1 proposed tiered testing strategy. The first
2 tier would attempt to reproduce effects
3 observed at low doses in rodents while the
4 second tier would attempt to extend these
5 observations through non-human primates. The
6 proposed studies would consume thousands of
7 animals' lives but could only delay regulation
8 that is needed now to protect public health.
9 The problems with the Tyl study
10 which we've heard so much about underscore the
11 difficulty in reproducing BPA's low-dose
12 effects. This study which wasted an
13 outrageous number of animals' lives, was
14 conducted with oversight by the EU's bisphenol
15 A steering group and the EU considers it the
16 gold standard definitive study of the
17 reproductive toxicity of BPA. However, even
18 exposing estrogen-sensitive CD-1 mice to a
19 wide range of doses. The researchers were
20 unable to reproduce effects on prostate and
21 mammary gland development and puberty observed
22 in rodents in many other studies.

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In any case, results in rodents are unlikely to predict results in humans due to physiological differences between species. For example, a 2002 study by Volkel et al using human volunteers showed that bisphenol A is metabolized to the non-toxic glucuronide and eliminated three times faster in humans than in rats due to the absence of enterohepatic circulation. Consequently, given the same dose, rodents are exposed to a higher plasma levels of free BPA compared with humans.

In addition the European Food Safety Authority in its recent report on toxicokinentics of BPA summarized from BPA analogs. These data show that in humans glucuronidation activity is induced during pregnancy, while in rodents it is similar in non-pregnant and pregnant animals. As a result, fetal exposure to free active BPA is expected to be higher in rodents than in humans.

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1 Finally, sexual differentiation in
2 rodents is controlled by estrogens, while in
3 primates it appears to be regulated by
4 androgens. Such species differences call into
5 question the relevance to humans of any
6 results in animals. Although the study by
7 Leranth et al published just last week raises
8 concerns that intravenous exposure to BPA can
9 result in neurophysiological changes in non-
10 human primates, given the lower sensitivity of
11 humans in other primates to BPA and the
12 observation of behavioral effects in rodents
13 only at low doses, it is still extremely
14 unlikely that behavioral effects will be
15 reproduced in non-human primate studies since
16 very large sample sizes would be required to
17 detect events expected to occur at such low
18 frequencies.
19 Also, as we have seen, it has
20 proven difficult to reproduce low-dose effects
21 in rodents in GLP studies. Instead, BPA's
22 low-dose effects are likely to be observed

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only in large scale epidemiological studies such as the recent study presented by Dr. Melzer this morning.

In summary, as Dr. vom Saal's stacks of paper demonstrate from this morning, there's already an extensive body of literature on the toxicity of BPA in animals. The FDA's proposed rodent studies are unlikely to reproduce effects observed at low doses. Also, since humans and other primates are far less sensitive to BPA than are rodents, it is extremely unlikely that behavioral development effects observed only at low doses in rodents will be detectable in non-human primate studies. The proposed animal tests are unlikely to provide more useful information. Instead, the time has come for concerns over BPA's developmental effects to be addressed by precautionary regulation. Thank you.

CHAIRMAN PHILBERT: Thank you very much.

Questions?

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1 Thank you for your presentation.
2 Next is Dr. Beck from Physicians
3 Committee for Responsible Medicine.
4 DR. BECK: Good afternoon. I'm
5 Dr. Nancy Beck and I'm a scientific advisor
6 with the Physicians Committee for Responsible
7 Medicine, PCRM, a non-profit organization with
8 over 100,000 members, promotes preventative
9 medicine, conducts clinical research and
10 encourages higher standards for ethics and
11 effectiveness in research.
12 We appreciate the opportunity to
13 comment today on FDA's draft assessment of
14 bisphenol A. And rather than discussing our
15 thoughts on whether BPA is safe or not, which
16 is what most of the comments today are focused
17 on, I'm going to address the research
18 recommended by the FDA in the draft
19 assessment.
20 We are troubled by the tiered
21 testing plan outlined in the draft assessment
22 which calls for additional studies in rodents

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and non-human primates. Despite myriad data from animals, the effects of BPA apparently remains controversial, therefore I question how yet more animal studies will settle the debate or provide clear insight into the impact of BPA on human health. Concern over the reproducibility of some rodent data and the applicability of rodent data for predicting human health effects has prompted the FDA to propose non-human primate studies.

The use of non-human primates is a troubling solution to this problem because there is no evidence to suggest that these animals will be any more predictive of human health outcomes than rodents. In addition to scientific concerns, the call for non-human primate research at a time when other countries are limiting research using primates also raises ethical concerns.

In order to explore BPA's effects on humans, we support an evidence-based toxicity approach built on a more accurate

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1 human hazard exposure and risk assessments,
2 including PBPK modeling, human biomonitoring
3 and large scale human epidemiological studies
4 like we heard about this morning to measure
5 exposure and effects in all age groups and
6 pregnant women.
7 Further research should also focus
8 on elucidating the pathways and mechanisms
9 through which BPA's reported developmental,
10 reproductive, behavioral, neurological and
11 metabolic effects are mediated. Recent
12 hypotheses concerning mechanism range from
13 direct effects on tubulin to binding of
14 estrogen-related receptors, cell surface
15 estrogen receptors and other receptors to
16 epigenetic mechanisms like DNA methylation.
17 Many different signaling pathways have been
18 implicated as well, but we still have no clear
19 understanding of BPA's true mode of action in
20 humans.
21 The FDA's reliance on classical
22 and outmoded regulatory toxicological

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approaches for BPA assessment is unfortunate. With the National Research Council of the National Academies of Sciences calling for a fundamental shift in toxicology away from whole animals towards mechanistic, human-based, in vitro, Omix, and computational approaches in its report, "Toxicity Testing in the 21st Century," and the Science Board itself in its report, "FDA Science and Mission at Risk," drawing attention to the dire need for FDA to modernize its scientific foundation, the FDA should consider a more forward-thinking strategy for quicker and more accurate assessment of BPA allowing the Agency to regulate it accordingly rather than stalling while more animal data with questionable human relevance is gathered. Thank you.

CHAIRMAN PHILBERT: Thank you very much.

Questions? Dr. Hu?

DR. HU: Does your committee have

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a position on what the regulatory option should be pursued at this point? Just forget about what the future studies should be.

DR. BECK: Oh, in terms of ban it, don't ban it, or --

DR. HU: That's right.

DR. BECK: We do not have a position on whether it should be banned or not, an official position. I could give you my opinion, but as a representative of PCRM, I will abstain from commenting. Thank you.

CHAIRMAN PHILBERT: Thank you very much.

Next is Dr. Rost from the North American Metal Packaging Alliance. Thank you.

DR. ROST: Hello, my name is Dr. John Rost and this statement is presented on behalf of the North American Metal Packaging Alliance. As chair of NAMPA, I appreciate the opportunity to speak this afternoon to the distinguished members of the BPA subcommittee and look forward to responding to your

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1 questions that you may have.
2 NAMPA represents the interests of
3 the North American light metal packaging
4 industry, including raw material producers,
5 resin formulators, metal packaging
6 manufacturers and converters, as well as food
7 producers, beverage manufacturers and other
8 allied entities. NAMPA is committed to the
9 safety of metal packaging products its members
10 produce.
11 Bisphenol A is a critical
12 component to the manufacture of epoxy coatings
13 used to line metal packaging. For over 50
14 years epoxy coatings have been used in metal
15 food packaging for the reasons of combination
16 of toughness, adhesion, formability and
17 resistance to a wide range of chemistries
18 found in food and beverage products, and the
19 ability to sustain the high temperature
20 required for sterilization that makes these
21 coatings unsurpassed and are without exception
22 the coating of choice.

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1 The use of epoxy coatings in metal
2 packaging is the most effective way to bring
3 nutritious wholesome foods to people
4 throughout the world because it dramatically
5 increases the shelf life of packed foods and
6 decreases food waste due to product
7 expiration. Moreover, no other food packaging
8 performs as well in situations such as
9 disaster relief, homeland security or famine
10 relief.
11 BPA may remain in trace quantities
12 after the polymerization and thermal curing
13 that converts the liquid coating into a light
14 metal packaging film. The very small residual
15 concentration of BPA, however, that may exist
16 in the film will not increase with time after
17 thermal processing, storage, hydrolysis or
18 even damage to the polymer from scratching or
19 denting.
20 NAMPA endorses FDA's effort to
21 assess the safety of BPA. In this regard,
22 FDA's draft assessment of BPA for use in food

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contact applications represents a thorough, comprehensive and objective review of the scientific literature focused on the end points of carcinogenesis and reproductive and development toxicity of BPA. FDA's rigorous assessment and studies were particularly crucial in evaluating the alleged low-dose development effects attributed to BPA.

NAMPA welcomes FDA's conclusion in the draft assessment that an adequate margin of safety exists for BPA at current levels of exposure from food contact use for infants and adults. Importantly, in reaching this conclusion, FDA used unmodified typical study type uncertainty factors and considers them conservative based on the large body of knowledge of BPA and the findings observed in these pivotal studies and thoroughly reviewed data on end points highlighted as the potential concern of recent reports such as developmental effects and prostate gland development, neural and behavioral toxicity.

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To the extent scientific uncertainties remain, the draft assessment exists, NAMPA supports FDA's proposed tiered testing strategy to decrease the uncertainties.

NAMPA, however, believes that the levels of BPA reported in food attributed to migration residual monomers from the epoxy coatings of metal food and beverage packaging are often significantly overstated. Unless an analytical methodology suitable for measuring very low BPA levels in complex matrices is utilized, the reported results can be influenced by interferences from other food constituents. Sampling to date often have been done using GCMS or gas chromatography mass spectrometry or high-performance liquid chromatography with fluorescence detectors that is prone to inferences from other substances naturally present in food. BPA exposure estimates would be more reliable if the residual data utilized to develop such estimates are collected with more robust and

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defensible analytical techniques and protocols.

