dr. Rocca if she would serve as Vice Chair of the Committee, because she compliments my expertise by her expertise in toxicology. And she has kindly agreed to do that.

I've also asked her to lead the discussion on the toxicology portion followed by Dr. Luderer. And then we have Dr. Klonoff-Cohen will lead the discussion on the epidemiology followed by Dr. Nazmi.

Also, what I've asked the Panel members who are -- although, we are all responsible for having read everything and we're all free to discuss everything, they will lead off by summarizing their thoughts about each of those aspects.

Also, what we're going to do is follow the lead

of the staff and discuss the male reproductive toxicity starting off with the toxicology and then doing the human studies, then the female reproductive toxicity, again toxicology, human studies, and then the developmental toxicity, recognizing that some of that gets involved perhaps with the female.

So that's the plan. And we've also talked about just not needing to go through every single study as the staff has already done that so well. But if there was a particular point about a particular study that they either disagreed with or felt needed embellishment, they would do that, but more it's the idea of sort of giving a summary of their sense of the state of the science, the strengths and limitations in helping us reach a decision.

So that's sort of the approach I think that we will take.

And we'll start with off Dr. Rocca.

COMMITTEE MEMBER ROCCA: Good afternoon. So I'm going to start out with talking about the non-clinical male reproductive effects of xylene. And in considering these studies, some of the things that are important to look at, I just wanted to list, which would be the experimental design, the number of animals per group that were tested, the route of exposure, what dosages were chosen, the maternal toxicity of the test article? Were

these studies reproducible?

Statistical considerations. And one of the things that's particularly important for developmental toxicity is that you use the litter of animals as the statistical unit as opposed to each fetus being its own unit, and that could make a profound difference in your statistics.

We also need to consider the biological plausibility of these effects. And taking all of these things into account, our charge is to come up with a weight of evidence as to what we think is happening here.

So the limitations on these studies that have been presented to us are that there's incomplete descriptions in many of them, as that these are published journal articles. And so descriptions of the methods, particularly of the purity of the xylenes is not specified.

And that there's just not all the results there. So sometimes it's a little tricky with the missing data to try to figure out what the value of the study is.

So those are the things I've taken into consideration when I've reviewed these studies. And I would like to thank the professional staff, Drs. Campbell and Kim for doing a excellent job in preparing the briefing document. It certainly made my job much, much

easier.

Thank you very much, ladies.

So coming to non-clinical male toxicity. There were four studies that we could consider. I think these study that holds the most weight is the study that was run by Biodynamics, that this study dosed animals for 131 days before they were mated. They went to doses as high as 500 parts per million for six hours every single day. And in that study, they found no ill-effects to male fertility.

This appears to be a very well run study. All the data is there. The information on the methods and statistics are there. And I give a lot of weight to that study.

The next one was the study by Nylen. This was a much shorter study in that it was only done for 61 days, which is not quite the entire length of the male spermatogenic cycle in the rat, but it still is quite a decent period of time. In that study, they went up to 1,000 parts per million for eight hours per day and also saw no effects there.

The two other studies I think have some deficiencies, and then I'm concerned particularly in Yamada study. That's the one where they just put animals in a exposure chamber until they reached anesthesia, so obviously quite neurally toxic.

The other issue is that these animals were about seven weeks old when they started with this, and they were concerned about looking at organ weights, for example. I'm not clear that at seven weeks of age all of these animals would have been truly sexually mature. And if it is that neurotoxic, you have to wonder what else is going on with them. And they did show decreased body weight in these animals, which would make me think that the anesthesia lasted pretty well and they weren't eating very well.

So the fact that the organ weights are lower, I have a hard time interpreting. The other thing that's interesting about this paper is that if you look at the table of organ weights, you'll see that each control group has very different organ weights. And so they must have run a concurrent control with each of them, but the weights are sometimes double. For example, the epididymal weight on the first one is 489. When you get to the last control group, it's 888. And it works that way that it increases in trends.

So I don't think it's clear what ages these animals were tested at, even though it talks about how old they were when they started. And so I'm not giving that a lot of credence.

And so that's kind of my assessment of the

reproductive toxicity. I think based on the weight of evidence of the studies that are here, I do not see any reason to feel that there's a clear effect.

CHAIRPERSON GOLD: Dr. Luderer.

COMMITTEE MEMBER LUDERER: Yes. Thank you.

I'd also like to thank the staff for the excellent briefing document. And I am very much in agreement with Dr. Rocca. I think that the Biodynamic study was the most well-conducted study in terms of the duration of exposure, the number of animals per group, the analyses.

The endpoints that were examined in that study were fertility and testis weights. So I think the only, for me, drawback was that there was no more detailed examinations of male reproductive endpoints, such as, you know, testicular histopathology or semen analyses, which would have been nice to have, since those are the endpoints that were observed to be affected in the other studies, which I agree are much less strong.

The Nylen et al. study I thought was severely limited by the very small N. It was an N of 3. And, you know, these are endpoints for which there can be quite a bit of variability. They looked at histological and semen abnormalities. And then I also agree that the Yamada study, as the staff pointed out, and Dr. Rocca mentioned

was severely limited by the lack of any exposure measurements, and the fact that their -- basically, their exposure was to loss of righting reflex, which is indicative of some significant neurological toxicity happening in those animals at that point, but doesn't really tell us about the dose.

So I would say that overall the weight of the evidence is not sufficient for me to conclude that this is a male reproductive toxicant based on these studies.

CHAIRPERSON GOLD: Thank you, both of you.

Does anyone on the Panel want to comment any further on the male reproductive toxicity studies, before we go to the human?

No.

So Dr. Klonoff-Cohen, you want to lead off talking about the human studies with regard to male reproductive toxicity.

COMMITTEE MEMBER KLONOFF-COHEN: Actually, Dr. Nazmi is going to do the male and I'll do the female.

CHAIRPERSON GOLD: I see. Okay. Thank you.

COMMITTEE MEMBER NAZMI: Thanks, Dr. Gold, and thank you to all our colleagues on the staff for doing such a bang-up job presenting these studies to us and writing up the findings in such a didactic manner.

I'd like to point out some key issues related to

these studies that I found salient for our purposes. And there are just a couple of them. I don't want to be redundant in my analysis at all.

