

**FDA RESPONSE TO
THE
SCIENTIFIC PEER REVIEW
OF
FDA'S DRAFT ASSESSMENT OF BISPHENOL A FOR USE IN FOOD CONTACT APPLICATIONS**

June 15, 2010

Background and Ongoing Work

FDA delivered its *Draft Assessment of Bisphenol A for Use in Food Contact Applications* to a temporary Subcommittee of the FDA Science Board for peer review on August 14, 2008. By October 31, 2008, the FDA Science Board considered and accepted the recommendations of the BPA Subcommittee and formally transmitted the Peer Review Report to FDA. FDA responded to the Science Board's Peer Review Report on December 3, 2008, and promised to further respond at a future time. Since then, FDA has provided updates on BPA at the Science Board meetings of February 24, 2009, and August 17, 2009. This is FDA's more complete response to the Peer Review Report to more fully address the comments and questions raised in the Peer Review Report and to describe FDA's plans for additional actions in response to comments raised in the Peer Review Report.

This response summarizes the work that CFSAN has completed to date, including a comprehensive re-assessment of those BPA studies that were considered adequate by NTP/CERHR for the endpoints identified in the NTP draft brief as cause for some concern. Also included in this re-assessment are studies examining those same endpoints, and other endpoints mentioned in the Science Board report, that became available to the Agency between April 2008, when the NTP bulletin was released, and June 2009. FDA has made CFSAN's re-assessment of these studies available for public review and comment along with the comments of five non-FDA, government experts who were requested by FDA to review CFSAN's re-assessment.

In the same docket, FDA has also made three new, related documents available for review and comment: 1) an update to CFSAN's low-dose review that includes relevant studies that became available after the assessment of low-dose studies was complete, up to October 2009; 2) an updated dietary exposure estimate for the food-contact uses of BPA in packaging for infant formula, baby and adult foods, and polycarbonate nursing bottles; and, 3) CFSAN's review of the available biomonitoring data on BPA. These documents may be obtained by searching www.regulations.gov for Docket Number FDA-2010-N-0100.

At this time, CFSAN continues to develop data, and to obtain data from other sources, to update the existing *Draft Safety Assessment of BPA for Use in Food Contact Applications*. To this end, CFSAN is currently investigating data needs with regard to adult foods for the purpose of improving the current exposure assessment of this population. In addition to this analytical work, the results of several studies on the safety of BPA are pending completion at FDA's National Center for Toxicological Research. Rat and non-human primate pharmacokinetic studies are near completion and will be used by FDA to develop a physiologically based pharmacokinetic model for BPA. These data will also be used to re-assess the utility of existing information regarding the quantitative safety assessment.

Rodent subchronic studies are in progress to characterize the oral dose-response curve for BPA relating to a number of endpoints including those of current interest in the prostate and mammary glands, and to explore metabolic and cardiovascular endpoint changes identified in the Peer Review Report. These

studies will include an *in utero* phase, mimic bottle feeding in neonates, and employ a dose range that will cover the low doses where effects have been previously reported, as well as higher doses where estrogenic effects have been measured in guideline oral studies.

In addition, rodent neuroanatomy and behavioral studies are in progress to determine if behavioral/neuroanatomical/neurochemical or hormonal endpoints are altered by developmental exposure to BPA. As with the subchronic study, this study includes a wide range of doses, *in utero* exposure, exposure mimicking bottle feeding, and examines a large variety of neurological and developmental endpoints. These data are intended to resolve inconsistencies described in the published literature regarding sexually dimorphic endpoints as well as the standard developmental neurotoxicity resulting from developmental exposure to BPA. FDA is still in the protocol planning stages regarding non-human primate studies to investigate growth and cognitive and pubertal development in rhesus monkeys

Introduction

On August 14, 2008, FDA delivered its *Draft Assessment of Bisphenol A for Use in Food Contact Applications* to a temporary Subcommittee of the FDA Science Board for peer review. Members of this temporary BPA Subcommittee were chosen for scientific expertise in disciplines related to the issues addressed in the Draft Assessment. The Subcommittee members included:

Martin A. Philbert, Ph.D.
(Chair, Member, Science Board)
Professor of Toxicology &
Senior Associate Dean for Research
University of Michigan School of Public Health

Howard Hu, M.D.
Professor of Environmental Health Sciences &
Chair
University of Michigan School of Public Health

Garret Fitzgerald, M.D.
(Member, Science Board)
Professor of Pharmacology & Chair
University of Pennsylvania School of Medicine

Howard Rockette, Ph.D.
Professor of Biostatistics & Chair
University of Pittsburgh School of Public Health

Philip J. Bushnell, Ph.D.
Research Toxicologist
Neurotoxicology Division
National Health and Environmental
Effects Research Laboratory
Office of Research and Development, USEPA

John J. Vandenberg, Ph.D.
Associate Director for Health
National Center for Environmental Assessment
Office of Research and Development, USEPA

Antonia M. Calafat, Ph.D.
Lead Research Chemist
National Center for Environmental Health
Centers for Disease Control and Prevention

A public meeting was held on September 16, 2008, at which the Subcommittee members received briefings from:

- X Food and Drug Administration on methodologies employed in preparing the Draft Assessment;
- X National Toxicology Program (NTP) on the approach used by NTP for their assessment of BPA; and

X Chapel Hill Bisphenol A Expert Panel on the conclusions of their review.