I'd be happy to take any questions.

CHAIRMAN PHILBERT: Thank you. Questions? Dr. Bushnell?

DR. BUSHNELL: Yes, I'm curious to know whether you are working on such analytical techniques and how close we are to being able to actually measure BPA levels in foods rather than estimating it from leaching.

DR. ROST: Well, we are working on that. Obviously, it's very complex because every food type has a different matrices you have to be concerned about. But there are standard methodologies for infant formula that use liquid chromatography mass spectrometry with tandem MSMS. And so those techniques reported that way, we do have confidence in.

DR. BUSHNELL: Okay. And do those estimates or those measurements of BPA in food correspond well with the estimates that have

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been produced and talked about today in the FDA report?

DR. ROST: Yes, they do.

DR. BUSHNELL: Okay.

DR. VANDENBERG: In your statement you indicate that the reported results can be influenced by interferences from food constituents. Would that be a bias towards toward the NOAEL?

DR. ROST: No.

DR. VANDENBERG: In other words, would the binding or the food matrix lead you to conclude that there was more or less BPA than actually was present?

DR. ROST: It would lead you to believe there's more BPA.

DR. VANDENBERG: More BPA.

DR. ROST: Because of that interference integrating that peak which likely came from a food constituent, not BPA.

DR. VANDENBERG: Thank you.

CHAIRMAN PHILBERT: Thank you very

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1 much.
2 We've had two cancellations and so
3 we have a little time and Dr. Tyl has
4 requested some time to present before the
5 subcommittee. At this time we'd like to
6 invite her to take the podium.
7 DR. TYL: Thank you very much.
8 Good afternoon. My name is Shelly Tyl. I am
9 a board certified toxicologist with a Ph.D. in
10 developmental genetics. I was study director
11 and first author on the two BPA
12 multigenerational studies in rats and in mice.
13 I am here at my own expense
14 initially to listen to the FDA deliberations
15 and the comments, but now to represent our
16 studies, my staff and me.
17 Dr. vom Saal's attacks on our
18 studies are unfounded and inappropriate. I
19 suppose I should be flattered, but apparently
20 if you can't criticize our study designs,
21 performance, statistical analyses or our
22 results, then you result to character

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assassination. I find that awfully uncomfortable to sit through.

My rebuttal is as follows: The design of both multigenerational studies were based on and exceeded the recently revised governmental guideline study designs. OECD revised theirs in 2001; the USCPAOPPTS revised in 1998. These studies have validated end points. The whole point of using guideline studies is to provide for validated end points, large number of animals in order to have statistical power and they are used for risk assessment. The small basic research studies which you have heard about today are used for hazard identification, but they cannot be used in risk assessment. That's part of the reason why most of the evaluations of BPA have relied heavily on the large multigeneration studies.

My staff and I have been examining and publishing our work on reproductive and developmental biology and toxicology in animal

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models for over 35 years. We work for RTI International in Research Triangle Park, North Carolina, a not-for-profit, independent research institute and our work is funded by both governmental and commercial clients. We are experienced and competent. We perform our studies including the BPA studies blind for dose to prevent any inadvertent bias. We also use power calculations as well as the guideline requirements to determine how many animals we would need to detect statistically significant differences in end points of interest.

Interestingly, our variance terms around the weights of organs of interest including the prostate are much smaller than the variance terms around the prostate weights in Dr. vom Saal's small study. If there were effects on adult offspring prostate weight and histopathology, or on any other effects, we would be more likely or better able to detect these effects than his small basic research

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1 study, and we didn't see it at low doses.
2 Dr. vom Saal's comparison of his
3 mouse prostate weights, approximately 40
4 milligrams, with our mouse prostate weight, 72
5 milligrams, is not due to our purported
6 incompetence or animal prostatitis. But on
7 age differences, Fred's mice were three months
8 old. Our mice were six months old. The
9 difference in age determines the growth rate
10 of the animal and the animal organs. So the
11 comparison is specious; it's apples and
12 oranges.
13 Dr. vom Saal also well knows that
14 prior to our mouse BPA study we performed and
15 published a one-generation and a two-
16 generation E2 dietary study in mice to
17 document the sensitivity of the test animal
18 system to dietary E2 from 8,000 micrograms per
19 kilogram per day to .16 micrograms per
20 kilogram per day and to identify those end
21 points that are associated with exposure to an
22 andogenous estrogen. We chose .5 PPM E2,

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which is about 80 micrograms per kilogram per day as the positive control in dietary dose to define and to compare the robust responses of the model to an andogenous estrogen versus its responses to BPA. The positive control worked perfectly.

We have also used 2.5 ppm E2 equivalent to about 120 micrograms per kilogram per day, which is rather similar to the mouse dose, interestingly enough, as a positive control in another published multigeneration dietary study in rats, again to define the sensitivity of the animal model and to compare the responses to EPA with those to BPA. The positive control in that case also worked perfectly. Our studies and our results have been repeatedly examined and confirmed by expert third-party consultants and auditors, the EPA and the German EPA made a visit to us after the rat study, in the NEPEPA low-dose workshop by expert reviewers for publication of our studies in the finest

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toxicological journals. We need to look at the studies based on their power and based on their performance. Who pays for them is irrelevant. It's the kind of studies that are done and the results that are found and I would hope that we would keep the discussions on that level. Thank you.

CHAIRMAN PHILBERT: Thank you. Before you depart, are there any questions for Dr. Tyl? Yes?

DR. VANDENBERG: To preface my question, I want to make it really clear, I'm not attacking you or RTI or your response. I just want to understand something. We have the benefit of having received the original reports that you had generated back in 2005 and 2006. And in reading through that, I have drawn my eye to the amended report statement that you provided in 2006 that your experience had evolved and expertise in evaluating mouse estrous data. And the thing that struck me was it said with the concurrence of the

4bdcdd16-71fa-4080-837d-6d72a5410102

sponsor this study was amended.

So my question again, just so I can understand it, is what was the role of the sponsor in designing and evaluating the results and the reports and conclusions? What was the nature of that concurrence? I just want to know what you meant by "with concurrence."

DR. TYL: Yes. That's a pro forma statement because in order to modify a protocol you have to have approval by the sponsor. The sponsor is one of the signatories on the protocol. But I wrote the protocol. We have our own SOPs, standard operating procedures, we perform the study, we collected the data, we interpreted the data, we analyzed the data, I wrote the report.

DR. VANDENBERG: Okay. So the sponsor wasn't involved in reviewing the results and commenting on that or anything?

DR. TYL: Well, they certainly had access to the draft report; that's part of the

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procedure. But they didn't change anything of substance.

DR. VANDENBERG: Okay.

DR. TYL: What else was I going to tell you? What happened was we had been doing rat estrous cyclicity data for so long and the mouse has a very different pattern than the rat. And although I had set up the SOPs to reflect both the mouse and the rat estrous cyclicity staging, it became clear to me that in fact the rat and the -- the mouse was even more different than I had seen before. So it was not - for example, estrous. Estrous in the mouse can last for two to three days. Estrous in the rat lasts for 18 to 24 hours. I mean, things like that that are really different. So determining whether a cycle is normal or abnormal, or missing an estrous for example which is common in the rat but not common in the mouse, needed to be adjusted and I thought it was inappropriate to continue using a system that I had determined was

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wrong.

DR. VANDENBERG: Okay. So in your amended report then, I think what you did is you altered it throughout and provided that in bold so we could see what the changes were.

DR. TYL: Yes, absolutely.

DR. VANDENBERG: So I think that's clear.

DR. TYL: Yes. Yes.

DR. VANDENBERG: Okay. Thank you very much.

DR. TYL: You're very welcome.

CHAIRMAN PHILBERT: More questions? DR. TYL: Yes, sir.

DR. BUSHNELL: Do I understand it correctly that your studies began exposure to the animals at birth, or shortly after birth?

DR. TYL: Before.

DR. BUSHNELL: Before birth?

DR. TYL: Yes, we used - in the rat it was a 10-week pre-breed period for one full spermatogenic cycle; in the mouse it was

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an eight-week pre-breed period for one full spermatogenic cycle in the mouse. So you're exposing them during pre-breed, then mating, gestation and lactation. Then of course the next generation is exposed. So they were never off exposure and they started during pre-breed.

DR. BUSHNELL: Okay. So the offspring were exposed during in utero?

DR. TYL: Yes, in utero and during lactation, at least potentially.

DR. BUSHNELL: Okay. Thank you.

CHAIRMAN PHILBERT: Other questions? Comments?

Thank you very much.

DR. TYL: Thank you very much.

CHAIRMAN PHILBERT: At this time I'd like to invite the members of the panel to come up and take their seats at the front.

While we're waiting for the last members to be seated, first of all, I would like to thank you all for making yourselves

4bdcdd16-71fa-4080-837d-6d72a5410102

available to the subcommittee today. We appreciate your time.

I would ask you first starting from my right hand side to introduce yourself, your affiliation, any potential conflicts of interest that you may feel are pertinent to the discussion. And please do not take more than 30 second each.

DR. HENTGES: I'm Steve Hentges. I'm the Executive Director of the Polycarbonate/BPA Global Group and so what I do in that role is the represent the manufacturers of polycarbonate plastic and bisphenol A.

DR. THAYER: My name is Kristina Thayer. I'm a scientist at the NTP Center for Evaluation of Risk to Human Reproduction. Worked on the NTP brief and I have no conflicts.

DR. GRAY: I'm Earl Gray. I'm a research toxicologist in the Environmental Protection Agency's laboratory in North

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Carolina in the Endocrinology Branch, Reproductive Toxicology Division and I don't have any conflicts of interest.

