U.S. FOOD AND DRUG ADMINISTRATION

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SCIENCE BOARD BISPHENOL A SUBCOMMITTEE

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PUBLIC MEETING

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TUESDAY,
SEPTEMBER 16, 2008

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The public meeting convened at 9:00 a.m. in the Executive Meeting Center of the Hilton Washington DC/Rockville, 1750 Rockville Pike, Rockville, Maryland, Martin Philbert, Chairman, presiding.

SUBCOMMITTEE MEMBERS PRESENT:
MARTIN PHILBERT, Ph.D., Chair
GARRET A. FITZGERALD, M.D., Member

SUBCOMMITTEE CONSULTANTS (SUBJECT MATTER EXPERTS) PRESENT:
PHILIP J. BUSHNELL, Ph.D., Advisor
HOWARD HU, M.D., M.P.H., Sc.D., Advisor
HOWARD ROCKETTE, Ph.D., Advisor
JOHN VANDENBERG, Ph.D., Advisor

INVITED PANEL:
LESLIE BENET, Ph.D., University of California, San Francisco
L. EARL GRAY, JR., Ph.D., Reproductive Toxicology Division, Office of Research and Development, National Health and Environmental Effects Research Laboratory, U.S. Environmental Protection Agency
STEVEN HENTGES, Ph.D., American Plastics Council

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INVITED PANEL (Continued):
SONYA LUNDER, Environmental Working Group
D. GAIL McCARVER, M.D., Co-Director, Department of Pediatrics, Birth Defects Research Center, Medical College of Wisconsin
KRISTINA A. THAYER, Ph.D., National Institute of Environmental Health Sciences, National Institutes of Health
FREDERICK S. vom SAAL, Ph.D., Division of Biological Sciences, University of Missouri-Columbia

FDA PARTICIPANTS:
CARLOS PE¥A, Ph.D., M.S., Executive Secretary
ALLAN BAILEY, Ph.D., Office of Food Additive Safety, Center for Food Safety and Applied Nutrition
LAURA TARANTINO, Ph.D., Director, Office of Food Additive Safety, Center for Food Safety and Applied Nutrition
MICHELLE TWAROSKI, Ph.D., Supervisory Toxicologists, Office of Food Additive Safety, Center for Food Safety and Applied Nutrition

NATIONAL TOXICOLOGY PROGRAM BRIEF:

JOHN BUCHER, Ph.D., National Institute of Environmental Health Sciences, National Institutes of Health

PUBLIC HEARING PARTICIPANTS:
ANILA JACOB, M.D., M.P.H., The Environmental Working Group

DIANA ZUCKERMAN, National Research Center for Women and Families
BETH JORDAN, Association for Reproductive Health Professionals
NANCY GREENSPAN, Healthy Child Health World
LIZ HITCHCOCK, U.S. Public Interest Research Group

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PUBLIC HEARING PARTICIPANTS (Continued):
JOHN PETERSON MYERS, Environmental Health Sciences
DAVID MELZER, Peninsula Medical School, United Kingdom

ELLIE COLLINSON, Breast Cancer Fund
URVASHI RANGAN, Consumer's Union
KIRSTEN STADE, Center for Science in the Public Interest
JOHN VAN MILLER, BPA producers, the Polycarbonate/BPA Global Group
SARAH JANSSEN, Natural Resources Defense Council
RACHAEL RAWLINS, Breast Cancer Action
JENNIFER ROGERS, Reproductive Health Technologies Project
NANCY HUGHES, American Nurses Association
AMBER WISE, Ph.D., Union of Concerned Scientists

JOSEPH MANUPPELLO, People for the Ethical Treatment of Animals

NANCY BECK, Physicians Committee for Responsible Medicine

JOHN M. ROST, Ph.D., Chair, North American Metal Packaging Alliance, Inc.

ROCHELLE W. TYL, Ph.D., DABY, Senior Fellow, Developmental and Reproductive Toxicology, RTI

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Adjourn

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P-R-O-C-E-E-D-I-N-G-S

9:02 a.m.

CHAIRMAN PHILBERT: Good morning, ladies and gentlemen. My name is Martin Philbert. I'm from the University of Michigan and I am the chair of this subcommittee of the Science Board on the bisphenol A draft from the FDA.

The Science Board is constituted to provide advice primarily to the Commissioner and other appropriate officials on specific complex and technical issues, as well as emerging issues within the scientific community. Temporary subcommittees consisting of two or more board members may be established by the Commissioner or designee as needed to address specific issues within their respective areas of expertise. Subcommittees make preliminary recommendations regarding specific issues for subsequent action by the full board.

The focus of this subcommittee is

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on the scientific peer review of the draft assessment prepared by FDA of bisphenol A for use in food contact applications. Members of the subcommittee were selected by the Science Board for their expertise in scientific disciplines relating specifically to the issues assessed in the FDA draft safety assessment.

It is the purpose of the subcommittee to provide advice and make preliminary recommendations regarding the FDA draft safety assessment for subsequent action by the full board. This activity is not an endorsement of any scientist, consumer group, or regulatory agency. This is a scientific peer review of how the FDA has assessed safety of BPA in food contact applications.

For topics such as those being discussed at today's meeting, there are often a variety of opinions, some of which are quite strongly held. Our goal today is that this meeting will be fair and open and that these

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discussions will be held so that individuals may express their views without interruption.

Thus, as a gentle reminder, individuals will be allowed to speak into the record only if recognized by the Chair. We look forward to a productive meeting.

In the spirit of the Government in the Sunshine Act, we ask that the subcommittee should take care that the conversations about the topic at hand take place in the open forum of this meeting.

Before we go any further, I'd invite the members of the subcommittee to introduce themselves and their affiliation.

DR. FITZGERALD: I'm Garret FitzGerald. I'm a professor of medicine and pharmacology and Chair of Pharmacology at the University of Pennsylvania.

DR. BUSHNELL: I'm Phil Bushnell. I am a neurotoxicologist with the National Health and Environmental Effects Research Laboratory at the U.S. Environmental

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Protection Agency.

DR. ROCKETTE: I'm Howard Rockette. I'm Chair of Biostatistics at the Graduate School of Public Health at University of Pittsburgh.

DR. HU: I'm Howard Hu; another Howard, Chair of the Department of Environmental Health Sciences and professor of environmental health, epidemiology and medicine at the University of Michigan Schools of Public Health and Medicine.

DR. VANDENBERG: I'm John Vandenberg. I'm the Associate Director for Health with the National Center for Environmental Assessment, which is part of the United States Environmental Protection Agency.

CHAIRMAN PHILBERT: Dr. Calafat from the CDC was unable to join us here today, but her information is provided in the materials handed out today.

At this time, I will hand the meeting over to Dr. Carlos Pena.

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DR. PENA: Thank you, Dr. Philbert.

Good morning, members of the subcommittee and members of the public. Welcome to the Science Board BPA Subcommittee public meeting.

The following announcement addresses the issue of conflict of interest with respect to this subcommittee meeting and is made part of the public record to preclude even the appearance of such at this meeting.

Today the subcommittee composed of two members from the Science Board parent advisory committee and five additional subject matters experts will hear and discuss the draft assessment of BPA for use in food contact applications, including oral presentations from the public.

In preparation for this meeting, members of the subcommittee and the subject matter experts have been screened for potential financial conflict of interests of

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1 their own, as well as those imputed to them,
2 including those of their spouse or minor
3 children and their employers. These interests
4 may include investments, consulting, expert
5 witness testimony, contracts, grants,
6 teaching, speaking, writing, patents and
7 royalties, and primary employment. Based on
8 the submitted agenda for the meeting and all
9 financial interests reported by the
10 subcommittee, it has been determined no
11 conflict of interest waivers have been issued
12 in connection with this meeting.
13 In addition, for all financial
14 interests reported by FDA staff participating
15 in this meeting, it has been determined that
16 no conflict of interest exists for FDA staff
17 presenting before the subcommittee.
18 With respect to all other
19 participants, including today's presenters, we
20 ask in the interest of fairness that they
21 disclose to the subcommittee any current or
22 previous financial relationship that they may

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have with any company or group that may be affected by the topic of this meeting.

As a reminder, we have two open public comment periods scheduled to begin, the first at 11:00 a.m. and the second at 1:00 p.m.

I would remind the subcommittee to turn on your microphones when you speak so the transcriber can pick up all that you state and turn them off when you're not speaking.

I also request all meeting attendees here to turn their cell phones and Blackberries to silent mode for the meeting.

Thank you.

CHAIRMAN PHILBERT: Thank you very much, Dr. Pena.

Given that our agenda is fairly full today, I would ask that all speakers keep to time and please don't consider me rude if I cut you off. It's just that many of us have flights to catch at the end of the day.

The Chair now recognizes Dr. Laura

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Tarantino from the U.S. FDA. Thank you.

DR. TARANTINO: Thank you, Dr. Philbert and members of the subcommittee.

On behalf of all of us at FDA, I want to express our gratitude for your willingness to spend your time and effort to assist us with your review of and your input on our draft assessment of bisphenol A for use in food contact applications.