To begin with in some of the background studies, just as a point of comparison, in 2011 California outdoor xylene was measured at between 0.15 and 0.40 parts per billion. And some data from Los Angeles takes those numbers to about 0.15 to 0.40 and 0.62 to 1.44 parts per billion. So if you guys could just keep that in your minds, between 0.15 and 1.44 parts per billion. That is salient to the De Celis 2000 study in Mexico, where workers were exposed to between 10,000 and 12,000 parts per billion in the workplace. That's about seven to ten thousand times higher than one would expect to be exposed to in the streets of Los Angeles.

That study, I thought, was -- had a couple of points that made me think a little bit. One was the obvious high concentration of xylene in the workplace, so high that the majority of these workers were suffering from acute symptoms of toxicity. Of course, that was at the mean duration of exposure of about 11 years, eight hours per day, six days a week.

I'd like to contrast that with the Xiao study from China that compared male colleagues in administrative positions and labor positions -- labor and industrial

positions where they were exposed to xylene. The men who were in the industrial and labor positions exposed to xylene had worse outcomes, including decreased prostate function, and the male colleagues in the Mexico study had lower sperm motility compared to their administrative colleagues.

So the point I'm trying to get at is that I think it's important that we consider people from the same workplace that are in positions that don't put them into contact with xylene compared to their colleagues who are in those positions where they do have, in some instances, significant exposure to -- significant exposure to xylene.

In relation to these same studies, I did find the Xiao article from China to have some pretty significant challenges, in terms of study design and in terms of study interpretation statistical methods.

At the same time for both studies and a lot of the human studies, for that matter, I think it's really important to consider that xylene because it's typically used in conjunction with a number of other solvents, it is very difficult statistically and methodologically for that matter to tease apart the effects of a single chemical. So in terms of design, I know this has been mentioned before by some of our colleagues on the staff, I find this to be a great barrier to the epidemiologic study designs.

Those are my general points. If we could go ahead and move on to the female studies.

CHAIRPERSON GOLD: Actually, can you hold on. I just want to see if there are any other comments from the Panel about the human male reproductive toxicity.

Dr. Baskin.

COMMITTEE MEMBER BASKIN: Yes. I would echo the previous comments. I just wanted to make one point with the Xiao study that there was a statistically significant difference in the semen glutamyltransferase activity, which they're equating to prostate function, but there's really no clinical or research data suggests it really has anything to do with prostate function.

So, to me, it's a chemically significant finding, but not a clinically or, in my opinion, research statistically finding. And also to echo the comment that it's -- I found it very difficult to separate xylene from all the other toxins, in all three of the epidemiologic studies, which is a difficulty in doing any type of these studies, but has to be taken quite seriously.

CHAIRPERSON GOLD: Okay. Thank you.

Any other comments on male reproductive toxicity before we move to the female from the Panel?

So we're going to start though with toxicology and then we'll come back to the human studies. So I'll

again call on Dr. Rocca to lead the discussion on the toxicology studies on female reproductive toxicity.

COMMITTEE MEMBER ROCCA: Thank you. As was pointed out before, the female reproductive toxicity studies are somewhat limited, and also we can include some of the data from the teratology studies, which looks at development.

So what I'm going to do, since some of these studies combine both endpoints, is to discuss both the female reproductive and developmental toxicity issues with these studies.

So there is a very long list of studies for this. Once again, I think the Biodynamic's study that treated both male and females for an extended time prior to pregnancy also treated the females all during gestation and all during lactation, and had a very good N and study design. And I give that study quite a bit of weight.

In that study, they didn't see any female toxicity. There were no effects really on the endpoints of implantations or fetal viability, so I don't find they're in this study to be reproductive effect.

In the teratology portion of it, they had only looked at two of the groups for this. They looked at animals that were -- the control animals given air, and those were both the males and females were treated with

500 parts per million.

And in this group they also saw really no effects that I would think are teratogenic. And this study, which I think is very well done, they found nothing.

The other study that I'd like to really bring up here is the one by Saillenfait in 2003. This is the most recent study and gives a very nice review within the paper itself of the results of the previous studies. This study animals were only treated during the period of organogenesis gestation days six through 20. They went up to doses as high as 2,000 parts per million. They did have maternal toxicity both in decrease in body weight gain and serious decrease in food consumption at both 1,000 thousand and 2,000.

There was no affect on female fertility endpoints on this, and the only teratological endpoint where they saw any real effect was that there appeared to be a decreased skeletal development delay at fetuses that dams were treated with 2,000 parts per billion, which as I said already, was quite toxic. So this is another study I consider to be negative for both those endpoints.

There are some other studies where the authors do conclude that it may be teratogenic. And I think part of the difference between my interpretation and theirs is what is a teratogen. That I don't consider skeletal

delays in development, where there is maternal toxicity that leads to lower fetal weights, to necessarily be teratogenic, because those animals will catch up and be fine.

The other study that I'd like to talk about also is the one in which they did three different species, which was very nice. That's the Ungvary of 1985. And in the rats, they went to a dose where one of the high-dose animals died. Very difficult to interpret whether or not that was a random thing or truly toxicity, when there's only one.

Unfortunately, they do not present any of the data per litter. They just give you the total for all the fetuses. There seems to be no effect on fertility, but they do say that there was decreased skeletal development for the lower body weight fetuses. This is in the rats.

With mice, they had very similar findings, the doses were lower for rats. And for rabbits, they did have quite a bit of maternal toxicity at the high dose of 231 parts per million. Unfortunately, they did not have any food consumption data, which can be a real confounding thing for rabbit studies not to understand that pattern. But they did have deaths and increased abortions and body weight decreases at that dose, but still found no teratogenic effects, and there was no effects to fertility

endpoints.

So those are the three studies that I think have the most validity for the female reproductive endpoints. I'd be happy to discuss any of the other ones, if anyone has any other questions.

CHAIRPERSON GOLD: Thank you.

Dr. Luderer, do you have something to add?

COMMITTEE MEMBER LUDERER: Yes. Thank you.

So I agree that there -- we have the one, the Biodynamic's study which did dose for the longest period of time again throughout -- prior to mating, during mating, and then subsequently during gestation. And that is a study that also I think had the greatest N. And there were a number of female reproductive-related endpoints looked at in that study.