DR. BENET: I'm Les Benet, professor biopharmaceutical sciences, University of California, San Francisco. And I didn't know anything about bisphenol A until I read this. I have no conflicts.

DR. McCARVER: I'm Gail McCarver. I'm a professor of pediatrics, pharmacology and toxicology at the Medical College of Wisconsin in Milwaukee. I'm also an attending neonatalogist at the Children's Hospital of Wisconsin where we take care of babies. I am a member of the American Academy of Pediatrics and the Society of Pediatric Research, and I chaired the NTP Board of Scientific Counselors during its review of the BPA brief. However, in the purposes of clarity, I am here as an individual and not representing any of the organizations I previously mentioned and I have no financial conflicts.

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1 DR. vom SAAL: My name is Fred vom
2 Saal. I'm a curates professor of biology at
3 the University of Missouri, Columbia. I
4 helped organize the NIH conference on
5 bisphenol A. I was a member of one of seven
6 people that were chairs of panels at that
7 meeting. We also analyzed bisphenol A in
8 products. I'm funded by NIH and some
9 foundations. I have no investments or
10 financial interest in bisphenol A or any
11 alternative products whatsoever that would be
12 used if bisphenol A were or were not banned.
13 MS. LUNDER: My name's Sonya
14 Lunder. I'm a senior analyst at Environmental
15 Working Group. We're a not-for-profit
16 organization 501(c)(3) tax-exempt organization
17 receiving money from charitable foundations
18 and individual donors with no financial
19 interests in BPA production or the production
20 and use of alternatives.
21 CHAIRMAN PHILBERT: Thank you.
22 The ground rules for this session are that

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you've been invited here to respond to specific questions that the subcommittee has regarding the charge in review of the risk assessment.

Questions may be directed to you individually or may be open for general comment. If you do have a comment to make, please indicate so to myself. If the response is adequate and addresses the question, that will be indicated to me by a member of the subcommittee and I will graciously terminate your comments.

With that being said, this is now open for questions and replies. Thank you.

I will take the chair's prerogative and open this up for general comment.

Are there specific health effects that you feel are tied to low-dose exposure, go through mechanism and end up with an identifiable, quantifiable, adverse health outcome?

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DR. BENET: No.

CHAIRMAN PHILBERT: Would you care to expand?

DR. BENET: I'm not sure I should expand here, because if you would allow me --

CHAIRMAN PHILBERT: Oh, sorry. Please identify yourself for the record.

DR. BENET: This is Dr. Benet, USCF.

CHAIRMAN PHILBERT: Thank you.

DR. BENET: My major contribution here is to comment on the proposed studies because I think you're lacking some major innovative words that we could look at to understand what's going here so. So I am not sure, I really don't, should I address that now?

CHAIRMAN PHILBERT: No.

DR. BENET: Okay. Yes.

MS. LUNDER: My name's Sonya Lunder. I would say that there are five high-

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quality low-dose studies that administer BPA to neonatal animals at the dose of 10 micrograms per kilogram per day. They are two for prostate effects and three for brain and behavior highlighted by the National Toxicology Program. And while Agency officials weren't charged with quantitative risk assessment and therefore may not be as comfortable commenting. From the advocacy perspective and from the basics of risk assessment, I feel like those studies are adequate and especially concerning given that the intensity of infant exposures at two to potentially five micrograms per kilogram per day through the first six months of their life call into deep question the safety of the risk assessment.

CHAIRMAN PHILBERT: So is it your position that there is continuity between low-dose exposure, mechanism and adverse health outcome?

MS. LUNDER: Well, the variety of

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mechanistic studies that support the changes to prostate and to brain and behavior would back up the findings of the oral exposure to juvenile animals. That's an extremely relevant study design and exposure route.

CHAIRMAN PHILBERT: Thank you. Yes, Dr. Gray?

DR. GRAY: Yes, I would like to comment. I was on a CERHR expert panel and have done some research with bisphenol A. I think that the position expressed by the NTP in their monograph and by our panel was that there was limited evidence of adverse effects at low doses. And so there's adverse effects at high doses of bisphenol A, which was over five milligrams per kilogram. I think the limited evidence that we identified as the expert panel was on the neurobehavioral effects based on 10 or 15 studies that we declared or felt like were of adequate experimental design and analysis with oral exposure. But they didn't provide a coherent

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1 picture of a disrupted neural pathway or
2 anything, or a clear consistent indication of
3 what might be going on in the nervous system.
4 For all the other effects, we had,
5 our panel had minimal or negligible concern
6 and that's obesity, puberty, cancer effects in
7 adults. And I think I still feel that those
8 are valid conclusions and I think what's
9 missing in a lot of the low-dose studies is
10 the understanding that you need to link these
11 mechanistic low-dose effects through the
12 pathway to an adverse effect. And I'm not
13 sure that there's a clear understanding of all
14 the investigators of what the regulatory
15 agencies call an adverse effect.
16 DR. THAYER: I guess I've been
17 thinking about this mostly in the context of
18 the prostate. We identified two critical
19 studies that we cited in the brief; the Timms
20 one that had dismorphometric changes in the
21 prostate and then the Ho study that had the
22 PIN lesions. So both of those studies had

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1 positive controls. Either 17 beta -- I
2 believe, or EER DES. So in that sense, gives
3 you some idea about whether you're seeing
4 something consistent with a positive control
5 estrogen. And they did give you an estrogenic
6 response, but in terms of completing what
7 you're asking for in terms of effect,
8 mechanism and adversity. So for the Timms
9 study what we had was an effect that was
10 consistent with the two positive control
11 estrogens, but then we had questions about the
12 long term adversity, because in that study you
13 looked at fetal reconstruction at proxy -- so
14 we didn't know what happened in the long term
15 or if that manifests as an adverse effect.
16 In the Ho study, which I think you
17 could argue that the PIN lesions would be
18 closer to something you would consider an
19 adverse effect, the issue there was that in
20 terms of trying to have a tidy story about
21 effect, mechanism and adversity was it seemed
22 that maybe the response in the BPA animals

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1 might -- it might have been more potent than
2 you would expected based on the literature
3 compared to that positive control. And I
4 think, but it harkens back to what Dr. Bucher
5 said in terms of the more we looked at this
6 literature, it became clear to us that it's
7 difficult to try to predict the in vivo
8 responses strictly based on, you know, ER-
9 alpha or beta receptor binding and there's a
10 lot we don't know about other effects.
11 So I think that, again, the short
12 answer is that I don't think there's a tidy
13 story for all of those. I think certainly
14 that it was estrogenic, but it didn't stack up
15 necessarily quantitatively in terms of potency
16 with the other literature on prostate, if that
17 makes sense.
18 DR. vom SAAL: Yes, one of the
19 important things is that neither the NTP or
20 the FDA looked into metabolism and the
21 consensus statement of the NIH panel is that
22 very low doses of bisphenol A are thought to

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be operating through the non-classical nuclear receptor system where all of my data is consistent that you never see in effect within 100 or 1,000-fold less than the difference bisphenol A and estradiol or DES or ethinylestradiol where bisphenol A is significantly weaker, although estradiol being effective below a part per trillion still puts bisphenol A below a part per billion in terms of it target zone, and I showed many data on that.

So the important point here is that if you look at the series of studies out of the Spanish group on the molecular mechanisms through this non-classical estrogen receptor and the 2008 paper shows that it's binding to an ER-alpha that is not in the nucleus, not interacting with an estrogen-responsive element in the nucleus, but instead is activating the IRC12 MAP kinase pathway and then depolarizing the membrane of the beta cell, I mean, they have this worked out in

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remarkable detail. They then see phosphorylation of CREB. They then see insulin production. And is there anybody here going to say high insulin levels followed by high glucose and then insulin resistance is an adverse?

CHAIRMAN PHILBERT: So again, to be clear, has this link been made from in vitro to in vivo? So is there data that shows insulenema in any species following low-dose?

DR. von SAAL: The same people in the same papers then gave 10 micrograms per kilogram per day to a mouse for two days and generated hyperinsulinema. Two days. Two doses.

DR. FITZGERALD: So I'd just like to continue on that a little bit because I'm sure the JAMA paper has caught the attention of a lot of people. And I must say I very much respect the initial gesture of human epidemiology that it brings us to. But in terms of conclusions from it, I think one has

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to be extraordinarily guarded.

So let's just come back to insulin and glucose because there's been lots of talk about that by you and others. Has anybody actually performed studies in humans showing that an insulin clamp, which is really the only way you can look at insulin sensitivity in terms of resistance, that humans have insulin resistance at any type of exposure of BPA? Because the very indirect approach that you cited in the JAMA paper is not significant in terms of a relationship to BPA in three out of the four ways that they looked.

DR. vom SAAL: Actually, are you familiar with the HOMA2 calculation?

DR. FITZGERALD: Yes, that's what I'm talking about, in the JAMA paper.

DR. vom SAAL: Right. And one of the HOMA2 measures is statistically significant.

DR. FITZGERALD: They have four measures.

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DR. vom SAAL: Yes.

DR. FITZGERALD: One is significant. Right?

DR. vom SAAL: And one is significant.

DR. FITZGERALD: I wouldn't take that too seriously.

DR. vom SAAL: And clearly what you're identifying is the kind of follow-up studies that need to be done in both animals and humans. So I totally accept that.

DR. FITZGERALD: Well, has anybody done an insulin clamp study in an animal?

DR. vom SAAL: No.