As you very well know, the issue of potential low dose effects of hormonally active agents or so-called estrogen disruptors such as BPA is an exceptionally complex one and a very active area of research over the last decade or more with reports and publications appearing regularly.

BPA has been used for decades in the manufacture of a wide variety of products including food contact materials. FDA is responsible for the pre-market review and approval of the can coatings and the plastics that are made using BPA.

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At the time these materials were first approved, the toxicity of BPA was recognized but was understood to be exhibited only at levels that were many orders of magnitude higher than those to which people would expect to be exposed through appearance of BPA in food.

When the research findings concerning the low dose effects of BPA started appearing, we closely started following and monitoring research and publications examining then-existing toxicity studies and conducted some analytical work in our laboratories to measure levels of BPA migrating into food. Then as will be discussed in more detail in a moment, about a year and a half ago, early 2007, we began a much more formal reassessment of bisphenol A in food contact substances in light of several factors, including the continuing and perhaps escalating appearance of research studies concerning the low dose effects, the availability of data from two

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large multi-generation rodent toxicology studies that included testing at doses that would be considered low and the conduct of a review by an expert panel that was convened by NTP Center for the Evaluation of Risk to Human Reproduction.

As you're aware, in April, after NTP published its draft brief on bisphenol A, FDA formed an agency-wide task force to facilitate the cross-agency review of the issues raised by the NTP report, as well as by several other contemporaneous reviews as they pertain to the use of bisphenol A in all FDA regulated products. The first charge to the task force was to produce a draft assessment of BPA as used in food contact applications. The task force process is continuing with an examination of BPA use in other FDA-regulated products. In fact, the Agency will very soon be seeking information from stakeholders about the use of BPA pertaining to these other uses.

In view of the complexity of the

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scientific issues surrounding the interpretation of the low dose studies, we were very concerned to insure that the draft assessment was made available for an independent objective peer review. As part of that process then, FDA has now submitted its draft assessment to you for your review of our analyses and conclusions. We look forward to your response back to the Science Advisory Board and to the presentation of your response to the Board at its meeting in October.

We welcome today the opportunity to discuss the draft assessment and answer any questions you might have. Drs. Bailey and Twaroski who are here representing the many agency scientists who contributed to the review of the data and to the preparation and to the review of the task force report on the draft assessment, are now going to now very briefly walk you through the report and the assessment, in particular outlining our analyses and how we reached our conclusions.

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Then I'll come back to very briefly review our initial recommendations for further steps and some studies to try to clarify some of the issues that are before us.

So with that, Dr. Twaroski?

DR. TWAROSKI: Thank you, Dr. Tarantino.

As mentioned, the purpose of our presentation today is to provide an overview of FDA's reassessment of the safety of bisphenol A as it pertains to food contact materials. We first want to describe how FDA's required to review and judge the safety of food contact substances like bisphenol A.

As with all safety assessments, there are two key components of the safety assessment; exposure assessment and toxicity assessment. First we will discuss how FDA has conservatively estimated the likely consumer exposure to bisphenol A. Then we will discuss FDA's assessment of the most recent toxicological data on bisphenol A. Although

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we have considered systemic and other toxicities from bisphenol A, our assessment in this presentation will highlight areas of uncertainty and concern that recent independent reviews have identified. We will then present our conclusions and some recommendations FDA has for resolving some of these uncertainties.

Before discussing the details of the assessment, it is worth noting that this presentation and meeting are part of an overall governmental review process. As such, this presentation is not meant to be inclusive of the draft document which is available on our website as noted here.

BPA is used as a chemical building block in plastic food contact materials because it imparts physical durability and chemical resistance to the plastics produced from it. Polycarbonate plastics are used to produce reusable food contact materials that can be easily cleaned and endure rugged use.

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Epoxy coatings are chemically resistant and can protect food cans from attack by acidic or other chemically-aggressive foods. This in turn helps the can protect the food from spoilage and microbial contamination. Food contact polymers such as polycarbonate in epoxy can coatings require premarket approval by FDA before they can be marketed.

Because bisphenol A is used in the manufacture of such materials, some unreacted residuals can remain and can and does migrate into food contacting material. Bisphenol A itself is not a food additive; hence, food is not wrapped in bisphenol A and cans are not coated in bisphenol A. However, because it is a component of polycarbonate plastics and epoxy can coatings, and it may migrate to food, its safety must also be considered in the premarket approval of such materials and it must be held to the same safety standard as food additives. Accordingly, bisphenol A is a food additive, impurity or constituent. It

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is not however an impurity of food such as methylmercury. As a food additive constituent it is subject to the same safety assessment approach as the food additive itself.

Although everyone in this room, as well as other international agencies, have individual standards for what safety may mean, the Food and Drug Administration's regulatory standard for food additives is legally defined in the Code of Federal Regulations. In 21 C.F.R. 170.3(i) it states that safe or safety means that there's reasonable certainty in the minds of competent scientists that the substance is not harmful under the intended conditions of use. It is noteworthy that the FDA standard not only considers reasonable certainty, but additionally considers the intended conditions of use. In other words, in considering probable human exposure, FDA requires industry to perform studies estimating migration from use under the intended conditions. This approach does not

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consider or require consideration of exaggerated conditions that are considered misuse of a product.

In the case of bisphenol A, this includes data generated in the literature that may include excessively-aggressive experiments using migration from baby bottles or cans.

A little more background on our approach is helpful to our planned discussion today. As with all FDA-regulated products, FDA's general approach to premarket review of food contact materials such as BPA mandates involvement by the submitter. This requires that industry make a scientific-based argument regarding the safety of the material requested to be regulated based on the intended use. Depending on the exposure and the information available, FDA requires that submitters perform robust guideline-defined studies examining toxic end points such as those detailed in our guidelines. Additionally, industry must submit all available data,

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1 literature and proprietary information, and
2 discuss the collective findings of that data
3 in relationship to the safety standard.
4 Once submitted, FDA conducts its
5 own independent evaluation of the information
6 submitted, as well as all relevant information
7 available through record or literature
8 searching. This includes a thorough and
9 critical assessment of any studies submitted
10 to the Agency or identified through other
11 methods. Noteworthy, FDA does not consider
12 the source of funding, but considers all data
13 solely on the merits of the science.
14 Once a chemical is on the market,
15 FDA continues to monitor and review the
16 scientific data, again regardless of the
17 source of information. Additionally, FDA
18 clearly states that responsible parties
19 contact FDA with health issues are noted with
20 the product. Our post-market process involves
21 an active dialogue with the regulated industry
22 and appropriate actions are initiated based on

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1 the concluded safety concerns.
2 Our meeting today represents an
3 important step in the post-market evaluation
4 process of bisphenol A.
5 Dietary exposure to bisphenol A
6 occurs at levels of less than 150 micrograms
7 per person per day. Based on FDA's evaluation
8 of existing toxicology data and information,
9 as well as other evaluations that have been
10 published for exposure of this magnitude, it
11 is as reasonable that the Food and Drug
12 Administration's safety evaluation ordinarily
13 focus on carcinogenicity or genetic toxicity
14 as an indicator of potential carcinogenicity.
15 However, as just mentioned, FDA also examines
16 all available information, including
17 literature, FDA documents and other regulatory
18 agency documents for information on the
19 chemical in question to determine if there are
20 gaps in the safety assessment that indicate a
21 need for a broader approach or the
22 consideration of recommending testing for

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other end points.

In the case of bisphenol A, the literature that has accumulated over the years clearly indicates the need to consider end points outside this general carcinogenicity-genetic toxicity scheme which is detailed at this exposure level. It is well known that bisphenol A binds to estrogen receptors, however, the affinity for those classical receptors is quite weak when compared to endogenous estrogen. However, in the recent literature several reports indicate that cross-talk, or binding to other receptors, may also be modes of action for bisphenol A, including membrane bound ER and estrogen-related receptor gamma.

As part of the post-market process, and as detailed in documents cited in the draft, FDA has actively considered data surrounding possible low dose effects of bisphenol A for many years. In 2007, the Center for Food Safety and Applied Nutrition

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formally began a reassessment of bisphenol A based on the availability of two well-performed extended guideline multi-generational studies in rodents and the need for a pharmacokinetic assessment. Based on the considerable amount of pharmacokinetic data available on bisphenol A and ongoing discussion as to which species is the most sensitive to this compound, FDA considered the pharmacokinetic analysis pivotal to the safety assessment. Pharmacokinetic information is essential to determine what animal species and what animal studies are most relatable to the human who is exposed to bisphenol A, including plausibility of the potential effects bisphenol A may have on humans.

FDA considers the Tyl and other studies to have been published pivotal because of the high quality of the study design and conduct, and because the Agency has full access to all underlying data, and so that we may reach an independent conclusion regarding

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the results. FDA considered these studies pivotal and more weighted than published studies examining the same or similar end points due to their robust study design, large sample size, life time exposure regimen, large dose range, and full availability of supporting data. These studies address with sufficient statistical power issues that had been raised in the literature at the time of their protocol development.