Again, the one thing that I would like to emphasize is that even in that study, although in that study they commented on a number of corpora lutea, there were no kind of detailed analyses in any of these studies of ovarian histology, ovarian follicle counts, anything of that sort, which would allow us to really be able to assess ovarian toxicity to any great degree.

However, there were in that study no effects on fertility. I did want to note that the related endpoints, except for one, which was somewhat inconsistent, however.

In several of the groups it was observed that the number of females who mated was significantly decreased in the two higher dose groups, the 250 and 500 parts per million. Although, the 500 parts per million was only in the study subgroup in which the females only were dosed, and not the study subgroup in which both the males and the females were dosed, which was somewhat puzzling.

But when you do look at the table, in terms of the percentages or the number of animals that was affected versus not affected, the percentages are quite similar, so we're talking about 36 out of 40 in the not significant group, and 17 out of 20 in the group that was statistically significant.

So, you know, maybe the difference in statistical significance there is not so important since the magnitude of the effects seem to be quite similar in the two groups.

And then there was also a significant decrease in the fetal weights only of the female fetuses, again, at the 500 parts per million dose. So there was some evidence of decreased mating index in the females and then fetal weights, again, only in the female fetuses.

I agree also that the remaining studies, which were predominantly -- they were, I think, 12 developmental studies, which also looked at some female reproductive endpoints, most of these also used rats.

And the Ungvary Tatrai, I thought was -- that particular study was important as well, because it looked at three different species, and there are limited data among the other studies on species other than rats.

That study does suggest that there are significant species specific differences in the response to xylene with the rabbits having resorptions and abortions at much lower levels of exposure, 115 parts per million, than did the rats and the mice, in which resorptions were noticed only at a very high concentrations. I think it was greater than 690 parts per million.

This is important, because we would always like to have data for more than one species, if possible. I agree that a big drawback in the methodology in that study, as well as the other studies by the same group, which I think we'll talk about more when we talk about the developmental toxicity, was that the analysis of the data was by pup and not by liver -- litter. And it's unfortunate that one can't go back and reanalyze those data by litter, which is what I found myself wanting to do.

So, overall, I think there is some suggestion from these studies of female reproductive toxicity, based on the observations in rabbits, rats, and mice of

increased resorptions and/or abortions in the rabbits, as well as the decreased maternal weight gain also in rats and mice. And that was based on the Ungvary studies, again where there was the problem with the statistical analysis.

CHAIRPERSON GOLD: Thank you.

Anyone else want to comment on the female reproductive toxicity from the animal studies?

Comments?

Okay. Then we'll turn you now to Dr. Klonoff-Cohen to talk about the human female reproductive toxicity study.

COMMITTEE MEMBER KLONOFF-COHEN: I also once again want to thank Dr. Campbell and Dr. Kim. They did a fabulous job.

But just because there was so many studies, I'll just sort of touch on a few points of the studies I'm going to talk about. So I'm going to start by talking about Sallmén, which was the Finnish study from 1995.

And that was a retrospective cohort of about 197 women that was taken from Lindbohm's 1990 study. And they followed for 18 years for xylene, but as well for five other solvents.

So they looked at the data on time to pregnancy and exposure, and they collected during the first

trimester. And so what they found was that an incidence density ratio was 9.3 -- 0.93, excuse me, for high xylene exposure and reduced fertility. Now, that was for a sample of 10 women and they adjusted for other solvents, recent contraceptive use, age at menarche, and the low exposure was not significant.

So exposure to organic solvents was associated with longer time to pregnancy and reduced fecundability in the study. However, there were some limitations. First of all, the time to pregnancy was collected eight to 18 years after pregnancy. There was a participation rate of 66 percent. And most of the women were exposed to other solvents.

And last of all when you consider fecundability, there are other important confounders that you might consider, including frequency of coitus or history of sexually transmitted disease.

So that's all I want to say about Sallmén's study.

The second study I want to talk about very briefly is Cho from 2001. And that was the Chinese study that evaluated low level exposure to organic solvents. And he looked at menstrual patterns.

It was a cross-sectional study, and there were 1,408 women, that was about a 95 percent response rate, so

that was great. And they were looking at exposure assessment based on the classification of workshops for exposure for benzene, toluene, styrene, and xylene, and also women's reports of actually handling those chemicals.

And they actually got the menstrual patterns through interview, and oligomenorrhea was defined in this study as an average cycle length of greater than 35 days.

And as was previously told to us, no women were exposed to xylene alone, but they did find an odds ratio of 1.63 for increased risk oligomenorrhea and exposure for xylene and other solvents while adjusting for age, BMI, enrollment, cohort, passive smoking, exposure to chemicals that weren't aromatic solvents.

And the limitations for this particular study were that the exposures were very low with xylene and toluene and styrene. They were below one ppm, and the fact that it was a cross-sectional study.

Now, there were other studies, which I will just mention very, very briefly, because none of them were reported associations specifically for xylene. And the first one was Wennborg which was in 2001. And he looked at a fecundability ratio for occupational exposure to solvents and found 0.79 after adjustment for cycle order, mother's age, father's age, father's lab work, and reported fertility problems.

In terms of for Reutman, once again a cross-sectional study. And when they analyze the continuous variable, the total BTX was not significantly associated with any of the measured hormone levels.

There was Chen, but in his study he found actually short luteal phase, but unfortunately it was all crude analyses. There wasn't any adjustment.

And then the last two studies, Wang in 1994, there were no values presented, because the article was in Chinese. And then Yang in 1997, there was no multivariate analysis for the results, so I won't present them.

CHAIRPERSON GOLD: Thank you.

Anyone else wish to comment on the human female reproductive toxicity studies?

Okay. So we've already talked a bit about the developmental toxicity. I would ask if there's anything further, Dr. Rocca or Dr. Luderer, that you want to add on developmental toxicity from the animal studies?

COMMITTEE MEMBER ROCCA: Thank you.

In several of these studies, they also looked at postnatal effects. And in several of these studies, the animals were exposed during gestation, and then they looked at neurobehavioral and developmental effects later on.

So the first study is once again the Biodynamic's

study, which was quite nicely done. In this study, some of the animals were allowed to deliver their litters. And they were exposed for the 131 days before mating, all during gestation, and during lactation. So it's hard to parse out where the exposure that caused the effects might be coming from.