DR. FITZGERALD: Because you talked about insulin resistance in animals as if it was established. And the other thing that I was a bit concerned about on the diabetes side was that in several examples you showed there was a biphasic dose response curve including in the adiponectin data. How do we interpret that? Does that mean if you

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1 take more BPA things get better, or what?
2 DR. vom SAAL: No, there's
3 actually an extensive literature in the
4 endocrine literature where if you take MCF7
5 cells, breast cancer cells, and you step
6 through very small doses, you see entirely
7 different arrays of genes turned on and off at
8 different doses. It's been known for a long
9 time and we see this in the prostate
10 mesenchyme cells.
11 DR. FITZGERALD: Yes.
12 DR. vom SAAL: The stimulatory
13 dose for different genes is very, very
14 different. It's not like one dose turns on
15 all genes and then one dose turns off all
16 genes.
17 DR. FITZGERALD: Sure, but that's
18 true for lots of things.
19 DR. vom SAAL: Well, that's the
20 point.
21 DR. FITZGERALD: I'm talking about
22 -- I mean, you and others refer to adiponectin

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as part of the evidence for the diabetes link, yet the data you showed with adiponectin had a biphasic dose response curve. How am I supposed to interpret that in terms of the diabetes link? What I'm trying to get at is the plausibility of the data in the JAMA paper. For diabetes I really don't see it there. For the cardiovascular data, based on a handful of cases, 46, 44 cases, there is a lack of internal consistency with respect to no signal with blood pressure, no signal with strokes. And the only reason I'm saying this is because I'm sure that paper in the context that's it's being discussed today is going to leave people with the message that it's been shown that BPA causes heart disease and diabetes and if that's true, I'd really like to hear the plausibility.

DR. vom SAAL: Well, one of the important elements is to focus on the dose that actually was maximally suppressive. And if you look at the range of doses that are

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1 found in the blood of humans and the
2 proportion of that that is in the
3 biologically-active free form, it is exactly
4 dead center targeted on the maximum
5 suppressive dose. If in fact there were a
6 huge discrepancy between the amount that you
7 would find in the average person and the
8 amount that maximally suppressed adipenectin,
9 I think that I would totally agree with you.
10 But since they directly conform to each other,
11 I would say that's a reason for concern
12 because that suppression occurs over, well
13 over an order of magnitude. So that is going
14 to encompass quite a large number of people
15 probably, given that the center point of that
16 suppression, according to the published
17 literature on amounts, in blood using a
18 variety of techniques. There's one technique
19 using a lye as a measure -- criticized, but
20 there lots of other techniques that have not
21 been criticized. It's dead center on that.
22 And again, this follows with a literature from

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the mouse that exactly that dose is what stimulates this new estrogen receptor system that is not as, you know, completely understood, but is clearly not the classical nuclear receptor system. That is exactly the same dose, that is maximally stimulatory for proliferation of prostate cells in culture, prostate cancer cells.

DR. FITZGERALD: But for example, in terms of actually getting to functional relevance as opposed to associations. People haven't done a study, or have they, where they've given BPA, shown an effect in the mouse that is not there if the adiponectin receptor is taken away from the mouse? Because that's the way that you'd approach the role of adiponectin.

DR. vom SAAL: Yes, actually there are studies, experimental studies of changing, manipulating adipenectin and seeing consequences of that in terms of --

DR. FITZGERALD: BPA effect?

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1 DR. vom SAAL: Well, damage to the
2 cardiovascular system.
3 DR. FITZGERALD: Well, I'm
4 familiar with those. But BPA --
5 DR. vom SAAL: Oh, no. You know,
6 so we're not at a point --
7 DR. FITZGERALD: Okay.
8 DR. vom SAAL: But if you were to
9 have something that manipulates adipenectin,
10 then there are physiological consequences.
11 But that's an experimental --
12 DR. FITZGERALD: One last question
13 which goes back to the JAMA paper. So a
14 handful of cardiovascular events in which
15 urinary BPA is measured, and probably given
16 the NHANES data set, people have had the index
17 event at very variable times relating to when
18 their urine was collected, what was measured
19 in the urine was free plus glucuronidated BPA,
20 because converted -- is there information, as
21 opposed to an assumption, as to the chemical
22 stability of the anylate over the period that

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1 covers the discordance between the time of
2 urine collection and the actual event, which
3 is actually at the center of the validity of
4 that paper?
5 DR. vom SAAL: Are you asking
6 stability of the anylate in the urine?
7 DR. FITZGERALD: Chemical
8 stability of the anylate, because --
9 DR. vom SAAL: That's not --
10 DR. FITZGERALD: So I'm not saying
11 does the anylate get -- I'm saying the
12 chemical stability of the anylate. So if I
13 freeze and unfreeze urines over five years --
14 DR. vom SAAL: But that's not an
15 issue because it's hydrolyzed and in fact
16 they're measuring total --
17 DR. FITZGERALD: No, I understand
18 that. Yes.
19 DR. vom SAAL: So whether it --
20 and the answer is it does degrade over time
21 from the glucuronidated to the non-
22 glucuronidated form, but --

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DR. FITZGERALD: Sure, but you're measuring total. Right?

DR. vom SAAL: That's right.

DR. FITZGERALD: Yes.

DR. vom SAAL: So it doesn't --

DR. FITZGERALD: So I'm saying --

DR. vom SAAL: Total free.

DR. FITZGERALD: Yes, I'm saying have people looked at the stability of the anylate of what is measured as total over the period of time that covers the discordance between --

DR. vom SAAL: Yes.

DR. FITZGERALD: Yes? Okay.

DR. vom SAAL: It's too bad Antonia isn't here, but they have --

DR. FITZGERALD: If the answer's yes, that's fine.

DR. vom SAAL: -- articles published on that.

DR. FITZGERALD: Okay.

DR. vom SAAL: What is not stable

4bdcdd16-71fa-4080-837d-6d72a5410102

is the glucuronidated form.

DR. FITZGERALD: Yes.

DR. vom SAAL: What is stable - Bisphenol A is a very stable molecule.

DR. FITZGERALD: Okay.

CHAIRMAN PHILBERT: Dr. Gray, did you have a comment?

DR. GRAY: No, my comment just was that Antonia Calafat's, one of the people in her lab had looked at the stability of the BPAG BPA complex over time. But the total wouldn't change. They found that the -- over several hours if it was stored at room temperature, there's a breakdown of BPAG to BPA so that the free levels were exaggerated by --

DR. FITZGERALD: I'm getting a side issue.

DR. GRAY: But what you're talking about was different.

DR. FITZGERALD: A different issues, yes. A urine that you got that's five

4bdcdd16-71fa-4080-837d-6d72a5410102

1 years old. That's what I'm getting at.
2 DR. BUSHNELL: I'd like to move
3 back to the neurobehavioral aspects again
4 along the same lines.
5 Earl, you've done some analyses of
6 these effects and there's a large variation in
7 the kinds of effects you see when you look at
8 behavioral effects, sex-dependent, gender-
9 dependent behavioral effects. And I was
10 struck in one of those papers of yours how
11 inconsistent the data were. That is,
12 sometimes there was increases in motor
13 activity say in males and sometimes it was in
14 females. And I'm wondering, you know, how the
15 mechanisms in terms of the effects of an
16 endocrinactic compound during development
17 could -- or have these mechanisms worked out
18 well enough that we could study these
19 behavioral effects in a mechanistic fashion
20 and come up with some conclusions about how
21 BPA is actually affecting animals in vivo.
22 DR. GRAY: Yes. Well, I hope it

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1 wasn't my paper you found the inconsistent
2 data in.
3 DR. BUSHNELL: Oh, no. Well, no.
4 No, it was not your data.
5 DR. GRAY: No. No. But no, we
6 did find there were 15 or 20 papers with
7 orally administered with adequate experimental
8 design that had some sort of behavioral, or
9 neuro-chemical, or some change in the brain
10 due to the low-dose BPA exposure. And that's
11 why we gave that a higher level of concern.
12 And I don't think we ever got to the point in
13 the CERHR panel where we sat down and really
14 looked at whether it was biologically
15 plausible based on what we knew about the
16 organization and activation of a particular
17 sexually-dimorphic behavior in a given
18 species. And so, if you're assuming that it's
19 mediated through estrogen receptor alpha, then
20 there are studies we can do in rodents. There
21 are some quite well characterized sexually-
22 dimorphic behaviors that are organized in the

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rat by estrogens. And then they are activated by other hormones in adult life. So estrogen's in the neonatal rat are critical for masculinization of the brain. They're also critical for normal development of the mouse prostate. And then those behaviors are activated in the adult by other hormones.

There are other behaviors in the rat that are organized in the neonatal period by androgens and not estrogens. So for some of the behaviors we do know enough to say whether we can produce and ER-alpha-mediated alteration with bisphenol A. And at one point we were in the middle of doing that. Well, we're still in the middle of trying that, and whether we'll be able to complete it, I don't know. But that's certainly possible.

I think there are many of the behaviors that we talked about. We don't know enough about the organizational influence of hormones. And some of the things were like protein levels or message levels in the brain,

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or things like that, which we have no idea. And there are a lot of inconsistencies in the papers and they were reportedly changing the behavior due to a hormone treatment, but they had no sex difference in the behavior between the sexes. So it's not clear how you'd produce this sexually-dimorphic alteration.

DR. BUSHNELL: Okay. But there are models that could be used where you do know enough about the organization and/or --

DR. GRAY: Oh, absolutely. If you were looking for an estrogen-mediated effect.

DR. BUSHNELL: Right.

DR. GRAY: And if it -- nuclear receptor-mediated. If you're looking for some other mechanism, then these would be more specific. But then the behavioral changes wouldn't be expected to be sex specific.

DR. BUSHNELL: But you would be able to determine whether BPA has an influence on those --

DR. GRAY: Absolutely.