FDA is aware that since the completion of these studies several studies have appeared in the peer review literature indicating possible concerns for end points which either were not addressed or were addressed using alternative methods in these multi-generational studies. These end points were recently highlighted by our colleagues at the National Toxicology Program, their expert panel and Environmental Canada, and include neuro and behavioral effects, effects on the prostate and mammary gland and acceleration of

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the age at which females attain puberty.

Additionally, over the years FDA reviewed numerous studies concerning migration experiments regarding infant consumer exposure. FDA considered this reassessment as an opportunity to reevaluate assumptions and update its assessment based on the literature concerning infant exposure. Accordingly, FDA expanded its reassessment of bisphenol A with the establishment of the Food and Drug Administration task force in 2008.

The FDA task force's charge was to update the assessment of bisphenol A from food contact applications with an examination of the infant exposure estimate and to review available data regarding these select end points. At a later date, FDA will incorporate the assessment from food contact materials into a broader assessment for all BPA-containing FDA-regulated products. Again, FDA's focus in this reassessment is potential exposure to humans during development.

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Now Dr. Bailey is going to discuss our approach to estimating exposure.

DR. BAILEY: Well, thank you, Dr. Twaroski.

Okay. As we discussed the details of the exposure assessment, it is noted that FDA's maximum exposure estimate for infants, a value of 2.42 micrograms per kilogram body weight per day is higher than the previously-relied upon estimate of 0.7 micrograms per kilogram body weight per day.

This updated estimate considers a number of conservatisms which indicate that actual infant exposure may be quite lower than the number calculated. Several qualitative conservatisms must be considered when responding to this value. These include:

(1) All formula is in liquid form as purchased and used by the consumer. FDA is aware that a large amount of infant formula is purchased in a powdered from. Powdered formula does not require the same heat

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sterilization process and therefore is not expected to be packaged in the same costly bisphenol A-based coatings as liquid formula. Accordingly, the assumption that all formula will be consumed in pre-packaged liquid form may be a gross exaggeration.

(2) All liquid infant formula is packed in cans coated with bisphenol A-based enamels. FDA is aware that not all liquid infant formula is packaged in containers coated with bisphenol A-containing coatings. Although a large portion of the market is bisphenol A-based coatings, a fraction of this market includes containers coated with other non-bisphenol A-based coatings.

(3) Consumers prepare and deliver all infant formula in thermally sterilized polycarbonate bottles. Although the draft document details calculations where thermal sterilization; that is, boiling the bottle containing the formula, is not considered standard practice such as with an older

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infant, FDA's use of the maximum estimate considers that thermal sterilization will always be conducted. Moreover, it is known that other types of infant bottles are used such as polypropylene bottles.

(4) Repeated use of polycarbonate baby bottles results in continuous exposure at the 10 microgram per kilogram level. FDA assumed that migration would occur at the highest level and used a number considered by other regulatory bodies; that is, a value of 10 micrograms per kilogram, assuming this amount would migrate on every use of the bottle. This scenario is conservative given the long service life time and general tendency for migration of polymer residues to decrease over time.

(5) Consumption of infant formula occurs at the maximum level as opposed to an average level over the one year period in which infant formula is generally consumed.

FDA is aware that the maximum

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calculated exposure value, a value of 2.42 micrograms per kilogram body weight per day, occurs in the first two months of an infant's life. After two months, the use of thermal sterilization as well as infant formula consumption decreases as the infant matures. The lower range of our exposure estimate from infant formula consumption in the first year of an infant's life is 0.15 micrograms per kilogram body weight per day. This maximum exposure is the value we used in our exposure estimate.

Our exposure reassessment relied on two contributions to bisphenol A in an infant's diet. The first is bisphenol A infant formula as purchased by the consumer, and the second is bisphenol A in infant formula as prepared by the consumer in polycarbonate bottles. We reviewed the data from the literature, EFSA, Health Canada, other groups, as well as data generated in FDA laboratories. These data informed our

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assessment regarding bisphenol A migration from polycarbonate bottles under different conditions of use and included data on bisphenol A at levels in liquid infant formula.

With regard to the contribution from polycarbonate bottles, our exposure assessment also considered the current recommendations from several organizations on infant formula feeding practices. Based on our assessment, we concluded that consumers may sterilize bottles, if they do so at all, in the first two months of an infant's life. Based on the numerous studies on polycarbonate bottles, our approach used a bisphenol A level of one microgram per kilogram to represent bisphenol A levels in formula prepared in bottles at room temperature and a value of 10 micrograms per kilogram to represent bisphenol A levels in formula prepared in bottles under boiling water conditions. Our final assessment only considers the maximum exposure

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resulting from sterilization of bottles and formula.

With regard to the contribution from infant formula, or exposure estimate conservatively only relied on - only the bisphenol A levels reported in liquid infant formula. This level, a value of 2.5 parts per billion bisphenol A in the formula, represents the maximum levels in packaged infant formula. As noted in the assessment, we concluded that bisphenol A would not be expected to be present in infant formula prepared from powdered concentrate.

With regard to infant formula intake, we updated formula consumption information for infants less than 12 months of age. The consumption data was evaluated on a per-month basis to obtain the maximum exposure as adjusted for the infant's body weight. Only this maximum formula consumption was used to estimate exposure from coatings on infant formula cans as it yields the highest

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consumption of bisphenol A.

To summarize, for infants, FDA used an estimate of 2.42 micrograms per kilogram body weight per day in the final assessment. As detailed in the draft and in these slides, this estimate is conservative on a number of levels and as such, consumer exposure may indeed be lower.

As for adults, the exposure estimate of 0.185 micrograms per kilogram body weight per day was determined using a similar approach. Bisphenol A exposure in an adult's diet would include contributions from bisphenol A in containers coated with bisphenol A-based coatings, as well as bisphenol A from polycarbonate-based articles.

Our exposure assessment for bisphenol A levels in canned fruits and vegetables relies on peer-reviewed analyses of can coatings in canned food representative of those used in the U.S. The highest mean value for migration from these studies was 22 parts

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per billion and we used this value to represent bisphenol A levels in both canned food and beverages. FDA then applied a packaging factor, a value of 0.17 or 17 percent to account for the fraction of food that is packaged in polymer-coated metal containers and we also applied our normal assumptions about an individual's daily food intake and body mass.

Once again, there are several assumptions, several conservatisms inherent to this approach. Of note, it assumes that all food and beverages are packed in cans coated with bisphenol A-based coatings and bisphenol A levels in those food and beverages are 22 parts per billion. FDA is aware that other non-bisphenol A coatings are used to coat metal cans which are in turn used to hold some food and beverages. Moreover, FDA is aware that nearly all beverages, as well as many foods, do not contain levels of bisphenol A as high as 22 parts per billion. In fact,

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1 studies indicate that bisphenol A migration to
2 beverages such as soft drinks is far less
3 because of the thinner coatings used in these
4 applications and the fact that most beverages
5 are not thermally processed to the same extent
6 as food containers.
7 Finally, because polycarbonate
8 food containers are made for long life and
9 durability, they are expected to contact a
10 large amount of food or beverages over their
11 service life time. Therefore, the
12 contribution to overall bisphenol A exposure
13 from this source is insignificant in
14 comparison to other sources of exposure.
15 Now Dr. Twaroski will continue
16 with the toxicology aspects of our assessment.
17 DR. TWAROSKI: Thank you, Dr.
18 Bailey.
19 One focus of FDA's assessment of
20 bisphenol A was the pharmacokinetics and the
21 potential species differences. In other
22 words, FDA conducted this aspect of the

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assessment to determine what animal studies are most relatable to a human who is exposed to bisphenol A, including informing the assessment as to the relevance of certain studies on human oral exposure. This pharmacokinetic analysis is essential to determine human relevance of much of the published data and is essential for understanding pathways of detoxification which inform us as to which species is the most appropriate for modeling human risk.

Based on reviewing these data, it is clear that bisphenol A uptake via oral exposure is rapid and significant in all species. The major metabolite of bisphenol A, bisphenol A-glucuronide, or BPAG, has no significant estrogenic activity. Therefore, conjugation was glucuronide results in detoxification are lost in the estrogenic mode of action. Fetal and neonatal exposure to bisphenol A can occur either via placental transfer or lactational transfer. In the case

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of lactation, earlier reports that were reviewed indicated that this is predominantly in the form of bisphenol A-glucuronide. However, there are some more recent reports indicating that more free bisphenol A is available than previously measured. In addition, if bisphenol A-glucuronide is absorbed via lactation, some free bisphenol A may be liberated in the neonatal animal via action of intestinal bacteria.

Lastly, much debate has occurred regarding the potential for neonatal animals to detoxify bisphenol A. FDA's assessment concluded that although there may be limited activity, some activity does exist. Furthermore, recent observations have suggested that alternative pathways such as sulfotransferase activity for detoxification may play an important role at this life stage. More research is required to definitively model bisphenol A pharmacokinetics in humans, especially in regard to infants.