And in this case, they did see that there was slightly lower pup body weights on postnatal days 14, 21, and 49 on the high-dose dams. However, these poor dams were being exposed for six hours a day to 500 parts per million of xylene during the entire lactation period. And it's not surprising to me that their pups are going to have slightly lower body weights later on. This was not an effect that was seen on the early postnatal days. It was just in the later ones.

So, yes, they claim there was an effect, but being that it appears to be a nutritional one from the dams.

The next study that found an effect was Hass '93. And in this one they went up to doses of 200 parts per million during the gestation period. And they found on two specific days out of testing, that there was decreased times spent on the rotarod.

However, this same group did -- repeated a very similar study in 1995, where they went to doses of 500

parts per million and found no effect. And so I think it's a case of just spurious findings when you're doing lots of statistics on multiple, multiple endpoints on studies. So I don't find that convincing.

The next study that saw some effects was another study by Hass. There's one in '95, and one in 1997. And the interesting part about this paper for me is that when you look at them very, very carefully, you realize it's the same study being reported.

So they're reporting the early effects in the first paper, and then they go on to report the later time point effects in the second paper, but this really is just one cohort of animals.

In this study, they had different housing conditions. They had groups of mice that were housed together in -- you know, enrichment sort of situations, which would be pretty much the norm for things these days. Although maybe not then. And they also had groups that were pair housed in just plain cages.

And what they found was that it took the animals who had only been pair housed, and these are only females, a little longer to find the platform for the water maze after it had been moved. On the memory tests, they did absolutely just fine. They could find the platform just as easily. It just took them a little longer to find it

when it had been relocated.

I don't see this as a major problem, because they did find it. They did remember it. And as I said, this is one group of animals that was tested over and over and over. So there really is no replication there of the data.

And the other studies that were done, and all of the other endpoints in all of these studies no postnatal effects were found. So, once again, based on the weight of evidence, I don't see any postnatal detriment.

CHAIRPERSON GOLD: Thank you.

Dr. Luderer, anything to add?

COMMITTEE MEMBER LUDERER: Yes. So I think my opinion is that the studies that are most concerning to me for developmental toxicity are the developmental neurotoxicity studies, by -- that were performed by Hass's group.

So as Dr. Rocca noted, there was the earlier study, the Hass and Jakobsen study, where they looked at time on the rotarod, which is a way of evaluating motor activity. And they did find decreased time in the females on two of the three days tested, and in the males on one of the days tested.

I think it is important that they did comment that the people who did the testing were not blind to

treatment group, which is -- was also noted in the staff document. And that was one of the reasons they gave for doing the second study, in which they used the higher exposure level of 500 parts per million.

In that study, they also did the rotarod test and they did not find statistically significant effects. However, they did note that there was a trend for a greater percentage of the exposed animals to fail to reach 30 seconds on the rotarod, so there was a suggestion of an effect. And that was also the study in which they did the Morris water maze test for learning and memory.

And I think that what's important is that at the -- they did test these animals at -- the females, they tested at multiple different time points. They tested males and females at three weeks, and then the females in the second paper -- if those were the same females. Although, that wasn't entirely clear I thought -- at 16, 28, and 55 weeks.

And I think to me what was important was that these effects in the Morris water maze did persist over time in the females, even into -- well into adulthood. So the effects were significant for basically increased distance that the females swam, at the three earlier time points. And at 55 weeks, there was a trend for that, but not statistically significant. And also when the platform

was moved, it took the females longer to find it.

I think that there are a lot of neurobehavioral differences between -- in terms of neurodevelopment, central nervous system structures, between males and females. And so, to me, the fact that the effects were observed in females and not in males does not necessarily -- I wouldn't necessarily conclude that therefore they were spurious or not important.

The other study that looked at developmental neurotoxicity looked at different endpoints. And also, that was the only study that did look at one of the specific isomers. It looked at technical and p-xylene and didn't observe any significant effects, but again, looking at different endpoints, though it's difficult to really compare. I think that was the Rosen et al. study with the Hass et al.

So my conclusion, based on the developmental and neurotoxicity studies is I think there is some concern for developmental neurotoxicity with xylene exposure during gestation, particularly in terms of the learning, and memory tested by the Morris water maze in females.

CHAIRPERSON GOLD: Thank you. Any other comments by the Panel on the developmental toxicity from the animal studies?

Okay. So we'll turn to the human studies now,

developmental toxicity, who's going first? Did you decide that?

Dr. Nazmi.

COMMITTEE MEMBER NAZMI: Yes. Thank you.

I just wanted to point out one study that I think is perhaps the most recent study. It's the Ghosh et al. Los Angeles County 2012 study. It's a retrospective cohort of traffic-related air pollution and with an N in the several thousands. So in terms of study design, in terms of sampling, I thought it was probably one of the more convincing studies, given that they had good sampling and good design. And I think it's really salient to pay attention to their findings, which did find adjusted odds ratios of about 1.03, which is a small but significant effect.

Given that there were more than 8,000 term low birth weight infants studied, I think there might be some indication that it might behoove us to pay attention to the effects on birth weight of xylene exposure in ambient air in large city environments.

That's all.

CHAIRPERSON GOLD: Thank you.

Dr. Klonoff-Cohen, do you have anything to add?

COMMITTEE MEMBER KLONOFF-COHEN: Yeah. So I'll start with the Ghosh study. Absolutely, it does have

8,181 low birth-weight infants versus the 370,000 term normal-weight infants. And it did, in fact, find the odds ratio of 1.03.

I think it's important to talk a little bit about the limitations for that study. It was noted that there is possible misclassification due to residential mobility, the use of birth certificates, and the distance from monitoring stations. They also excluded pre-term babies, which might introduce selection bias. So they might have had greater exposure to air pollution. So that's all I want to say about the Ghosh study.

So I want to go back and say that there's nine studies in total on the development outcomes of xylene, and that there were six studies on pregnancy loss, and that there were two statistically significant studies that found that xylene was, in fact, associated with spontaneous abortion.

So I'm going to start with the Taskinen study from 1994, which was a case-control study of 206 cases and 329 controls, and it was two to one matching on age and race. And they found an odds ratio of 3.1 for spontaneous abortion, and that was associated with frequent defined as greater than three days per week exposure to xylene in the first trimester.