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1 DR. BUSHNELL: Okay. That's what
2 I was looking for.
3 CHAIRMAN PHILBERT: Dr. vom Saal?
4 DR. vom SAAL: Yes, I think an
5 important follow-up to that is, I agree
6 completely with what Dr. Gray said and I also
7 agree with the interpretation of the National
8 Toxicology Program that it's the sum total of
9 the outcomes from a very wide variety of
10 experiments done in very different ways. And
11 we even have data from our own lab that we're
12 just writing up in the locus ceruleus where we
13 see in the female due to response to perinatal
14 bisphenol A just a loss of tyrosine
15 hydroxylase containing neurons in the female,
16 but no change in the male whatsoever. That's
17 consistent with the kind of thing Bev Ruben
18 has shown in the medial preoptic area -- is
19 medial or anterior? Anyway, there are studies
20 of morphological and neurochemical changes all
21 over the brain where in the control animals
22 there are sex differences. And in non-control

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1 animals there aren't.
2 Actually, I'd be happy to give you
3 a paper that's in press in environmental
4 research coming out in just a week; I don't
5 think they'd mind me doing that, where a
6 colleague and I reviewed that literature, and
7 on bisphenol A. So I think that would maybe
8 be helpful. The studies were all done in very
9 different ways, so it doesn't fit a classic
10 replication. But what the National Toxicology
11 Program said was what was consistent is where
12 somebody had looked for a sex difference and
13 given bisphenol A that sex difference was
14 gone. Sometimes the female just changed or
15 sometimes both the male and the female
16 changed, or sometimes the change was bigger in
17 the male than the female. And that's where,
18 as Dr. Gray just mentioned, there are so many
19 different mechanisms. It isn't just like
20 estrogen controls one thing. You see
21 different things.
22 DR. BUSHNELL: And this is I think

4bdcdd16-71fa-4080-837d-6d72a5410102

a different topic maybe that, you know, you have all of these effects, various treatments, various doses, various animals, various end points. How in the world do you put all the stuff together in some kind of a quantitative risk assessment and then maybe something we -- I don't know whether we're ready to move to that point with this right now, but that would be my question to you, is how in the world do you do that? You have to come up with a number. The FDA and the EPA too, when they do these assessments have to come up with a safe number. How do you make these comparisons of apples and oranges?

DR. vom SAAL: But then you have to look at the public saying I care about the gender of my baby. And if this were to apply to humans and you were to say you were neutralizing the gender of offspring, that's going to concern people.

CHAIRMAN PHILBERT: To be clear, are you saying that bisphenol A neutralizes

4bdcdd16-71fa-4080-837d-6d72a5410102

gender differences?

DR. vom SAAL: That's what the data -- the data show that where there are sex differences in control animals through a variety of different systems, sometimes the female becomes -- and Dr. Bucher showed those data where as a result of exposure to bisphenol A, that difference in anxiety that you saw where the female was much less than the male. As a result of bisphenol A exposure the male stayed exactly the same and the female came down and looked exactly like a male. The sex difference was gone. There is a very large literature on that.

CHAIRMAN PHILBERT: So, I think you've alluded to that data already, but your statement was somewhat more encompassing, all encompassing in fact.

DR. vom SAAL: Yes, actually probably Kris Thayer could give us some kind of a number, but there are a substantial --

CHAIRMAN PHILBERT: Is it your

4bdcdd16-71fa-4080-837d-6d72a5410102

assertion that BPA abolishes sex differences in the brain or other organs of the mammal?

DR. vom SAAL: Well, other organs, it's a little bit different.

CHAIRMAN PHILBERT: The brain.

DR. vom SAAL: Okay. Just the brain. And I would say the literature is very consistent that that is an outcome. And that was the conclusion in the NTP brief.

CHAIRMAN PHILBERT: Dr. McCarver?

DR. McCARVER: Thank you. While I agree that the data are quite worrisome in the animal model, I think the NTP, and I was there, so I will try to speak as honestly, but I think the consensus opinion was while we were concerned, we did not really relate that directly to human risk. And I think that is something we must keep in mind here. Many of the things that we see in sexual dimorphism in rodents simply do not have a correlate in humans. And so while we didn't fail to consider it, one of the reasons I think the

4bdcdd16-71fa-4080-837d-6d72a5410102

1 risk level was set lower is that we really do
2 not have an easy way to extrapolate that data
3 into humans.
4 CHAIRMAN PHILBERT: Dr.
5 Vandenberg?
6 DR. VANDENBERG: Maybe to take the
7 discussion a little differently, is I know
8 that we have a couple of members of the
9 committee that helped participate in the
10 discussion about weight of evidence. And what
11 I'd like to ask you, and perhaps Dr. Bucher
12 would like to contribute to this as well, is
13 I'd like to really understand the difference
14 between "some" and "minimal." And in the
15 statement here in the NTP conclusions, it
16 says, "Some evidence for adverse effects for
17 developmental toxicity for fetuses, infants
18 and children with effects on brain, behavior
19 and prostate gland." I'm not sure I really
20 understand what "some concerns for adverse
21 effects" -- this is at environmental levels --
22 means in this context. Whoever would choose

4bdcdd16-71fa-4080-837d-6d72a5410102

to comment.

DR. GRAY: Well, I think we should give separate answers because we came to those levels of concerns as the expert panel. And then that was advice to the NTP and they might have had their -- or certainly had their own --

DR. VANDENBERG: Fine. Fine, will you both comment, please. Yes.

DR. GRAY: So I mean, when we went through, there are the five levels and so many of the things we felt were negligible and that's the lowest level. You can't have no concern, because there's always a -- you know, okay. So that's pretty low. And so there were some issues where there were studies, there were positive studies that were well designed. There were a couple of them, like puberty in the female and the female mouse was accelerated in two or three studies and there weren't any studies that couldn't replicate that. So that was enough we felt to elevate

4bdcdd16-71fa-4080-837d-6d72a5410102

it to minimal. It was not consistent in the rats, so we didn't feel like that elevated it more.

And then there were several things like the prostate where our committee felt like it was minimal because we had low-dose effects and PIN lesions in the prostate, but it was subcutaneous and we were concerned about the metabolism, and it was a preneoplastic PIN and hadn't been shown to be cancer. So we call that negligible and they felt it was more serious, which is not a big difference, so they called it some.

DR. VANDENBERG: But you considered the Timms study as well, correct? Timms?

DR. GRAY: We considered that. Yes, we felt like that was an adequate study. It was well designed. It was small and it showed the enlarged prostates. But then you don't know that it would become an adverse effect. And when people looked in mice, they

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1 didn't consistently find large prostates or
2 small prostates. So the PIN lesions, we
3 elevated that. And the reason why
4 neurobehavioral was the higher level of
5 concern by our advisory committee was that
6 there were more studies there. And I don't
7 the literature on sex dimorphisms is
8 consistent and those were studies were all
9 reviewed recently by Abby Lee. And so are a
10 lot of studies looked at locomotor activity
11 and they didn't all find differences, but
12 there were enough well-designed studies with
13 different, not just behavior, but DH receptor,
14 DH message.
15 DR. VANDENBERG: So it's greater
16 weight of the evidence is what you're saying?
17 DR. GRAY: It's greater weight.
18 There is more there, but my feeling about
19 "some," and this would be my opinion, because
20 the CERHR panel didn't ever get to the point
21 where we discussed that, but this, to me, it
22 really indicates there's a research need, but

4bdcdd16-71fa-4080-837d-6d72a5410102

we haven't demonstrated an adverse effect.

DR. VANDENBERG: Okay. So and then, Dr. Thayer, perhaps you want to comment.

DR. THAYER: Right. So, you know, you've seen our five-point scale. "Some" is right in the middle. There's not clear boundaries. In general, those levels of concern are driven by how clear is it that you have an adverse finding in either laboratory animals or humans, and also what we know about human exposures. So, you know, there was limited evidence of adverse effects, but then because those effects were being reported at doses that were similar to human exposures, that is how we got to "some."

So in our draft document, we presented all the health effects, behavior, prostate, mammary gland and effects on puberty or sexual development as presenting some concern. And it basically came from some of the language that we saw in the expert panel report dealing with brain and behavior. They

4bdcdd16-71fa-4080-837d-6d72a5410102

basically said that there's a number of well-designed studies that are reporting effects that we can't fully interpret, but we can't dismiss. And we felt that applied to all of the end points that we highlighted in the brief to support a level of concern.

During the peer review process, we sort of took them one by one. We presented them, you know, rather than that package deal, we presented them one by one. And then I think it fell out right.

DR. VANDENBERG: You mean by end point or by study?

DR. THAYER: By end point.

DR. VANDENBERG: By end point?

DR. THAYER: And I think it fell out correctly. I mean, it was clearly in terms of the number of the studies, number of well-designed studies or reporting something at brain and behavior, there were some. The prostate we elevated basically because we felt that we could perhaps better interpret the

4bdcdd16-71fa-4080-837d-6d72a5410102

subcutaneous administration to a neonate and that was a critical issue in the Ho study. I mean, if you look at the expert panel evaluation of that study, it was pretty positive that seemed to be the only reason why it wasn't considered in its highest utility category.

And then there was a new publication that reported the subtle effect related to estrogen. So that's why we increased it.

The mammary gland, that one, you know, you had the subcu administration to adult animals which we did not think you could interpret as readily as an oral exposure. And then there were just more technical issues with those studies.

So, on balance, I think that a minimal concern for those effects is probably okay.