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1 As mentioned, only free bisphenol
2 A causes effects. Metabolized bisphenol A or
3 bisphenol A-glucuronide does not appear to
4 possess the ability to act through the
5 estrogenic mode of action and it is eliminated
6 from the body quickly. FDA's review of the
7 pharmacokinetic data indicates that the rodent
8 model results in confounding prolonged
9 exposure to free bisphenol A per dose.
10 In primates, bisphenol A-
11 glucuronide is rapidly formed and eliminated
12 via the urine. However, in rodents,
13 elimination occurs through the biliary tract.
14 This results in the ability of free bisphenol
15 A to be reformed through the activity of
16 bacterial enzymes. Once formed, bisphenol A
17 can be reabsorbed. This reabsorbed bisphenol
18 A is then active, it's in the active form and
19 can interact with potential target organs.
20 This prolonged free bisphenol A in circulation
21 indicates that the rodent model likely
22 overestimates the potential toxicity of

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bisphenol A as compared to humans.

In addition to the issue of species differences, FDA considered the inclusion of studies beyond those conducted using the oral exposure route. As with all food additives, FDA's preference is experiments conducted in a food matrix. This best models human exposure. However, FDA is aware that a considerable amount of research has been conducted using other routes of exposure, including subcutaneous and intraperitoneal which by nature would eliminate an organism's ability to detoxify bisphenol A prior to it being circulated in the body and reaching a target organ.

As mentioned, most of bisphenol A in primates that is ingested orally is detoxified quickly and eliminated leaving very little available to be circulated or reach a target organ.

An argument has been made for the inclusion of these studies using alternative

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1 routes when considering fetal and neonatal
2 animals. However, FDA's review of the
3 available data indicates that insufficient
4 information is available and concludes that
5 although low, neonatal metabolic activity is
6 present and can contribute to detoxification
7 of low doses of bisphenol A.
8 In addition to their route of
9 exposure limitations, as discussed in the
10 draft, these studies were not planned for
11 regulatory purposes, but were designed to
12 probe specific scientific questions, therefore
13 their interpretability and use in a safety
14 assessment was limited. As these studies are
15 not indicative of what may occur following
16 oral exposure to bisphenol A, FDA has
17 concluded that they may not be comparable to
18 typical human dietary exposures to bisphenol
19 A.
20 A lot of discussion and written
21 comments have focused on FDA's determination
22 regarding which studies were pivotal in the

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decision making process of this assessment. Prior to discussions on particular end points, it may be helpful to draw upon issues discussed in the draft. Regarding studies identified in the public literature, though peer reviewed and informative, are cutting edge science. These studies are not designed as toxicology studies, but probe very specific end points. As such, not only are they difficult to interpret with regards to human safety assessment, but they have limitations that greatly affect FDA's ability to use them. Many of the limitations are highlighted on the slide, though not all the studies identified contained all of these limitations. Additionally, though many studies appear in the bisphenol A data set, discussions have centered on a limited number of studies which lack independent replication.

FDA's ability to reexamine data submitted in support of approvals with regard to action on existing approvals is critical to

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reaching an independent conclusion based on our scientific expertise and experience with chemicals in question, as well as FDA's procedures and to allow for public challenge. As such, this is of such critical importance that FDA receive full reports that it is stated many times in our guidance and throughout the Code of Federal Regulations. This is not to say that FDA ignores information in the literature. It is to say that FDA reviews and considers this information very seriously and weights the data as to its influence on the safety assessment.

Studies well conducted and well reported may be used in an assessment, however, most studies, such as those described for bisphenol A, lack comprehensiveness and are used to generate discussions regarding recommendations for additional testing and extended end point analysis. FDA notes that it is the research reported in the public

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1 literature that drives the science and helps
2 formulate better formal testing procedures.
3 Again, FDA's initial reassessment
4 of bisphenol A began with an evaluation of two
5 studies conducted using acceptable regulatory
6 guidelines. These studies were multi-
7 generational studies in rats and mice. Both
8 studies used an expanded dose range allowing
9 for the identification of not only low dose
10 findings, but also dose responses including U-
11 shaped. These studies were multi-generational
12 feed studies allowing for continuous exposure
13 through a feed as expected for food additives.
14 Additionally, these studies evaluate the
15 systemic toxicity following in utero exposure
16 as they maintain animals on tests for an sub-
17 chronic period. As there were a large number
18 of replicates, these studies were designed to
19 identify unknown effects, but additionally
20 they included expanded protocols to examine
21 end points that were of concern for BPA at
22 their time of initiation.

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1 Lastly, these studies adhere to
2 international recommended guidelines, and as
3 such, were submitted in full with all
4 individual animal data and reports for FDA's
5 independent analysis.
6 FDA has reviewed these studies
7 using information provided in the full study
8 reports, although we note that they have been
9 published as indicated. This slide provides
10 the dose levels and the no-observed adverse
11 effect levels. For both studies, no-observed
12 adverse effects levels, or NOAELs, of five and
13 50 milligrams per kilogram body weight were
14 noted for systemic and reproductive and
15 offspring end points, respectively.
16 Noteworthy, no adverse effects were observed
17 at low doses in either species.
18 One of the issues that has been
19 raised regarding bisphenol A is the potential
20 for developmental exposure to predisposed
21 animals to developing cancer later in life
22 with regard to the mammary gland and the

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1 prostate gland. Cancer is a very complex end
2 point and the Center for Food Safety and
3 Applied Nutrition has a formal committee of
4 experts for evaluating this end point, the
5 Cancer Assessment Committee. This committee
6 which has been in existence for over three
7 decades and has made decisions on a large
8 variety of chemicals evaluated bisphenol A in
9 2008. Their review included an national
10 toxicology bioassay, the most comprehensive
11 bioassay available currently, and various
12 studies published in the literature regarding
13 the prostate gland and the mammary gland.
14 CFSAN's Cancer Assessment
15 Committee concluded that there was no evidence
16 in the national toxicology program study that
17 bisphenol A is carcinogenic under the
18 conditions tested. However, the CFSAN
19 committee also concluded that its conclusion
20 was influenced by the limitations of the
21 studies, including the fact that this study
22 was quite dated and the experimental design

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1 was quite dated and it lacked an in utero
2 exposure period. Newer data regarding the
3 prostate gland and mammary gland are of
4 questionable usefulness regarding the
5 potential enhancement of neoplastic effects.
6 In both cases, these data sets are very
7 limited in their interpretability, either due
8 to select findings, the dose selection or the
9 route of exposure.
10 Lastly, FDA considered the
11 available data in totality and noted that the
12 NTP bioassay, though limited, lacked adverse
13 findings for mammary gland or prostate gland.
14 FDA has reviewed data currently
15 available with regard to the acceleration of
16 puberty in females and with regard to the
17 alteration of the prostate and urinary tract
18 development in males. In both cases, FDA has
19 concluded that the collective findings do not
20 support concern at a lower dose than the
21 offspring NOAEL that was cited in the Tyl
22 studies of 50 milligrams per kilogram body

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weight per day.

Of the data reviewed, the largest and most varied was that concerning neurotoxicity. These studies had many limitations that are worth noting and are extremely difficult to interpret for risk assessment purposes based either on the reported information or the findings. Limitations in most but not all the studies included a lack of concurrent examination of toxicological end points with novel findings, a lack of consistent effects, either in a study or across studies, a lack of a clearly concluded adversive finding in the animal model and the plausibility of a link across species to indicate human relevance. And many studies only examined one sex or dose inhibiting interpretability for clear sex comparisons or dose response curves.

Based on our assessment, data collectively suggests that more research using validated studies and feeding protocols

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modeling human exposure are necessary prior to examining a no-observed adverse effect level for this end point for use in regulatory safety assessment.

Safety data FDA reviews must be put into a regulatory context for decision making. As with any safety assessment, regulators use assumptions based on uncertainties in the data set. In the case of bisphenol A, some assumptions used in FDA's conclusions indicated conservativeness or worst case scenarios, whereas others are made due to insufficient data to support an alternative approach.

As detailed in the draft, these include:

(1) The rodent model is the most appropriate. Based on our pharmacokinetic analysis, given a defined dose, rodents will have a prolonged exposure to free estrogenically-active bisphenol A as compared to primates or humans. The impact of using

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the rodent model likely leads to an over estimate of effects in humans.

(2) Studies using oral exposure are most relevant. The first pass metabolism or detoxification of bisphenol is considerable and results in inactive bisphenol A-glucuronide. Regulatory guidance studies adequately model human infant bisphenol A exposure. Pharmacokinetic data indicates that embryonic neonatal animals are the critical population. Exposure of infants to bisphenol A occurs through bottle feeding or infant formula feeding. Guideline studies use a large range of doses; however, internal dose measurements were not made of neonatal animals in these studies. The development of the nervous system and its responses to hormonally-active compounds is comparable across species. Many of the end points examined regarding observed neural changes following bisphenol A treatment are of unclear relevance to human adverse effects.

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Additionally, hormonally-active, sexually-dimorphic brain development and higher hormonal control of sexually-dimorphic brain development in higher organisms may be differentially regulated across species. Bisphenol A acts mainly as an estrogenic compound. It is known that stero-receptors are susceptible to cross talk that may have indirect effects on ligan-bound receptors.