And they adjusted for employment, smoking,

alcohol, parity, previous miscarriage, failed birth control, and febrile disease during pregnancy. The limitations of this particular study were the exposure to multi-solvents, excluding females with multiple spontaneous abortions, and they didn't actually present statistics for birth weight.

The next study I wanted talk about, the Swan study was from 1995, and that was a retrospective cohort with 189 exposed and 683 unexposed, 18- to 44-year old women. And they became pregnant while working at one of 14 semiconductor companies.

The industrial hygienists used first trimester exposures and job activities to classify their exposure and it ranged anywhere from zero, which was none, to the three which was highest. And they defined spontaneous abortion as a pregnancy terminated by 20 weeks. And they excluded ectopic molar and elective terminations.

So xylene was used among seven agents, and they were strongly associated with spontaneous abortion. And the adjusted relative risk was 2.3 for women exposed to xylene level at two or three, which is medium and high, while adjusting for smoking, age, education, income, ethnicity, pregnancy history, year and stress.

As well, workers in masking had 2.72 times the risk of spontaneous abortion exposed to medium and high

xylene levels.

I'm not going to talk about the other four studies because they didn't have a statistically significant effect and multivariate analyses. And we talked about the Ghosh study for fetal growth. There was, in fact, another study by Taskinen that found that xylene exposure, at most two days per week, was associated with an increase risk of birth weight, but there weren't any statistics.

Then there was a third study by Axelsson, but did not find a statistically significant effect. There are three studies on congenital malformations and none of them found a statistically significant effect.

The Panel did introduce the study on Lupo, but the problem was after adjustment for potential confounders that effect disappeared. And then, in fact, there was one study on cytokine secretion profile of the cord blood T-cells. And even though the results looked very interesting in terms of the crude analyses, unfortunately the multivariate analyses for the results actually disappeared from the crude analyses.

So that's all I have to say.

CHAIRPERSON GOLD: Thank you.

Does anybody else have any anything to add regarding the human studies on developmental toxicity?

Okay. Hearing none. I believe it's time now to go to public comments. And I'm aware of one, is that it?

So Steve Risotto. Please introduce yourself.

MR. RISOTTO: Yes. Good afternoon. Thank you Madam Chairman and distinguished members of the Committee. My name is Steve Risotto. I'm a Senior Director at the American Chemistry Council speaking on behalf of the xylene manufacturers.

I, too, want to congratulate the Committee members for their appointment and want to acknowledge your commitment to public service. I guess I just hope you know what you're getting into for signing up.

(Laughter.)

MR. RISOTTO: I also want to thank the Chair and the staff for granting our request for additional time to talk this afternoon. Unfortunately, we weren't able to get industry experts to come to Sacramento in the short -- with the short notice. So I'm afraid you're stuck with just me, and I promise to take much less than the 20 minutes we had requested. In fact, probably no more than the five allotted.

Now, you'll note that the proposal from the staff is based on their own assessment of the scientific evidence for xylene. It is not based on the review by another Authoritative Body. In fact, despite a number of

studies, as has been described, and several toxicity reviews, xylene -- no authority has listed xylene as a reproductive toxicant.

These reviews include one by U.S. EPA's Office of Research and Development, and also one by EPA's Office of Pollution Prevention and Toxics, reviews by Health Canada, OECD's Cooperative Chemical Assessment Program, and by the Federal Agency for Toxics Substances and Disease Registry.

Notably, the peer review panel that looked at the evidence under EPA's voluntary Children's Chemical Evaluation Program concluded that the conduct of a two-generation reproductive study was not warranted, because it was unlikely to generate any additional useful data.

Now, as described in the hazard identification document -- there it is. Sorry, I'm trying to get my tablet to turn sideways and it's not doing it, so I'm having to read a little -- and as has been discussed, the epidemiology study of xylene are of limited value in assessing the potential reproductive and development tox effects, because none of the cohorts were exposed to xylene alone.

All of the groups were exposed to other solvents, and which obviously, and has been discussed, introduced a significant confounding factor, and one that cannot be

teased out. So we really -- as a consequence of that, I think we really are left to looking at the animal data to assess the reproductive and developmental effects.

And the hazard summary, and it has been discussed, indicate there's a number -- a large number of studies to be considered looking at both male reproductive, female reproductive, and developmental tox.

For male reproductive, as has been discussed, and I'll -- because it has been so thoroughly reviewed, I don't need to cover it -- I don't think I need to cover it too much.

Four studies -- four animal studies, three by inhalation, one by I.P. injection. The studies found no effects -- adverse effects on fertility, pregnancy, or mating indices. The two better conducted animal studies found no evidence of adverse effects on testes weight, gross or histological morphology, levels or sperm count or morphology.

The two studies that did report male developmental effects had serious limitations as has already been discussed. In one case, an unusual route of exposure and one that likely of little relevance to humans, namely I.P., and then, in addition, a lack of exposure information, small sample size, and a lack of information on effects on other organs.

Of the 13 animal studies that looked at female reproductive toxicity, ten found no effects. The three that did find effects were -- again, had limitations. Those limitations include evidence, in EPA's words, of severe maternal toxicity, questions about the purity of the test substance, a fair amount of contamination with ethyl benzene, and inappropriate statistical analysis, as has been discussed, looking at the pup as the statistical value, rather than the litter.

Then finally, the staff identified 15 animal developmental toxicity studies, 13 by inhalation and two by oral administration. Among these studies, none observed effects on offspring viability of the -- at levels that did not result in maternal toxicity.

Regarding fetal growth, while effects were seen in some, but not all studies, and as has been evaluated by several, the effects on fetal weight appear to be secondary to maternal toxicity. So again, a concern about the level of the exposures.

The evidence for malformations among the offspring of pregnant rats exposed to xylene, also is equivocal. And this study considered the most reliable by both EPA and ATSDR. However, the authors concluded that neither technical grade xylene or any of the individual isomers were teratological effects up to 2000 parts per

million. The skeletal effects that were observed at the highest level may again be secondary to maternal toxicity.

As noted in the HID, some evidence of developmental neurotoxicity has been observed in rats, but that evidence is relatively weak. The two studies reported such effects were both conducted at a single dose, providing no opportunity to do a dose response evaluation. The effects were confirmed -- were not confirmed in subsequent studies by the same researchers.