And the same thing with puberty. I mean, in the expert panel report they

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1 expressed minimal concern for puberty and it
2 was based on these two mouse studies. There
3 wasn't essentially anything in the rat
4 studies, but based on the expert panel report
5 there was nothing in there to say we think
6 this sort of general negative literature in
7 the rat studies trumps these two mouse
8 studies. And that's why it stayed on the
9 table for us.
10 DR. VANDENBERG: As I understood
11 one of the comments that Dr. Bucher made
12 earlier was that NTP has not identified
13 prostate cancer in any of the NTP bioassays.
14 So when you look at these sort of early
15 changes from early life exposure, do you have
16 a sense of what the relevance might be to that
17 in the long term, or you just don't know?
18 DR. THAYER: Well, no, I think for
19 the PIN lesions, and you'll correct me if I'm
20 wrong, they use a hormonal model to bring out
21 the PIN lesions that -- estradiol and
22 testosterone that was supposed to mimic the

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hormonal profile in an aging male. It seems to be an established model in the prostate cancer rodent world. It seems that that model, those PIN lesions do progress in that model. It wasn't demonstrated in the BPA study. That was a comment noted in the expert panel report. We had a workshop a few years ago to try to figure out what we can do to better improve the cancer bioassay for looking at some of these hormonally-mediated tumors and one of the pieces of advice we got for prostate was to consider using these non-conventional models, because you're just probably not going to get there if you don't tweak the system or use a genetically-modified animal. And also to consider the perinatal exposure.

DR. VANDENBERG: So this is consistent with sort of that --

DR. THAYER: Right, they said that you might have to use sort of the pre-tumor lesions.

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1 DR. VANDENBERG: Right.
2 CHAIRMAN PHILBERT: Dr. Gray and
3 then Dr. vom Saal. DR. GRAY: In the study
4 that we did with bisphenol A and
5 ethinylestradiol as a positive control, with
6 ethinylestradiol perinatally you do get
7 prostate lesions, non-cancerous prostate
8 lesions, prostatitis and inflammation in a
9 normal dose-related manner and we did not see
10 those prostate changes with bisphenol A at low
11 doses, or any doses. Our bisphenol A was
12 three doses, 220 and --
13 DR. VANDENBERG: Sorry, I was
14 referring to the Timms study. There was just
15 one dose. When you were reviewing the
16 literature.
17 DR. GRAY: Oh. Oh, okay.
18 DR. VANDENBERG: Yes, sorry.
19 DR. GRAY: When we were reviewing
20 the literature. Yes, Timms had one study.
21 DR. VANDENBERG: One study.
22 DR. vom SAAL: The one thing I'd

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like to add to that is that in addition to the reconstruction of the prostate we took the sections where there are glands and we immunostained them. And one of the things that we saw, and anybody who studies glandular development knows that if you see rapidly proliferating glands growing at an abnormal rate, particularly due to something like the basal cell, which whether you refer to it as a stem cell or a progenitor cell, it clearly is the progenitor cell from which the secretory epithelium regenerates. And then following up showing that that was the target for bisphenol A and these other estrogens, hyperplasia, then not covered in this report, but published after the NTP was finished, is the Ogura paper showing that in adulthood with immunostaining you can see basal cell abnormalities and squamous metaplasia. And then if you're familiar with prostate cancer, you know the basal cell disappears and is thought to be the transforming cell that

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1 becomes the neoplastic lesion. And in the rat
2 model where that -- Nobel was the one who
3 started back in the '70s, if you take those
4 animals out another six months then what you
5 see is in the cranial, in the anterior
6 prostate and in the dorsal and the lateral
7 prostate, you see metastatic tumors. But you
8 have to leave them a lot longer than four
9 months. You see dysplasia and neoplasia at
10 four months, but you have to let the animals
11 go a lot longer and then they start
12 transforming into actually metastatic tumors.
13 So in the rat, anyway, if you let
14 them go long enough, that happens. The reason
15 that I think what we did was interesting is we
16 saw that basal cell abnormality right at the
17 front end. Ogura is then talking about
18 squamous metaplasia progressing from
19 hyperplasia, metaplasia, go through dysplasia
20 to neoplasia. I mean, there you have the
21 cancer progression. We've got a fair amount
22 of that outlined there. So that I think

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should really fit into this picture.

CHAIRMAN PHILBERT: Thank you. Other questions? Yes?

DR. FITZGERALD: On a completely different part of this topic, I'd just like to come back to this discussion we had several times today around the conservatism or not of calculating the no-effect dose issue. And, you know, one of the things that stuck in my mind was the use of sort of average plasma concentrations or average measures of exposure and then their extrapolation. And maybe this is something Gail can help me with.

Is the intraindividual variability in plasma concentrations of bisphenol A, or is it known, under chronic exposure - particularly in young people, like infants - is that so variable that we should actually not be using average levels? Should we be pivoting off something like an upper band or like something else from which to make our extrapolations?

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1 DR. McCARVER: Well, you ask a
2 very relevant question and that unfortunately
3 we have no data of bisphenol A levels in the
4 group at largest risk, which I believe is the
5 one to two-month-old age group. And
6 furthermore, we have no data in premature
7 infants which is not even addressed in this
8 report and I will remind you that there are
9 roughly 500,000 premature babies born in this
10 country every year, which are also exposed to
11 many other forms potentially of environmental
12 compounds that may act like BPA in our
13 nurseries that are filled with plastics.
14 So to answer your question, the
15 brief, no, there are no data. To answer it a
16 little more fully, I believe the exposure
17 assessment in the FDA document is flawed. I
18 do not believe it is sufficiently
19 conservative. My reasons for that are, first
20 of all, they took the data largely from that
21 Biles paper, which I think was alluded to
22 earlier, 14 cans that were measured in the

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1 Washington, D.C. area and they took an average
2 from that. I am presuming that is all the
3 data that we have that addresses this, as far
4 as I know. But if one takes those 14 cans,
5 one could easily make the argument that
6 realistically one should be going off of the
7 maximum can value and not the average can
8 value.
9 Secondly, the assumptions also
10 looked at the average of the mean eaters, I
11 believe, is what it was called. That too I
12 have a problem with. I do not believe that we
13 should be protecting our children at an
14 average level. I believe the NTP estimate is
15 probably a little bit closer. I believe it is
16 in excess of the FDA's estimate by about 5.5-
17 fold, I think on the max value that the report
18 was a 13.2, and I would strongly recommend to
19 you that you increase the exposure assessment
20 and the assumptions and then also change the
21 margin of safety to take those kinds of things
22 into consideration if we are going to put this

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1 forward to the public as a conservative
2 estimate. I do not believe that will stand
3 credibly.
4 MS. LUNDER: Thank you. I'd like
5 to elaborate just on one other aspect of the
6 exposure assessment which is that FDA divided
7 all the BPA measurements and formula by two,
8 assuming that there was one for one dilution
9 with water because they happened to test
10 concentrated formula which parents are
11 supposed to dilute. However, 11 percent of
12 infants are fed ready to eat formula that
13 comes directly from the can, so it's a 50
14 percent underestimate, as well as noting that
15 that ready-to-feed formula is what's given out
16 in NICU's. It's given to the most medically-
17 vulnerable children when there's any concern
18 about water contamination or the child's
19 health.
20 DR. McCARVER: Thank you for
21 pointing that out. That's true. And the
22 other thing I'd also like to point out, there

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1 was a comment made that there was assurances
2 based on the fact that a large number of
3 people in this country use powder. I would
4 suggest to you that the people in this country
5 predominantly who use powder are the more
6 affluent elements in our society. Certainly
7 we know in terms of our WIC programs, they
8 give out largely again ready-to-feed, as was
9 just mentioned. So I think we have to take
10 that also into consideration and I would urge
11 you not to put that in the public forum
12 document to say that, you know, because most
13 people use powder we think we can be assured.
14 CHAIRMAN PHILBERT: Dr. Hentges?
15 DR. HENTGES: Yes, coming back to
16 the exposure assessment, in particular looking
17 at the infant formula, I think you're right
18 that FDA did base their assessment on their
19 data from however many years ago. That's not
20 the only data. I believe there is more recent
21 data that perhaps is in one of the supporting
22 memoranda, for example, from Health Canada,

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very recently measured bisphenol A in a larger sample of canned infant formula and I believe the numbers are fairly similar.

CHAIRMAN PHILBERT: One moment, doctor. Ms. Lunder, do you have a clarification?

MS. LUNDER: That's true. They measured 21 samples of formula from last year, 2007. I have the abstract for the publication that was released this summer and also Environmental Working Group, my organization tested six cans of formula and found a maximum concentration of 17 parts per billion, which if substituted for the 2.5 parts per billion used in FDA's estimate, would more that double the infant exposure estimate.

CHAIRMAN PHILBERT: And have you made this information available to the subcommittee or --

MS. LUNDER: Our research was referenced in the draft document by FDA.

CHAIRMAN PHILBERT: Okay.

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MS. LUNDER: And as was Health Canada, but it's now in a peer-reviewed publication which I can get and circulate to the committee.

CHAIRMAN PHILBERT: Thank you very much.

To return to Dr. Hentges.

DR. HENTGES: Right, thank you. And then regarding whether you would use an average value or the highest value ever measured anywhere, I think the average value probably is still appropriate. The reason being that the bisphenol A is in the can coating. It's not an intentionally added component at a specific level, but rather it's a residual level and it's going to have some natural variations. So even a single brand of formula or any single brand of any can is going to have some variations. So if you measure a high level today at the upper end of the range, measure that same product next week or next month, it's going to vary somewhat.