Alternatively, the data reviewed also indicate that potential for other pathways to be involved in bisphenol A's mode of action. Exposure to bisphenol A is continuous throughout life. Studies which used multi-generations which include continuous exposure through mating, gestation and development are most relatable to safety assessment for bisphenol A. Bisphenol A considers the short term studies to be informative for potential hazard assessment and informative to end points which should be assessed in future multi-generation studies.

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1 (2) Exposure occurs from multiple
2 routes. FDA used the maximum exposure of 2.42
3 in its overall assessment for infants,
4 therefore maintaining the assessment's
5 conservativeness. It is clear from the
6 information reviewed that infant formula
7 consumption and BPA exposure decreased with
8 age over the first year of life. However, FDA
9 has conservatively considered only the maximum
10 exposure estimate for this assessment.
11 Based on FDA's review of the
12 totality of the data set, FDA has concluded
13 that the most appropriate no-observe adverse
14 effect levels to use in the safety assessment
15 are those reported in the Tyl and other
16 studies. From the pivotal studies FDA has
17 determined no-observe adverse effect levels of
18 five and 50 milligrams per kilogram body
19 weight per day for systemic, reproductive and
20 offspring effects, respectively.
21 Using the maximum value for
22 infants of 2.42 micrograms per kilogram body

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weight per day, the lowest margin of safety is that for systemic toxicity, which is 2066. In other words, infant exposure is over 2,000 times lower than the levels that show no adverse effects in animal studies. For data sets such as this, FDA considers a product safe if this level is at least 1,000. This can be said for all adult exposures and reproductive and offspring infant exposures as well.

In conclusion, FDA has considered the available data and determined that the margin of safety for bisphenol A exposure in all populations is adequate and the continued use of bisphenol A in the manufacture of food contact substance is concluded to be safe. Data currently available are insufficient to suggest an alternative no observe adverse effect level or conclusion based on the end points of carcinogenesis, alterations of the male reproductive tract, early onset of puberty, or neurotoxicity.

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Now Dr. Tarantino will discuss future recommendations to resolve some of the uncertainties in the data set for bisphenol A.

DR. TARANTINO: I recognize we're close on time, so I'll be very brief with these remarks. I think I do want to reassert though the conclusion that Michelle just gave us.

We have determined that the most appropriate no effect level to use in our assessment is derived from the multi-generation rodent studies. And using that NOAEL, a margin of safety exists that is adequate to protect consumers, including infants and children, at current levels of exposure.

Further, we've concluded that the currently available information and data we've reviewed on the other end points of interest are not adequate to support a change in NOAEL at this time.

The conclusion is consistent with

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that of other national regulatory bodies with responsibility for the safety of food packaging. They have concluded that upon a review of the available information there is not a health risk to consumers, including children, at current levels of exposure and there's not evidence sufficient to change the determination that the current margins of safety are protective. However, we agree with the findings of NTP and others that the animal studies that suggest a potential for developmental or neurobehavioral effects cannot be dismissed and we further agree that more research is needed.

So we are proposing then to work with our colleagues at FDA's National Center for Toxicological Research, NTP, CDC and other partners to elaborate a plan to conduct studies to clarify the relevance of the end points that have been cited as concerning to human health and to minimize those uncertainties that Dr. Twaroski mentioned

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1 underlying our conclusion that there's an
2 adequate margin of safety at current levels of
3 exposure.
4 We've outlined our initial
5 recommendations in the draft assessment and
6 have explicitly asked for your input on the
7 strategy and studies proposed in the draft in
8 one of the questions we have given to you.
9 Importantly we want to ensure that any studies
10 we conduct will be robust, well-designed and
11 most relevant to regulatory decision making
12 and that studies we undertake will give us
13 useful data for both oral and non-oral routes
14 of exposure, because we will be looking at
15 other FDA-regulated products.
16 Our initial recommendations for
17 investigations to address the data gaps are
18 laid out, so I will just mention the first
19 three of those all get at the notion of what
20 infant and human exposure is very, very
21 broadly speaking. We are talking about
22 further studies to clarify rodent

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pharmacokinetics in terms of the ability of rodents as a model species. And getting data that can be used for modeling human pharmacokinetics used either rodent information, as well as non-human primate. Same with biomonitoring. The biomonitoring data we have don't get down to the populations of interest of kids and infants and children. We want to pursue that and we do want to do further work on our estimated daily intake, all getting at sort of an essential underlying question on a lot of these uncertainties is what are the internal doses for humans.

And then we would like to explore well-conducted studies in non-human primates. We think that those are very likely to be the best way to access the data that are most relevant to evaluating potential human toxicity of BPA.

While regulatory decision making is always accompanied by uncertainty, we recognize the need to resolve the questions

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that are raised by the potentially concerning studies that have been reported and reviewed in order to be able to reach the best scientifically sound regulatory decisions regarding the use of BPA in food contact applications.

Again, we're very grateful for your careful attention. We've laid out our analyses, our current conclusion based on that analysis and our initial recommendations for further work.

I now commend to you the 10 questions we have asked you to consider. We look forward to your input and if you have any questions for any us, all of us are available. Thank you.

CHAIRMAN PHILBERT: Thank you Are there any questions for the presenters?

Hearing none. Thank you very much for your presentation. And we will move directly to Dr. John Bucher from the National Toxicology Program.

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DR. HU: Martin, can I ask a question?

CHAIRMAN PHILBERT: Yes.

DR. HU: Dr. Tarantino, you like the members of the panel, have seen a lot of the very recent studies that you may not have had an opportunity to include in this report.

DR. TARANTINO: Yes.

DR. HU: I just want to point out also that one of the studies that I reviewed that I did not see cited as a potential mechanism of action has been a study in the proceedings of the National Academy of Sciences last year that noted a potential epigenetic mechanism for bisphenol A's impact on health. You know, we all recognize that studies that haven't had the time to have proper view cannot be properly included in the report. But I wonder if you could just say for us, put your finger on the studies that have been recent that the FDA has not had an opportunity to review in depth and that, you

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know, signal potential critical need to review the next report.

DR. TARANTINO: As opposed to talking about individual studies, because you're right, studies are appearing rapidly and of various types and I know you're aware of a study last week in PNAS and then today in JAMA, among others.

I think the important thing is, obviously, our monitoring and our following of the data doesn't stop with the preparation of the draft report. The draft report summarized the information that we had reviewed focusing largely on some of the papers and end points that NTP discussed, but perhaps not a one-to-one, but I think the important point is, yes, we are going to be reviewing those. I know they're available to you. Clearly at any time, whether it is before the draft assessment was done, after it was done or after the Science Board, we will be fully considering articles as they appear in journal

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1 studies and publications as appropriate. So
2 those are going to be reviewed and have begun
3 to be reviewed, as it turns out, the ones in
4 the past week.
5 CHAIRMAN PHILBERT: Dr.
6 Vandenburg.
7 DR. VANDENBERG: Thank you very
8 much. I think one of the questions that the
9 panel has been asked to do is to evaluate the
10 scope of the studies that are being considered
11 and how are you using those both qualitatively
12 and quantitatively.
13 The question I would ask is in
14 regards to the weight of the evidence approach
15 that's been taken; and that is; there are a
16 number of studies, many studies that have been
17 evaluated in the report and in many instances
18 they were referred to also as having been
19 considered by the Center for the Evaluation of
20 Risk to Human Reproduction. In some of those
21 instances, the studies by Timms, for example,
22 on prostate, the Center had judged the study

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to be adequate and of high utility in the assessment. But what I find is that in the FDA report that study wasn't carried through, at least quantitatively to be considered.

So, could you address how in a weight of the evidence evaluation you weigh the diversity of studies, because it seems as though you've ended up focused on a couple of studies, the GLP studies versus the large number of other studies that have not been brought at least quantitatively and some of these it's not even qualitatively.

DR. TARANTINO: Right.

DR. VANDENBERG: Could you speak to that?

DR. TARANTINO: I'll answer in the very general sense, and, Michelle, if want to discuss any particular studies.

I think the comment that Dr. Twaroski mentioned a couple of times is that it really was weight of the evidence. These weren't ignored, but the problem I think was

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either of dose selection, the model -- I mean, I think that we've been focusing on GLP and that's not really the only issue. I think the main issue with these studies is that they are the sets of studies that looked at low dose. They're the best ones we have in the sense that they looked at low doses. They measured those end points at least. At the time that the studies were being planned were those of most interest. I think we did look at most of the other studies in exactly that, a weight of the evidence and/or are the limitations of the studies such that they were not going to be sufficient to allow us to change the NOAEL that we had. And I think you really need to look at what we talked about and what we said about the studies in the appendices for the specific details.

Want to say anything further?

DR. TWAROSKI: I'd just say two of the things that I think were mentioned in the last questions, the two questions, they're

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very important. One concerning epigenetic events that predispose cancer to occur later. And the Timms study which looked at a 3-D analysis of the prostrate and the urinary tract in males. All these studies are very informative and we take them very seriously. Certainly none of the studies were dismissed, as it might come off in the black and white language in the draft and that's what we're getting feedback from you here on today, is not just the process but how we've discussed the process.