Taken together, ACC does not believe that the data support a conclusion that xylene has been clearly shown, through scientifically valid testing, according to generally accepted principles, to cause reproductive toxicity

Our view is shared by EPA's Office of Research and Development, and the Office of Pollution Prevention and Toxics, by OECD, and by ATSDR.

We trust that after a careful evaluation, the DART will reach a similar conclusion. Thank you for your attention and your consideration.

CHAIRPERSON GOLD: Thank you for your comments.

Are there any other public comments?

Hearing none.

It's now time to open the discussion to the Panel, sort of a more open discussion before we take a

vote.

I would suggest perhaps we ought to, similarly like we did our other discussion, start with male reproductive toxicity, and just get the Panel's feelings on this and then we'll go to female and then developmental. Okay.

So I'll open the discussion for this and ask if anyone wishes to make some further comments or share their feelings about male reproductive toxicity.

I see indications of no further discussion.

Okay. What about female reproductive toxicity?

Dr. Baskin.

COMMITTEE MEMBER BASKIN: I just want to ask a very general question, whether there's a known level of xylene for immediate toxicity, not reproductive and not developmental, but for its use in the laboratory or in industry?

CHAIRPERSON GOLD: So I will put that question to the Panel or to the staff, if anyone feels they can answer that.

Dr. Rocca.

COMMITTEE MEMBER ROCCA: I'm doing this from memory, so I will defer to the staff. But depending on the endpoint, it's either 100 or 200 parts per million for, I believe it's, an eight-hour exposure in humans.

Does that sound right?

DR. CAMPBELL: That's sounds like that would be about right. I don't -- it's in the document. I mean, I'm going to have to go back and look for it, because I don't actually remember, but that sounds about right, because that's when they -- that's about the level where they start reporting. Yeah, neurological effects over 100, sedation, disorientation, ataxia. So you'd certainly want to avoid that.

CHAIRPERSON GOLD: Dr. Luderer, did you have anything to add to that?

COMMITTEE MEMBER LUDERER: No, I was just going to point out that same part of the document.

CHAIRPERSON GOLD: Okay. Anything else on female reproductive toxicity?

Okay. Any further discussion on developmental toxicity by the Panel?

Dr. Baskin?

No.

Others?

Okay. Does this mean we're ready to vote -- oh, sorry. Dr. Luderer.

COMMITTEE MEMBER LUDERER: No. I did have one -- I just wanted to mention one of the other studies, which I don't think we really talked about very much, the Litton

study, which this was a study that was done in rats as well, CRL:COBS CD (SD) BR rats exposed to 0, 100, or 400 parts per million xylene from gestational days six to 15.

In that study, they did comment on unusual skeletal changes, which they didn't really describe in detail, but they actually, I guess, thought they were so unusual that they separated them out from the more common skeletal defects that were also observed in the controls.

And they found there was a significant increase in those changes, but not only when they analyzed pups, but again not when they did the analysis per litter. Although, one of the things I wanted to ask was how the litter analyses were done, whether they were looking at litter averages or whether they were doing some of the more currently used statistical methods, such as using generalized estimating equations to adjust for litter and still be able to use the pup data.

I assume they didn't, since it was in 1978.

DR. CAMPBELL: Yeah. I'd have to go back and dig for that. I don't know off the top of my head. But it's such an old study, I wouldn't expect it to be very advanced.

COMMITTEE MEMBER ROCCA: I think I can make a couple comments on that. My recollection, once again, is that they did indeed take the total number of fetuses

divided by the total number of things they found.

The other thing about that study when you dig into the methods, and it's interesting that it's almost kind of hidden, three of the high-dose animals, which is where they're saying they think they saw something, were actually pretty sick. And one of them actually had no access to water for an entire week during gestation.

So I -- based upon that, and the lack of using the per litter, because that would have helped us sort that out, which is why the litter is so important. We would have known the three dams that had the serious toxicity and been able to parse those out. That's why I haven't given much weight to that finding.

CHAIRPERSON GOLD: Thank you.

Any further discussion about developmental toxicity?

Okay.

Does this mean we're ready to vote?

Oh, you have one more thing. Dr. Rocca.

COMMITTEE MEMBER ROCCA: Yes. I just had one more comment about the post-natal. And I wanted just to bring up the study where the Morris water maze differences were seen. What was striking to me about that study is that if you had animals in group housing as opposed to just pair housed in bare cages, they didn't see the

effect.

So it really had to do somewhat with the housing as well as the exposure. And as I said, once they found the platform, they remembered where it was, that they had no problem with the memory. And when it was in the opposite quadrant, they knew to look there, so that they could figure that out. It was just when it was placed in someplace completely different like the middle, that they had an effect. And it was only in that one group, so that's why I find it very difficult to give that enough weight to list it for that reason.

COMMITTEE MEMBER LUDERER: Yeah. I mean, I think it was the -- sort of the more challenging task of finding the platform that was not where they were expecting. It was the one that there were significant differences in.

I think that the housing -- I think that's actually very interesting that the enriched housing did seem to be a benefit, and seemed to be able to overcome some of the adverse neurodevelopmental effects of the xylene exposure.

I think another interesting thing about that study that we haven't talked about is that there were some actual -- some changes and some neuro -- some developmental endpoints that were actually advanced, which we hadn't really commented on before in the xylene exposed

animals.

But in my opinion, the fact that these changes in -- or these differences in the Morris water maze. Although they only occurred in the not enriched housed group, the fact that they persisted well into adulthood, I still find that to be a significant effect, in terms of the neurodevelopmental toxicity.

CHAIRPERSON GOLD: Thank you.

Anymore discussion of developmental toxicity?

Okay. Do we feel ready to vote on these three outcomes?

Yes.

Okay. So I have wording to follow. Do I have to do them in exactly this order?

Okay. So has xylene been clearly shown, through scientifically valid testing, according to generally accepted principles, to cause developmental toxicity?

All those who say yes, could you please raise your hand?

(Hand raised.)

CHAIRPERSON GOLD: Yes. One yes.

Okay. Those who vote no?

(Hands raised.)

CHAIRPERSON GOLD: Those abstaining?

(No hands raised.)

CHAIRPERSON GOLD: I guess that would be zero.

Okay. Next, we go to has xylene been clearly shown, through scientifically valid testing, according to generally accepted principles, to cause female reproductive toxicity?