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1 So I think for an infant, even using the same
2 brand for a period of time, you're going to
3 find that that infant is going to be exposed
4 to an average level, not consistently at a
5 particular high or a particular low level. So
6 I think the average probably is appropriate.
7 CHAIRMAN PHILBERT: Dr. Rockette,
8 is this on point?
9 DR. ROCKETTE: To this particular
10 point, I mean, relative to your comment on the
11 appropriateness, I mean, given that we have a
12 limited number of scenarios that the exposure
13 was measured in, so there's lots of
14 variability there, and given that we're using
15 the average on what appears to be somewhat of
16 a skewed distribution if you look at some of
17 the other data. I mean, it would seem to me --
18 but I'm interested in the comments of the
19 panel, that it would not be unlikely that 20
20 or 25 percent, who knows what that number
21 would be of the infants two months and younger
22 would in fact not have this MOS that's 1,000

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or above, that that would not be -- or do people feel that they're very confident that that 1,000 criteria would be met for say 95 percent of the infants? It doesn't look to me like with the variability you're talking about that that would be the case, but I'd be interested in your comments.

CHAIRMAN PHILBERT: Ms. Lunger?

MS. LUNGER: A couple of minor points. I disagree about the characterization of using average formula because the three highest samples of levels of BPA detected above 10 parts per billion were all Enfamil brand formula, which if you're only looking at 20 tests and your three highest are all one brand would suggest to me that there could be significant brand differences. Also a child who's light or who is hungry will likely be on the lighter end of the spectrum or the hungrier end of the spectrum throughout that period of intense formula feeding, which could be the first six months.

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1 CHAIRMAN PHILBERT: Dr. McCarver
2 and then Dr. vom Saal.
3 DR. McCARVER: There are a couple
4 more subtle things that I don't think we
5 really know; at least I don't know the
6 information on. And those include things like
7 what happens when cans sit in warehouses and
8 when they sit on trucks, and when they sit
9 before delivery? They are not temperature-
10 controlled. And so I don't know that we have
11 data. I mean, I know the provocative testing
12 that was done for leaching from baby bottles,
13 but I don't think we have much in the way of
14 data to say, you know, what does it matter in
15 terms of, you know, if the shipment sits and
16 whatever. And this may be the kinds of things
17 that are going affect variability.
18 And so I think that is one factor.
19 And then as she mentioned this issue of
20 eating, another thing that was not in the
21 estimates, which I thought was a relatively
22 minor thing, but I'll mention it here, is that

4bdcdd16-71fa-4080-837d-6d72a5410102

many infants do eat far more than the average. And the ones that don't typically as they get older tend to eat foods that sometimes are brought forward out of canned products. So I think that some of the things of the variability we cannot know, but I would argue that I do believe that the best interests of children is to protect at the higher level, rather than at an average level.

DR. ROCKETTE: What about a dishwasher? I mean, that may seem a dumb question, but I mean a lot of people, it would seem to me, might use a dishwasher which is hotter; I don't know hot it gets, but for longer periods of time than the few minutes of boiling.

DR. McCARVER: As a general pediatrician, I can tell you that my recommendation is if people were on city water, that dishwashers were fine. The other thing that the document states is that people don't typically sterilized bottles after two

4bdcdd16-71fa-4080-837d-6d72a5410102

1 months. That's typically true in our urban
2 areas where water supplies are secure. But in
3 our out areas, our out rural areas,
4 recommendations are generally made to families
5 to continue sterilization for even longer than
6 that. So I do applaud the FDA because I
7 believe what they did here is the correct
8 thing; that is, that they took for it as if
9 sterilization occurred longer and I believe
10 that part of the equation was done correctly.
11 CHAIRMAN PHILBERT: Dr. vom Saal
12 and then Dr. Hentges.
13 DR. vom SAAL: There are two
14 issues. Often bisphenol A contamination of
15 products is presented, as Dr. Hentges just
16 did, as residual bisphenol A remaining after
17 polymerization. Bisphenol A is ester-bonded
18 polymer into this resin and under conditions
19 of increasing heat and increasing acidity or
20 alkalinity you have breakdown of the polymer.
21 You have hydrolysis of the ester bond. You
22 all remember this from undergraduate organic

4bdcdd16-71fa-4080-837d-6d72a5410102

chemistry. I mean, this is a condition that occurs. It's not residual bisphenol A; it's degeneration of the bond. And I have a paper from DuPont that shows that under 10 percent sodium hydroxide and elevated heat within, you know, a month or so you had 50 percent of the polycarbonate was gone, completely dissolved into solution. So where these cans are, what they're subjected to, is going to be a factor in the continued degradation rate and we've actually measured something like tomato sauce where we get 50 micrograms in a can of tomato sauce because of the acidity combining with the heating process occurred during the sterilization.

The other really critical thing that since we just published that paper that everybody's throwing around about the neonate and whether neonatal mice do or do not discriminate between how they're injected; that came out of my laboratory, and what we showed is in a neonatal mouse whether you

4bdcdd16-71fa-4080-837d-6d72a5410102

inject bisphenol A at a dose way above the safe dose or below the safe dose, injection and feeding give you absolutely identical 24-hour blood levels of free bisphenol A. And so, what that suggests is at least in the rodent there isn't this 20-fold, 10 to 20-fold difference in the rate of metabolism that you see in the adult. We have no data on this in the human newborn. And so any talk about what is going on in a newborn baby is just based on a guess, an assumption. And that's a really critical part of this. This is a black hole of information in terms of how -- At least we know in the newborn rodent they don't have the ability to metabolize this, so they're not discriminating at all between oral and non-oral uptake. Whether the neonatal human is or is not remains to be determined.

CHAIRMAN PHILBERT: Thank you. Dr. Hentges and then I would like to move the discussion because this is very interesting discussion, but we need to cover a couple of

4bdcdd16-71fa-4080-837d-6d72a5410102

other areas.

DR. HENTGES: Thank you. Just a few clarifications. When I was speaking earlier about bisphenol A as a residual component, we were talking about infant formula which is an epoxy resin can coating. Bisphenol A is indeed a residual component there. It's not formed by degradation of the epoxy resin.

There is some data on heating cans, because the cans are actually heated when they're filled to sterilize them. And I think it is understood that that residual component leaches into the formula at that time when the can is retorted, when it's sterilized, so it doesn't increase over time as the can is stored or shipped or whatever.

Regarding dish washing, I assume you were talking about baby bottles there, polycarbonate baby bottles. There is a study that was published just recently from the Norwegian Food Safety Authority looking in

4bdcdd16-71fa-4080-837d-6d72a5410102

1 detail at what happens with polycarbonate
2 bottles in a dishwasher. And that study; I
3 believe it's in the exposure assessment
4 already, so I won't go into any detail on
5 that, but it does clarify that dish washing is
6 appropriate for polycarbonate bottles.
7 And then finally regarding
8 degradation of bottles, that has been a
9 controversial area whether additional
10 bisphenol A is formed or not as the bottle is
11 used. Another paper very recently published;
12 it's also in the FDA assessment from
13 researchers at the University of Athens,
14 looked at a variety of conditions, real life
15 use conditions, and concluded that bisphenol
16 A is not formed by degradation, but rather it
17 is, under real life use conditions it is
18 released as a residual component. But that
19 data is all in the FDA assessment already.
20 CHAIRMAN PHILBERT: Great. Are
21 there any other questions?
22 DR. vom SAAL: I appreciate Dr.

4bdcdd16-71fa-4080-837d-6d72a5410102

Tyl's concern that I was trying to attack her personally, whereas what I was talking about was the methods used in the test. And I'm sitting here looking at her paper, and on page 13 and page 93, in two different places, that identifies that the males used were weaned at day 21 and then after three months they were tested. So they were three months and 21 days old. And that's the data very similar to the weight that I presented at three months in my animals. I don't know where she came up with the six months. If they did that, then they're not accurately describing what they did in the actual published paper. So in a published paper, they say the animals were three months old and a 70 milligram -- even at six months a diseased prostate would be a problem.

CHAIRMAN PHILBERT: Thank you for that clarification. I think we need to move on.

John?

4bdcdd16-71fa-4080-837d-6d72a5410102

DR. VANDENBERG: Yes, this may be actually a question for the FDA staff, and that is in regards to the dose response that was employed. In looking at the studies I see that there's a focus on the NOAEL or the LOAEL rather than looking at like a benchmark dose level. At the EPA, we typically look at studies and evaluate whether or not we can model the dose response shape and thereby reflect the strength of the study in terms of the number of animals per dose group and use a benchmark dose as the point of reference or as a point of departure for the application of uncertainty factors rather than using the NOAEL or the LOAEL as a fixed point. There's actually more information gained by doing benchmark dose modeling.

So my question would be whether that was considered and if it was feasible given the nature of the data that was evaluated.