But in looking at that, in our experience and engaging our pathologists, we did not see the evidence that is needed to then say that something was a carcinogen. That does not mean that there isn't information that's informative available that perhaps suggests that it's interesting and that these are key events in cancer. And perhaps if better designed studies were out there that inform that, that we'd look at that

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again. It's just that the information as presented was not information that we could use to then do anything quantitative with in our minds and after looking at it from our pathological experience and our regulatory experience.

DR. HU: Just a point of information. The epigenetic study I was mentioning related to obesity.

DR. TWAROSKI: Okay.

DR. HU: Not to cancer.

DR. TWAROSKI: Yes, we're familiar that there are end points beyond what was discussed in the draft. And certainly as I mentioned with the multi-generational studies, this has been a long process and the end points that were of concern when those studies were initiated were studies that then were looked at in formal regulatory guideline studies. The information that we did an in-depth analysis on at this time was studies and end points that are currently -- have been

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discussed as potential concerns at this exposure level. Obviously, there are over 8,000 publications on bisphenol A and they run the gamut as to what they discuss.

CHAIRMAN PHILBERT: One very brief question.

DR. VANDENBERG: Thank you very much.

The question is for Dr. Bailey regarding the exposure assessment. And as you presented the results, you characterized it as conservative. That word was used in a variety of settings here. But my question is, when I look at the table on page 12 where the selection was made from the tested baby formula, you used an average of 2.5 instead of the upper end of the range, or some form of a distribution was not used.

So my question is, have you looked a trying to characterize in a more distributional way what the percentiles might be to put, say, a 95 percent level to

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1 associate that with the word conservative, or
2 something? Because the word conservative to
3 me suggests conservative throughout the
4 process and I'm not sure I see that in the
5 analysis presented here.
6 DR. BAILEY: No, we haven't
7 attempted to use any kind of mathematical
8 modeling such as a distribution. With regard
9 to food packaging, our approach in the safety
10 assessment usually involves the knowledge that
11 consumers have a choice of packaging out
12 there. Not only a choice of packaging, but
13 they also have a choice of food that it's
14 packaged in. And so, we try to focus on a per
15 capita or average exposure estimate.
16 Now that being said, there are a
17 number of conservatisms that were pointed out
18 in there in the draft assessment with regard
19 to both the infants and the adult exposure.
20 So you could say that, while our estimates are
21 not upper bound estimates, they could be
22 classified as above the average, above or

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beyond the average.

DR. VANDENBERG: Okay.

CHAIRMAN PHILBERT: Thank you very much.

Next presentation is from Dr. John Bucher of the National Toxicology Program. Thank you.

DR. BUCHER: Thanks very much, Martin. And I appreciate the opportunity to talk to you today about the review that was carried out by the NTP Center for the Evaluation of Risks to Human Reproduction, Bisphenol A, with regard to whether current exposures to bisphenol A might pose a risk to or a hazard to human reproduction and development.

This review was carried out by the Center, the CERHR, as I indicated, under the direction of Michael Shelby and Dr. Kris Thayer, who's going to be on the panel this afternoon, is also here today, and played a major role in the production of this report.

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The outline of the presentation, I'm going to go briefly over the CERHR process and give you the results of the NTP brief concerning the conclusions on BPA and then I want to spend a few minutes discussing a number of different points that we felt were critical in our evaluation.

First of all, the CERHR announced its intent to evaluate bisphenol A back in December of 2005. And as with other chemicals, we convened an expert panel to go through the literature, which is, as you heard, a very considerable literature of probably about 1,000 papers at this point that are relevant to the evaluation.

This expert panel held public meetings in March and August of 2007 and issued its final expert panel report in November. At that point, we took this expert panel report under consideration, all the public comments that we had received during that process, as well as looking at new

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1 literature and put out what we call the NTP
2 brief, which includes our interpretation of
3 the science and our conclusions concerning the
4 potential risks posed by current exposures to
5 BPA. A draft report was released in April and
6 in June we brought this report before our
7 Board of Scientific Counselors for peer
8 review. In September we issued our final
9 draft, or a final of the NTP brief. The
10 literature review cut-off date was June 1 of
11 2008, and there were numerous opportunities
12 for public comment during this process.
13 So going through briefly the
14 conclusions that we came to based on
15 epidemiological studies in humans. The weight
16 of evidence that BPA causes adverse
17 developmental or reproductive effects in
18 humans was considered insufficient to reach a
19 conclusion. And this again is based on the
20 human studies, epidemiology studies which is
21 a very limited database.
22 The weight of evidence that BPA

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1 causes adverse developmental effects in
2 laboratory animals was split into two groups,
3 as you've already heard: the high-dose studies
4 and low-dose studies. The cut-off between
5 these two is 5 milligrams per kilogram per
6 day. We agreed with the FDA evaluation in
7 considering the high-dose developmental
8 toxicity studies and we viewed these as
9 providing clear evidence of adverse effects in
10 these studies. However, the margin of
11 exposure between the dose levels required for
12 these effects in these studies and current
13 human exposures was so large that these did
14 not present a concern to our panel, or to the
15 NTP.
16 What I'm going to spend most of
17 the rest of the discussion is the low-dose
18 developmental toxicity studies that our panel
19 and the NTP considered to provide limited
20 evidence of adverse effects.
21 First of all, the conclusions to
22 continue, with regard to fetal or neonatal

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mortality, birth defects, reduced birth weight and growth, the NTP concluded that there was negligible concern over these end points based on the totality of the literature. We did, however, find minimal concern for adverse effects, specifically with regard to developmental toxicity for the fetus, infants and children, and these were based on animal studies that collectively indicated effects in, our estimation, on the mammary gland development and an acceleration of puberty in female animals.

The highest level of concern expressed during our review was some concern for adverse effects, and this was for developmental toxicity for, again, fetuses, infants and children based on studies showing effects on development of the brain, behavioral effects and development of the prostate gland.

Are people exposed? Yes, we agreed in general with the numbers put forth

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by the Food and Drug Administration. We also, in our review, found that the highest exposure groups were formula-fed infants. The range of exposures that we had in our report was one to 13 micrograms per kilogram per day, and this encompasses the point estimate that FDA used in their document.

Now, I'd like to spend a minute and go over some of the mechanistic considerations and assumptions that we had when we went through the bisphenol A report.

As you know, bisphenol A has been known to be a weak estrogen since the '30s, but we did not consider BPA effects solely within the context of the relative binding affinity for ER-alpha and ER-beta. As you've heard, this is lower, much lower than that from estradiol, but there are an increasing number of studies that suggest the involvement of other receptor systems and these could have effects in two ways, as we sorted through the literature. Exposures to BPA during

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development might alter the expression patterns of different receptor levels in the brain, such as AR or dopamine receptor systems. Or, BPA may have in fact high affinity receptor activity for certain other receptors than the ER-alpha and ER-beta. These include ERR-gamma, the non-classical membrane ER, GPR30 and others. But at this point it's not clear at all if these interactions are responsible for biological effects of BPA as determined in other studies.

Just to go through this briefly, one of the receptor systems that was mentioned earlier, the estrogen-related receptor-gamma. You can see on this slide the relative binding affinities for BPA, 4-hydroxytamoxifen, which is a little bit stronger binder. DES binds to this particular receptor. This is an orphan receptor that's structurally related to ER-alpha. It does not bind estradiol and it is expressed at high levels in brain and in other tissues, as well as during development.

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1 This is high basal constitutive
2 activity and BPA, when binding to this
3 receptor, preserves this activity. DES and 4-
4 hydroxytamoxifen repress the molecular
5 activity of this particular receptor.
6 Another example, GPR30 is a 7-
7 transmembrane G-protein-coupled receptor that
8 responds to estradiol, up-regulating a number
9 of signaling transduction pathways. BPA has
10 a relative binding affinity which is lower of
11 course than that of estradiol to this
12 particular receptor, but it is much higher in
13 relation to the relative binding to ER-alpha
14 or beta.
15 DR antagonists, the ICI compound
16 and tamoxifen are agonists for this particular
17 receptor and DES is not bind at concentrations
18 up to 10 micromolar.
19 And then there's the non-classical
20 membrane-bound ER, which has been described in
21 pancreatic islet cells regulating the movement
22 of calcium channels, modulating insulin and

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glucagon release. BPA activates this particular receptor at one-nanomolar levels, which is similar to that of DES. This is insensitive to tamoxifen and the ICI antagonists compound.

So you can see that from this review that it's very difficult when you think about designing a study using positive controls to figure out exactly what kind of a positive control would be most likely, would be most reasonable under these situations.