If you wish to vote yes, could you please raise your hand?

(No hands raised.)

CHAIRPERSON GOLD: I see no yeses.

Those voting no?

(Hands raised.)

CHAIRPERSON GOLD: No abstentions.

And finally, has xylene been clearly shown, through scientifically valid testing, according to generally accepted principles to cause male reproductive toxicity?

If you wish to vote yes, please raise your hand?

(No hands raised.)

CHAIRPERSON GOLD: That's a zero.

Voting no?

(Hands raised.)

CHAIRPERSON GOLD: Six. And no abstentions.

So the result, as I see it, is for developmental toxicity, there was one vote yes, five votes no.

For female reproductive toxicity no yes votes,

six no votes.

And for male reproductive toxicity, no yes votes and six no votes.

Okay. Thank you, everyone.

So we can now go to the next part of the agenda, which is update on Section 27000 list, chemicals which have not been adequately tested as required and the staff has a presentation, is that correct?

(Thereupon an overhead presentation was presented as follows.)

CHIEF COUNSEL MONAHAN-CUMMINGS: Right. Yeah. There's one slide.

DR. CAMPBELL: Is this it?

CHIEF COUNSEL MONAHAN-CUMMINGS: Okay. This is Carol Monahan-Cummings again.

I mentioned to you this morning that you had one kind of odd duty under the statute that has to do with identifying chemicals that don't have sufficient testing. And this is a section of the law that's called Section 2700 within our regulations. It is required by the statute that the State's qualified experts determine whether or not these chemicals have been adequately tested.

So what we do, in order to help the Committee make this decision, is we poll the Department of Pesticide

Regulation and U.S. EPA and ask them if they can identify any chemicals that can be taken off the existing list, because there's been sufficient testing or if there are any chemicals that need to be added to the list, because they have insufficient evidence of sufficient testing.

And so we did that for you the last couple months, and we have up on the slide -- I am not going to try and pronounce all of these. But the Department of Pesticide Regulation has identified the three chemicals that are on this slide as chemicals that now have sufficient testing. And they recommend removal of them from our list.

And then the second list is those reported by U.S. EPA as having sufficient evidence -- or sufficient testing that can be removed from the list.

This Committee doesn't have to determine whether or not there's sufficient testing. You can rely on the EPA and DPR findings, because they're the ones that make the requirements for the testing.

So essentially, what we're asking you to do is ratify what DPR and U.S. EPA have said about these, and then we can go ahead and remove them from the list.

Do you have any questions on that?

So if you could just raise your hand, if you agree that we should go ahead and remove these chemicals

that are up here on the slide from our list of chemicals that have not been adequately tested?

(Hands raised.)

COMMITTEE MEMBER NAZMI: Could you say that again, please.

CHIEF COUNSEL MONAHAN-CUMMINGS: I'm just asking you to raise your hand if you agree with DPR -- or the Department of Pesticide Regulation and the U.S. EPA that we can go ahead and remove these chemicals from our list because they've been adequately tested? So if you could raise your hand if you agree with that?

(Hands raised.)

CHAIRPERSON GOLD: Dr. Klonoff, do you have a question.

COMMITTEE MEMBER KLONOFF-COHEN: I just have a really quick question. I'm sorry. I'm might have phased out. So you're asking us -- there's been sufficient testing, you're asking us to, or there's been insufficient testing, you're asking us to agree? I guess I'm not understanding.

CHIEF COUNSEL MONAHAN-CUMMINGS: I'm sorry. Yeah. We're removing them from the list, so that means that these two agencies have said that there is sufficient -- there is sufficient testing. Sorry.

COMMITTEE MEMBER KLONOFF-COHEN: There is

sufficient testing. Thank you.

CHIEF COUNSEL MONAHAN-CUMMINGS: Sorry. Okay. So we'll try one more time.

(Laughter.)

CHIEF COUNSEL MONAHAN-CUMMINGS: Trying to get unanimous here, not that I'm trying to influence you.

(Hands raised.)

CHIEF COUNSEL MONAHAN-CUMMINGS: Okay. Thank you very much.

CHAIRPERSON GOLD: So the next item on the agenda is staff updates regarding administrative listings, and safe harbor level development and litigation.

And, Ms. Oshita, you're going to do this.

MS. OSHITA: Yes. Good afternoon.

The Committee last met in July 2011. And since then, OEHHA has administratively added 16 chemicals to the Proposition 65 list. Two of them were added as chemicals known to cause reproductive toxicity, and 14 were listed as chemicals known to cause cancer.

And on these slides here they will list the additions of the chemicals, along with the effective dates for which they were added to the list. This first slide here will show the chemicals that were -- the two chemicals added for reproductive toxicity. The next two slides will cover the chemicals that were added as known

to cause cancer.

This slide here showing those added September 2nd 2011, November 4th, 2011, and February 3rd, 2012. And followed by the additions made on June 22nd, 2012, July 24th, 2012, and most recently November 2nd, 2012.

There are still yet some other chemicals that are under consideration for administrative listing. They include bisphenol A, hydrogen cyanide, cyanide salts as causing reproductive toxicity, as well as tetraconazole, beta-myrcene, and pulegone as causing cancer.

The public comment period for bisphenol A was recently extended and will now close on March 27th, 2013. The data call-in periods for all of the other chemicals have since closed. We received comments on all of those, and they are under review.

We had issued a notice of intent to list styrene last month on January 4th. However, we decided not to proceed with the proposed listing at this time, and we've withdrawn that notice. In the event that we decide to proceed with the proposed listing for styrene, we will issue a new notice, and provide yet again an opportunity for public comment.

Since the last meeting, OEHHA has also adopted a Maximum Allowable Dose Level for avermectin b1, and six no significant risk levels. The chemicals and their

respective levels are shown here on this next slide. The one MADL for avermectin b1 and then the six corresponding no significant risk levels, NSRLs.

With the exception of bisphenol A, which is still open for comment, staff are currently working on the final rule-making packages for each of the other chemicals, and we expect to submit them to the Office of Administrative Law for approval very soon.

Thank you.

CHAIRPERSON GOLD: Thank you. Does counsel have some more comments?

CHIEF COUNSEL MONAHAN-CUMMINGS: I'm back.