CHAIRMAN PHILBERT: If there's

4bdcdd16-71fa-4080-837d-6d72a5410102

1 somebody from the FDA who wishes to respond,
2 please use the podium. And please identify
3 yourself.
4 DR. TWAROSKI: Dr. Twaroski. I
5 think that's a very good question as to
6 whether or not there are other techniques that
7 can be used to try to identify what's really
8 going on here.
9 First of all, all the studies that
10 were listed in the report were considered. In
11 terms of modeling the studies, based on the
12 information that was published in a lot of the
13 academic literature, we did not feel that they
14 could then be put into any type of model. So
15 it's true that we used our traditional
16 approach in looking at just a threshold type
17 of event with those two guideline-based
18 studies, the Tyl studies. Whether or not you
19 could model a benchmark, we just did not feel
20 that the literature data set was that
21 confident to do that at this --
22 DR. VANDENBERG: Is that the case

4bdcdd16-71fa-4080-837d-6d72a5410102

1 though with the Tyl studies? Because you
2 actually have the original data.
3 DR. TWAROSKI: We have the
4 original data, but we did not approach it in
5 that manner.
6 DR. VANDENBERG: Okay.
7 DR. TWAROSKI: Okay.
8 DR. VANDENBERG: All right.
9 DR. TWAROSKI: But it's a good
10 suggestion and we welcome those types of
11 suggestions from the committee.
12 DR. VANDENBERG: Thank you.
13 CHAIRMAN PHILBERT: Thank you. I
14 think in the interest of time we do need to
15 move on. We only have five minutes remaining.
16 I know it seems like we've only spent five
17 minutes here.
18 I'd like to return to Dr. Benet if
19 I may and the reason that you have -- excuse
20 me for one moment. Oh, sorry. We have until
21 3:30. Oh, joy.
22 Dr. Benet, you had some --

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1 DR. BENET: Yes, thank you, Dr.
2 Philbert.
3 First of all, I'm an expert in
4 pharmacokinetics. I'm an expert in drug
5 metabolism and I've done a lot of
6 glucurondation work over the years.
7 I'm accepting what I gather
8 everybody believes, that the glucuronide
9 itself doesn't have toxicity and the concern
10 is with the free drug. This would be very
11 consistent with the FDA's concern about oral
12 dosing versus any other route because there
13 are glucuronide metabolites in the intestine.
14 And this compound is certainly metabolized in
15 the intestine, as well as in the liver and
16 therefore you would expect to see this
17 difference.
18 It is very obvious to me, if you
19 asked me a few years ago to study this drug,
20 what I would have done is gone back to the one
21 paper that I see here that identifies the
22 enzyme that metabolizes this compound in the

4bdcdd16-71fa-4080-837d-6d72a5410102

1 rat liver, Ugt2b1. But that enzyme is not in
2 the gut. There are probably other enzymes for
3 this drug. So, what needs to be characterized
4 to figure out what's going on here and what
5 you need to do in the studies you're proposing
6 in the animal models is to understand whether
7 the enzymes that are metabolizing this
8 compound. Then the easiest thing to do is to
9 make a knockout animal of those enzymes.
10 Therefore, you are only looking at the free
11 drug because the animal will not able to make
12 the glucuronide. And if I accept Dr. vom
13 Saal's data that says in these neonates he saw
14 no difference between oral and IV, that would
15 be because there's no glucuronidation and
16 therefore the drug is completely absorbed. I
17 haven't seen the data.
18 But that's the kind of information
19 and the kinds of studies that you want to do
20 in terms of finding a dose response
21 relationship. And in addition, if we are
22 convinced that the drug is 100 percent

4bdcdd16-71fa-4080-837d-6d72a5410102

completely absorbed, then you can give it orally, but once you've knocked out the enzyme, you can give the drug IV and you know exactly how much you've done and you do your dose response studies both in terms of toxicity and in terms of the concentrations that relate to this.

In addition, in all probability in humans there's a pharmacogenomic aspect to these enzymes. Therefore, if it's only the free drug that's having a response, there's going to be some people that have low levels of that enzyme and are making less of the glucuronide and therefore you do a characterization of their gene sequence in terms of the enzyme and go back and look at your human data to say do I have some kind of correlation that relates to the free -- if I can't measure the free levels, that goes back that I would expect to see higher levels.

So I think the studies proposed are flawed because you could get much more

4bdcdd16-71fa-4080-837d-6d72a5410102

information in your animal studies and address a lot of useful information to figure out what's going on with this compound.

CHAIRMAN PHILBERT: Thank you.

Dr. McCarver and then Dr. Hu. And then Dr. Hentges and then Dr. Thayer. So please remember who you're behind.

DR. McCARVER: Glad I got in early.

Following along with what Dr. Benet had to say, I think the other thing that's striking here is that we actually haven't done the appropriate in vitro work even to determine which of the human Ugts are most efficient and what those kinetic constants are. You know, we've sort of made the assumption that it's Ugt2b7 based on the fact that the sequence is homologous to the rat 2b1, although it may be handled by 2b17. But that really needs to be done.

Once we have done that, that gives us a little bit more insight because we actually do have data on human babies. We do

4bdcdd16-71fa-4080-837d-6d72a5410102

1 know the ontogeny of the expression of those
2 enzymes. We do know that 2b7 is expressed in
3 the fetus at 15 to 20 percent of the adult
4 levels. We know that it takes about two to
5 three months to hit full expression levels on
6 average. So again, this would be very
7 insightful for us then to begin to do the PBPK
8 modeling. I think the document refers to PBPK
9 modeling, but then it doesn't really talk
10 about the things that would need to know in
11 order to make that happen that would be very
12 useful. There's been a lot of chatter about
13 whether or not BPAs actually also undergoes
14 sulfation. The sulfotransferases have also
15 been characterized in terms of their
16 ontongeny. So again, if we knew exactly which
17 enzyme was capable and what the kinetic
18 constants were, we would be much further
19 along.
20 So saying that, there are no data
21 that I'm aware of to show that babies or
22 anyone else -- I should say babies, are able

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1 to sulfate BPA. So I don't think we can use
2 it. In fact, I think that's one of the big
3 differences I see in the NTP assessment and
4 what I see in the FDA assessment, is I believe
5 that NTP relied a little more heavily on some
6 of the data coming from the pump studies as
7 well as some of the other routes, whereas the
8 FDA really focused in more on the oral. And
9 I think if you're talking about babies, the
10 issue really is that they probably are not
11 able to conjugate and that we're looking at
12 probably things -- if you look at morphine,
13 for example, as a similar type of drug handled
14 by 2b7, is also sulfate a little, we know the
15 overall clearance of morphine differs in
16 neonates by about two-fold. We know the
17 fractional metabolic clearance down the 2b7
18 pathway differs by about five-fold. So that
19 the human data actually does support the
20 animal data to say that at least in the early
21 infancy, there is a problem with conjugation.
22 DR. BENET: I just want to make a

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quick comment about this. That probably is a liver enzyme and I bet there's a gut enzyme that's different.

DR. McCARVER: I would agree.

DR. BENET: So in doing all this stuff, make sure you look elsewhere.

DR. McCARVER: I agree. Do both. Yes.

DR. HU: As we talk about these enzymes, do we know anything about actual functional SNP genetic polymorphisms that would probably be involved and what their prevalence might be in the population, and how it might impact the metabolism and levels of the BPA?

DR. BENET: Not of BPA, because I don't know what enzymes do it. But I do know that we do have the genetic polymorphism of a number of the Ugts and some of them are very polymorphic with large differences. I mean, this is not my area. So somebody's got to find out what the enzymes are. We probably

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have the data on the polymorphisms, we just don't know what the enzymes are.

CHAIRMAN PHILBERT: Dr. Hentges and then Dr. Thayer, and then we'll come back to you.

DR. HENTGES: Just to add a couple more points, because some of what I was going was covered. But on the 2b7, I think the paper that you were referring doesn't say that 2b7 is the only enzyme, but it acknowledges that it is one of the Ugts that will glucuronidate BPA.

But again we can't forget about sulfation. There are a couple of papers that I'm aware of; Suiko, et al 2000 and Nishiyama et al 2002, both of which show that a number of different sulfotranserfases do sulfonate bisphenol A. So there is some data, although I agree I don't think there's any data directly on human infants. Yes, not in human infants. Right.

CHAIRMAN PHILBERT: Dr. Thayer?

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DR. THAYER: Okay. Well mine was just sort of a place holder, that from our conversation before there was a conversation about looking at the literature and finding a dose level for health effects and I just had a follow-up on that. But I can hold it until we're done with this discussion.

CHAIRMAN PHILBERT: Dr. vom Saal, were you referring to an earlier point?

DR. vom SAAL: No, I could actually lead into the one Dr. Thayer is going to have, but I was going to answer that this is not published yet, but in our CD-1 mice that are adult females, when we delivered bisphenol A to about 20 animals, they have about a 20-fold variation in the rate of clearance. And this is an outbred mouse. And this gets back to some of the other issues, how variable is this system. It is really quite variable.

And the other question that I wanted to ask related to what Dr. Vandenberg

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said before about threshold doses is it's always been a curiosity to me since I study endogenous estrogens what the threshold dose is for an exogenous estrogen when the endogenous estrogen is already above threshold.

DR. VANDENBERG: I didn't use the phrase "threshold dose."

DR. vom SAAL: No, no. I understand. But the FDA is assuming that there is a threshold dose. There's a wonderful paper EHV published by Dan Sheehan a former FDA senior scientist where he did this wonderful study where he showed that the background levels of estrogen are where you extrapolate down to. You never extrapolate down to zero. You just extrapolate down to the background level of estrogen that's there. So the whole concept of zero activity at some level when there's an endogenous hormone already active underneath the added hormone is obviously just a flawed assumption and yet

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it's a core assumption of using the threshold model and the safety factor model to try to determine safe doses. And it doesn't work for hormones that are already active inside your body.

DR. VANDENBERG: The point I was trying to make is that there are a variety of approaches to look at points of departure for the application of uncertainty factors. And that is that you can use a NOAEL or LOAEL approach, or you can use a benchmark dose approach to identify point of departure. I think your point is in regards to certain biological processes that may not have a threshold that you're adding to background. That's a different approach to modeling than what I was referring to. I was trying to see if in fact there are ways to characterize that point of departure that is consistent with what the FDA did, but I'm not disagreeing with you at all, that in fact adaptivity to background process is in fact a different set

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of ways of modeling things. But in effect what we have in the FDA approach is there's no model. And so you would have to consider that in a variety of ways if you're looking at adaptivity of the background as a different set of modeling tools than what I was referring to.

DR. vom SAAL: And just the last thing I was going to say is glucuronidation is a clearance pathway. When you sulfate something, you can desulfate it. So everybody knows that. Just think about what the fetus does and the placenta, the maternal placental fetal unit. There's a lot of sulfating and desulfating going on. It's part of the cycling system. So, sulfation and glucuronidation are not the same thing.

CHAIRMAN PHILBERT: Is there anything known about the expression of these enzymes in the pregnant female? Is there any evidence that they change? Are they under hormonal control?

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