So overall, continuing the consideration of effects as we went through this process, we focused on effects highlighted by the CERHR expert panel and other recent evaluations such as the Chapel Hill evaluation. We looked at this in the totality as to whether the in vivo effects were biologically plausible that were being reported in the literature. Have the in vivo effects been reproduced? Do the in vivo effects represent adverse health findings in laboratory animals and/or in humans? And what

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1 would be the potential impacts of limitations
2 in experimental design for these particular
3 studies?
4 First of all, I'd like to consider
5 the non-oral route of administration that we
6 heard about in the last talk. We agree
7 overall with the conclusions that have been
8 reached concerning BPA metabolism and route of
9 administration, that clearly the unconjugated
10 BPA is the biologically active form. Oral
11 studies are considered the most relevant for
12 human risks. BPA is glucuronidated in gut and
13 liver, and adult rodents metabolize BPA more
14 quickly following oral administration compared
15 to subcutaneous injection. And this does in
16 fact limit the utility of the subcutaneous
17 injection studies for an evaluation in adults.
18 But neonatal rats metabolize BPA
19 less actively than adults at a given
20 administered dose base because of the
21 immaturity of the relevant enzyme systems and
22 in fact there is evidence in humans for

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1 immaturity of glucuronidation systems as well
2 in infants.
3 So the NTP considered studies that
4 use subcutaneous injection to neonatal animals
5 as useful in its evaluation. The subcutaneous
6 route of administration to adult animals,
7 including to pregnant dams, was used only for
8 identifying potential hazards, not for making
9 quantitative estimates. And when we had this
10 particular point reviewed by the Board of
11 Scientific Counselors, when we looked at the
12 draft NTP brief, the ad hoc reviewers and the
13 board members all supported consideration of
14 the subcutaneous injection studies to neonates
15 in the evaluation of BPA's effects.
16 This is based on information such
17 as in this slide, the age-dependent metabolism
18 in rats. The neonatal rats do have higher
19 concentrations of unconjugated BPA and a
20 longer half life than adults at the same dose
21 given in the study of Domoradzki et al.
22 Here's an example. At a 10 milligram per

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kilogram oral dose, the difference in the C-max between the adult animal and the PND4 animal is 2,000-fold in males, 160-fold in females. At lower oral doses where metabolism is more complete in the adult and actually the material, free material cannot even be found in the blood, in this particular study, there is still measurable concentrations in the PND4 animal.

So the assumption that subcutaneous administration produces irrelevantly high internal concentrations of BPA compared to the oral administration does not apply to neonatal animals because of their undeveloped metabolism systems.

I'm going to spend a few minutes talking about specific end points that have been mentioned already in the low dose effects that were considered to support some or minimal concern for impacts on human development in the NTP review.

With regard to the brain and

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1 behavior, there were a number of well-designed
2 studies, three oral studies reporting effects
3 at 10 micrograms per kilogram per day and
4 other oral studies reported effects at less
5 than one milligram per kilogram per day.
6 These evaluated a collection of different
7 types of end points including maternal
8 behavior, novelty-seeking behavior,
9 exploration, reward response, anxiety,
10 cognition and other end points. Collectively,
11 the literature suggested that there was a loss
12 of sexual dimorphisms in non-reproductive
13 behaviors with regard to behavioral end points
14 or brain structures, or biochemical end
15 points. Certain of these behavioral responses
16 indicated that there might be specific effects
17 on the dopaminergic systems.
18 I'll give you some examples of
19 some of these studies. An Italian study
20 looking at CD-1 mice, a single dose of BPA
21 orally to the dam, gestation day 11 to post-
22 natal day eight. This is the normal response

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and a test of anxiety, which is an open field response; how much time male or female animal offspring will spend in a lighted portion of an open field. And this is a normal sex difference that you see. Females seem to be less anxious in this particular instance. When one gives BPA to the dam and put the pups in this kind of an open field apparatus, the differences go away.

Anxiety behavior was also demonstrated in another study by a different investigator, Ryan et al, looking at C57 black-6 mice, either giving two or 200 micrograms per kilogram per day BPA orally to the dam from gestation day three to post-natal day 21, looking again at the light-dark chamber. In this study they only looked at females, so the female control is the solid bar on the left and the pups exposed through the dam to two micrograms per kilogram per day are in the next bar. And 200 micrograms per kilogram per day are in the next bar showing

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a more anxious phenotype, if you will. And the control estradiol, ethinyal estradiol showing also the change in the same direction.

So although I've shown you two very, I think, convincing examples of the effects on anxiety there, overall it's difficult to evaluate the reproducibility of a lot of the effects that are seen in the literature. Most of these laboratories have very specific ways of doing their studies and they're not often repeated exactly from laboratory to laboratory. We do believe that the effects would not have been detected in guideline-compliant multi-generational studies. Behavior was not assessed in the Tyl studies. And in the Ema study, the rat multi-generational study did include some neural behavioral end points, but they did not report in their paper sexual dimorphisms in any of those end points, so it was difficult to tell whether they could have seen any particular diminishing effect on sexual dimorphisms.

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Overall, the data limitations include the fact that the adverse consequences of the effects are not known as to how these might affect behavior as the animals age, and it's also difficult to completely associate these kinds of changes with the relevance to the human situation.

Concerning the prostate gland, there were two technically well-conducted studies that reported the effects on the prostate gland development at 10 micrograms per kilogram per day. These included the preneoplastic intraepithelial neoplasia -- or I'm sorry, these included reported preneoplastic changes in PIN lesions in the Ho study, which was a study looking at subcutaneous administration to neonatal Sprague-Dawley rats. And there were also effects reported in the Timms study which was just mentioned, which looked at morphometric effects related to the ductal development of the prostate in giving oral administrations to

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1 pregnant CD-1 mice. These findings were
2 interpreted as potentially predisposing the
3 prostate gland to disease later in life.
4 With regard to reproducibility of
5 prostate, clearly the NTP two-year bioassay
6 did not report prostate gland tumors in the
7 BPA-treated rats or mice. However, these
8 models are very insensitive to the development
9 of prostate cancer. We have never seen a
10 prostate carcinogen in the NTP bioassay
11 program. And our animals in this particular
12 study did not include perinatal exposures.
13 These effects would not, in our estimation,
14 have been likely to have been detected in
15 guideline-compliant multi-generational studies
16 because there was no morphometric analysis in
17 these studies. PIN lesions are difficult to
18 detect in these particular models, and in fact
19 in the Ho study required administration of
20 estrogen and testosterone to develop these
21 lesions and some estrogenic effects that do
22 occur in the prostate are not seen with the

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typical HNE staining.

But there are data limitations of course to the prostate gland information as well. The long term consequences of these morphometric changes are unclear, as seen in the Timms study. It's not clear whether these effects are permanent or in fact adverse, and it's unclear if the reported PIN lesions in the Ho study do progress to cancer.

With regard to the mammary gland, there are two reports of preneoplastic lesions in mammary gland. These include ductal hyperplasia and possible carcinoma in situ. Human correlate lesions have in fact been described as risk factors for invasive breast cancer in humans and mammary gland was also identified as a BPA target tissue in other studies. And in general, these other studies showed increases in undifferentiated structures which are considered to be more prone to the development of cancer throughout the life of the animal.

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I should mention that all of the starred studies used a route of subcutaneous administration to adults and therefore these are used for the estimation or the assessment of targets for potential BPA action and are not considered in a quantitative sense.

With regard to reproducibility, the NTP two-year bioassay again did not report effects on mammary gland tumors in BPA-treated female rats or mice. It did not include perinatal exposures or whole mounts, which are in general required to be able to pick up some of these potentially preneoplastic findings. The effects may not have been detected in guideline studies. The rat study of Tyl did not look at the mammary gland and there were no whole mounts in either the Tyl 2008 study or the Ema study.

So there are many data limitations of course to this as well. The interpretive limitations include the fact that it's unknown if these reported lesions would progress to

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1 cancer, and I mentioned already the
2 subcutaneous route of administration to adult
3 animals was only useful for hazard
4 identification. There were also a wide
5 number, a large number of technical
6 limitations to the studies in this collection
7 of data, and I won't go through these in any
8 detail, but overall the conclusions of our
9 expert panel, or the conclusions of the NTP
10 brief were that, collectively, the mammary
11 gland findings supported minimal concern for
12 effects on human reproduction and development.
13 And finally, the puberty issue.
14 The CERHR expert panel expressed minimal
15 concern for effects on puberty in female mice
16 based on two oral mouse studies that provided
17 limited evidence for an effect. The NTP
18 reviewed all of the relevant studies in rats
19 and mice with regard to the potential for
20 acceleration of puberty. There were eight
21 low-dose studies in rats. Only one of these
22 was interpreted to be positive; seven were

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negative. And the mouse study showed more of an inconsistent pattern. There were three potentially positive studies and three negative studies.

When we looked at these, we determined that the most consistent difference between the studies, the mouse studies that were positive and negative was that the positive studies assessed first estrous as the end point of evaluation; negative studies assessed vaginal opening. First estrous is in fact considered to be the more appropriate measure of puberty in mice and it's not necessarily coincident with vaginal opening and it suggests that in fact there are some differential triggers for these events in mice.

The data limitations. I've already gone over some of these. The negative studies, the use of vaginal opening as an indicator of puberty. In some of these studies the positive control response didn't

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show exactly the kind of response one would have anticipated. There was either a failed control, positive control in the Ashby study or there were concerns over the ability, the sensitivity of particularly the Tyl study to pick up classic estrogenic effects of low doses. With regard to the positive studies, there were also some issues related to the interpretation of the actual measurements that were used or the sample size in the particular study, or again, the route of administration. Overall, these were considered to provide support for minimal concern for potential adverse effects on human reproduction and development.