I just want to give you quick update on litigation that has occurred in the last year or is continuing at this time. Most of the litigation that we're dealing with has to do with carcinogens, but I thought you might be somewhat interested in the way the cases have gone.

There's a case that was very recently decided in October of 2012 that had to do with the chemical styrene. And we had proposed the listing of styrene as a carcinogen under what's called the Labor Code Listing Mechanism. We mentioned that earlier. It has to do with occupational exposures under the Hazard Communication Standard.

And we were sued by the Styrene Information and

Research Center. They alleged that we didn't have sufficient evidence that the chemical caused cancer. And we were unsuccessful at the trial court level, and at the appellate court level in convincing the judges to the contrary.

And so under that case, the court has -- the appellate court has determined that in order to list chemicals under the Labor Code mechanism based on a report from the International Agency for Research on Cancer, we do have to have either sufficient animal evidence or sufficient human evidence. And those can't be supplemented by other mechanistic or other data that the agency actually has to say that it's sufficient in one or the other.

The next case I wanted to mention had to do with the listing of the chemical 4-MEI, 4-methylimidazole. You noticed I think that we also have adopted a safe harbor level for that chemical.

We were originally sued by the California League of Food Processors, the American Beverage Association, Grocery Manufacturers Association, and the National Coffee Association for proposing the listing of the chemical.

We were successful in the trial court in arguing that the chemical did meet the criteria for listing based on a report that -- a technical report that was issued by

the National Toxicology Program. And so that case was not appealed, and so the chemical is on the list and we have adopted a safe harbor level for it.

There's also a case pending currently in the superior court here in Sacramento. It was brought against OEHHA by Syngenta Crop Protection. It has to do with our proposed adoption of a -- actually our adoption of a safe harbor level for the chemical chlorothalonil. We actually had previously had a safe harbor level for that chemical, and last year we proposed to lower the safe harbor number. And Syngenta disagrees with how we are -- how we adopted that number.

That case has not been resolved yet. It's in the -- somewhat the pre -- very early in the process of answering and demurrering and things like that. So hopefully by the time you have your next meeting -- well, not the next meeting, because that's in March. But perhaps by the end of the year, we'll have a resolution in that case.

And then I mentioned to you that there was a case that involves your sister committee, the Carcinogen Identification Committee. And in that case, we're in the Alameda County trial court. That case has been pending for over six years, and it was filed by the Sierra Club among others, and -- against the Governor and also the

members of the Committee, Dr. Alexeeff, and the Secretary of CalEPA.

And it has to do with listing processes for all our listings, other than the formally required that I mentioned early this morning. It has somewhat peripheral impact on this Committee, because it really -- the only thing that affects you directly is the prioritization process for bringing chemicals to the Committee. And there's a challenge to whether or not that's sufficient and quick enough.

So we have been working for the last two years to try and settle the case. And we seem to be very close frequently, but we have not yet been able to resolve the case. It was recently set for trial this fall, and we're hoping to either resolve it by trial or by settlement within the next several months.

Does anybody have questions on those?

I'll let you know if you get sued, okay?

Thanks.

CHAIRPERSON GOLD: Okay. Are there any other staff updates of which I'm not aware?

George.

DIRECTOR ALEXEEFF: Sort of a staff update. Well, it's actually a comment. As it was mentioned in the staff updates that we had adopted a MADL, a Maximum

Allowable Dose Level, and it was also mentioned in Carol's earlier presentation before lunch, that this Committee has a responsibility to review those documents.

So what I was thinking of that maybe we should have an agenda item sometime, either the 18th or the following time, just sort of discussing that process of how we calculate those levels, give some examples, and that kind of stuff, and talk about what type of input, you know, you could give, just because we're trying to increase your interest in that area. So that was kind of one comment.

The other one has to do with our next meeting on March 18th. And in that meeting we'll be discussing the chemical deltamethrin. And we have the -- you know, we had already sent you the document, but now we have the public comments. So we'll be giving you the public comments either here or by email, but they're ready to provide to you.

And then we are also in the process of making some changes, not a large number of them, but some changes to the original staff document that we had sent you. So we'll be sending you those sometime in the next few days.

CHAIRPERSON GOLD: Thank you.

Any other staff updates?

Okay. The next item is general public comment

period.

I don't -- I'm not aware of any. Are there other public comments?

Hearing none.

Then I'll turn it over to Dr. Alexeeff to summarize today's actions.

DIRECTOR ALEXEEFF: All right. So, in summary, today, we considered whether xylene has been -- or the Panel considered whether xylene has been shown, through scientifically valid testing, according to generally accepted principles, to cause either developmental toxicity, female reproductive toxicity, or male reproductive toxicity. And it was not found to cause either -- any of those toxicities, in terms of a Committee vote. And the votes were for developmental toxicity, one yes, five no; and, for female and male reproductive toxicity, there were six noes.

Also, the Committee also voted to remove several compounds that were recommended by the Department of Pesticide Regulation and U.S. EPA from the list of chemicals that require additional testing.

So that's all for the report. And I want to thank the Panel for their, I thought, very thoughtful discussion of the day.

CHAIRPERSON GOLD: Okay. I, too, would like to

thank the Panel for their careful review of the documents and their articulate statements. And thank the staff for their very hard and diligent work on the chemical that we reviewed today.

And hearing nothing further from the Panel or the public, we can draw this meeting to a close. So I wish to say that we'll adjourn now.

Thank you all.

(Thereupon the Developmental and Reproductive Toxicant Identification Committee adjourned at 2:08 p.m.)

C E R T I F I C A T E O F R E P O R T E R

I, JAMES F. PETERS, a Certified Shorthand Reporter of the State of California, and Registered Professional Reporter, do hereby certify:

That I am a disinterested person herein; that the foregoing California Office of Environmental Health Hazard Assessment, Developmental and Reproductive Toxicant Identification Committee was reported in shorthand by me, James F. Peters, a Certified Shorthand Reporter of the State of California, and thereafter transcribed under my direction, by computer-assisted transcription.

I further certify that I am not of counsel or attorney for any of the parties to said meeting nor in any way interested in the outcome of said meeting.

IN WITNESS WHEREOF, I have hereunto set my hand this 7th day of March, 2013.

JAMES F. PETERS, CSR, RPR
Certified Shorthand Reporter
License No. 10063

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