So in summary, the quote-unquote low-dose studies in laboratory animals provided limited evidence for adverse effects in our estimation, but the fact that these effects were occurring at BPA exposure levels similar to those experienced by humans, therefore we felt that the possibility that

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BPA may alter human development could not at this time be dismissed, and clearly much, much more research is needed to better understand the implications of these findings for human health.

That's the end of my remarks. Thank you very much.

CHAIRMAN PHILBERT: Thank you very much for a clear presentation.

I had a quick question before I open it up to the subcommittee. Are you aware of any data that suggests that binding of BPA to ERR-gamma or to GPR30, ncmER, et cetera, results in a pathological phenotype or an adverse health outcome?

DR. BUCHER: There are some short-term studies in animals that would suggest that binding to the NMCR affects pancreatic function and may lead to effects on insulin release, modulations of insulin release and glucagon release.

CHAIRMAN PHILBERT: Are these in

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vivo?

DR. BUCHER: They are in vivo.

CHAIRMAN PHILBERT: Thank you.

Any other questions?

DR. BUSHNELL: You gave us a couple of examples of effects on behavior, on the anxiety behavior, at doses that were quite a bit lower than the FDA NOAEL. And I was wondering whether it was the opinion of your panel that these studies were consistent enough that a reevaluation based on those studies could produce a NOAEL that would be lower than the current value.

DR. BUCHER: Well these studies were in fact the ones that were driving the highest level of concern for the panel. But I think I indicated to you also that our expert panel, in looking at these, felt that the data were not consistent enough at this point to elevate their level of concern and there are a couple of higher categories that we have available to the expert panel, as well

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as to the NTP. And we agreed overall with that conclusion, as did our peer review panel. So, it's an area of intense interest and I think more follow-up is needed.

DR. BUSHNELL: All right. So it's an indication that more work is needed in this area.

DR. HU: Question. You noted that the NTP bioassay has never identified a prostate carcinogen. Surely there must be some sort of positive control that you use. And I seem to recall that cadmium was an animal carcinogen not proven in human studies, but it is a prostrate carcinogen.

DR. BUCHER: Cadmium has been shown to be recently a prostate carcinogen when given during the perinatal period. And in fact, this is one of the driving forces behind NTP's consideration to make perinatal exposures more of the default assumption, rather than the exception in our design.

CHAIRMAN PHILBERT: Are there

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other questions?

Hearing none, thank you very much.

DR. BUCHER: Thank you.

CHAIRMAN PHILBERT: Our next presentation will be by Dr. Frederick vom Saal from the University of Missouri, Columbia.

DR. vom SAAL: I appreciate the opportunity to present the lecture here today and one of the things you'll see is I'm talking about the issue of connecting the dots. And the one thing I think that's most important about this document; there's really no attempt whatsoever to link the literature that's reviewed here together in any kind of coherent way and I will attempt to do that for a small number of the studies.

I'm here, for one reason of a couple, and that is to present information from an NIH conference that was held on bisphenol A put together by Dr. Jerry Heindel at NIH. Aand in addition to this consensus statement, there were five major reviews

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published in August of '97 in Reproductive Toxicology that covered all of the available literature that we could get a hold of at that time, about 700 articles. And you just heard Dr. Bucher go through the neural papers. These are just related to the animal studies on neural effects. Okay?

One of the things that I thought was kind of interesting is the idea that none of these relate to humans and are of concern to humans. I'll come back to that.

These are the studies of effects of bisphenol A in animals on the female reproductive system. What wasn't talked about but was reviewed by us is these are the effects in wildlife and the Canadian government has declared bisphenol A an aquatic toxicant because these are aquatic species, and there is a mass of literature showing harm at exceedingly low doses. The estimated no-effect concentration in water being somewhere around seven parts per trillion.

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I'm going to be covering a little bit of information about the male reproductive system, in particular some of the articles on the prostate which Dr. Bucher covered. And the last set of information that I'll cover, which is a literature that nobody has talked about because it didn't come under the purview of the Center for the Evaluation of Risk to Human Reproduction or the FDA panel, is the literature on metabolic effects, and as you know, those are becoming quite important.

So one of the important issues that was distinctly lacking from the discussion this morning is, there is actually fair literature showing the amount of bisphenol A present in the blood of adults and of fetuses. And one of the things we've tried for years is to get people in pharmacokinetics to back-calculate as to how much it would take to get this much into a woman, a man or babies. And one of the things that Dr. Bucher covered is we have no idea, there are no data

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on how much bisphenol A is in newborn babies, how they metabolize it, so all of those conservative statements made by the FDA officials were nothing but absolute guesses because there are no data on that, and that, of course, is of extreme concern.

One of the important things is that you've heard something about the brain, the reproductive system; you didn't hear anything about wildlife. And I'm going to use the prostate as an example of how one should connect the dots. I'll then move on and talk about metabolic diseases and particularly some new information. But since the effects on the brain were deemed irrelevant to humans, I thought I'd show this next study which is a series of studies from Neil MacLusky -- an outstanding neuroscientist, and his group published a series of papers in rats, and more recently in monkeys. And what they show is these points of contact on the receptor neuron, the dendrites, the axons that lead to

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the neurons, they lose their connections. This is happening in a young adult brain of rats and monkeys, therefore monkey is a good model for humans. And that is what the brain of a senile individual looks like at death. If that's not relevant to humans, I'm a little confused. Maybe it's because I've been exposed to too much bisphenol A and I'm already senile.

The scientific literature here, one of the things I want to emphasize is there really is a very strong consistency here, but it does require what we call connecting the dots between this literature. These are just studies of animals. If I had brought -- I couldn't bring them because I just didn't have enough room in the airplane to get them here -- the cell culture studies and other studies that the 700 studies that our panel reviewed is much bigger than this. So these are just studies where bisphenol A was administered to animals. And one of the important elements

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1 between the studies, the two Tyl studies used
2 by the FDA and this literature conducted by
3 government scientists and academic scientists,
4 is, as you'll see, and Dr. Bucher, I think,
5 very adequately addressed, is that there is
6 really a very marked difference between the
7 scientific tools used by people whose grant
8 proposals are submitted to NIH. They have to
9 be state of the art. You have to be a highly
10 credible person whose research has been
11 replicated and validated by other scientists
12 in order to be funded by NIH; which my first
13 grant was in 1976, so you can guess how old I
14 am. And then you go through doing the
15 experiment. You submit that to a peer review
16 journal like published in Nature, Science,
17 Proceeding of the National Academy of
18 Sciences, Environmental Health Sciences. I
19 publish in, and all of these articles are
20 published in the world's top journals. And
21 they go through a very rigorous peer review
22 process and then they're independently

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1 replicated. GLP is not intended for
2 replication. They keep talking about
3 replicates. But these are studies that are
4 often presented by industry and not
5 replicated.
6 So here's a situation where what
7 we have is a series of studies, some of which
8 Dr. Bucher covered, showing that, for the
9 prostate, going back to work that a former
10 graduate student of mine, Susan Nagel, did as
11 her Ph.D. thesis, and we showed that at two
12 micrograms per kilogram; that's a little bit
13 below the NOAEL, and given to a pregnant
14 female in feeding, caused enlarged prostate.
15 Dr. Gupta exactly replicated that study. She
16 used 50 micrograms per kilogram, but not only
17 did she find an enlarged prostate throughout
18 adolescence into adulthood, but she found that
19 the prostates became hypersensitive to
20 androgen by increasing androgen receptors.
21 And then she showed that the enlarged prostate
22 occurred if she took the prostate out of the

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1 animal and looked at it in cell culture. And
2 exactly the same thing happened with DES. And
3 in cell culture that happened at .5 parts per
4 trillion DES and 50 parts per trillion of
5 bisphenol A it enlarged the prostate, led to
6 more prostate glands.
7 And then my colleague Barry Timms
8 and I got together and we published in 2005
9 that bisphenol A, the hormonal drug
10 diethylstilbestrol, the hormonal drug
11 ethinylestradiol, using computer
12 reconstruction, we showed that it dramatically
13 increased the size of the prostate glands and
14 led to also a hyperstimulation of the basal
15 cells, the stem cell population in the
16 prostate. That's interesting because Ogura
17 showed that, although he wasn't reviewed by
18 the NTP or the, excuse me, the FDA, that you
19 could see transformation of the basal cells
20 into what we call squamous metaplasia, an
21 abnormal cell type. And then the Ho study
22 showed that you develop prostate cancer and

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we've actually replicated that and will be publishing it.

But all of these studies, the word dismiss, I mean, the studies weren't used, so however you want to describe them, they were not used in the final assessment by the FDA, but these are the statements made by the National Toxicology Program about them. These are adequate and useful, adequate and high utility, adequate and high utility. The Ho study was criticized because they used an injection. We did a study that has been bandied about here. It was done by my colleague Julia Taylor and Wade Valshontz and I. And what we showed was exactly identical blood levels of bisphenol A throughout a 24-hour period after oral or subcutaneous administration in newborn mice.

So one of the things that these have shown is increased prostate gland number, increased prostate androgen receptors, basal cell hyperplasia and metaplasia, changes in

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