In addition, there was an open public hearing, followed by a discussion between the Subcommittee members and a panel of scientists invited by the Subcommittee. Information about, and transcripts of, the meeting may be accessed from www.fda.gov, by following the *Advisory Committees* link under About FDA, then the *Committees and Meeting Materials* link in the second box down on the left, and then the *Science Board to the Food and Drug Administration* link in the left column.

On October 31, 2008, the Chairman of the BPA Subcommittee, Dr. Martin A. Philbert, presented a report of the Subcommittee's findings at a meeting of the FDA Science Board for discussion. The FDA Science Board considered and accepted the recommendations of the Subcommittee, and transmitted the peer review report to the FDA with the added stipulation that Science Board members may send to the FDA, within a week, any additional considerations for further studies that members would recommend. No suggestions for further studies have been received by FDA. The peer review report is available at <http://www.fda.gov/ohrms/dockets/ac/08/briefing/2008-4386b1-24.pdf>.

FDA greatly appreciates the hard work and long hours that the FDA Science Board and its BPA Subcommittee have invested in the peer review of FDA's *Draft Assessment of the Use of BPA in Food Contact Applications*. Each of the Science Board's suggestions and the comments contained in the peer-review report are summarized below with FDA's response.

Overall, the Science Board agreed with FDA's focus on dietary exposures to children due to the potential for greater exposure and susceptibility relative to adults. However, the Subcommittee also concluded that the Assessment:

- X would be strengthened by including a cumulative exposure assessment, and an assessment of differential risk in neonates;
- X lacks an adequate number of infant formula samples;
 - relies, in the exposure estimate, on averages rather than accounting for variability;
- X does not articulate the criteria used by FDA to select studies for inclusion;
- X lacks adequate characterization of uncertainties in both estimates of exposure and effects;
- X should include studies judged to be adequate by the National Toxicology Program/Center for the Evaluation of Risks to Human Reproduction (NTP/CERHR); and
- X indicates that the available data may support a more conservative margin of safety.

Finally, the Subcommittee concludes that the "weight-of-the-evidence," including studies identified by CERHR as adequate and having utility, provides scientific support for a point of departure at least one or two orders of magnitude below the 5 mg/kg bw/day determined by FDA. These comments, and others found in the Science Board report, are addressed in detail below.

Peer Review Comments Responding to Charge Questions and FDA Responses

Question 1 Does the assessment report objectively and transparently identify the data and methodology used, explain how data were selected, and identify what criteria were used to determine the suitability of the data? Does the report identify the scientific support for these criteria and methods?

Comment 1: The Subcommittee found that FDA’s assessment did not account for cumulative effects of non-food-contact exposures, and excluded the use of biomonitoring data that could have shed some light on cumulative exposures and inter-individual variability in internal dose.

Response:

FDA agrees that the final safety assessment of BPA must be based on knowledge of the cumulative exposure to BPA from all FDA-regulated products, and that biomonitoring data may be useful for validating cumulative exposures and inter-individual variability in internal dose.

FDA’s *Draft Assessment of Bisphenol A for Use in Food Contact Applications* represents the first step of a multi-part assessment of exposure and risk to BPA. Estimates of exposure from other FDA-regulated products have been underway in FDA’s other product Centers and ultimately are intended to be combined into an assessment of cumulative exposure and risk. Available biomonitoring data on BPA have been reviewed, as recommended by the Science Board, with a view to their utility for informing the cumulative exposure estimates.

A multi-step approach to exposure and risk assessment is necessary because each of FDA’s product Centers has information, methodology, and expertise specific to the types of products they regulate. For instance, the information and methods for estimating dietary exposures would be very different from the information and methods for estimating exposure to BPA migrating from medical devices. The introduction to the *Draft Assessment of Bisphenol A for Use in Food Contact Applications* will be revised to clarify that the present assessment is only the first step in a larger, multi-part, safety assessment of BPA.

Comment 2: The Subcommittee found that the data used for the exposure assessment was limited both in size and in geographical and temporal distribution and therefore could not account for variability in potential exposures. In addition, age specific estimates of BPA exposure in infants used mean values rather than 95th percentile or maximum values, and assumptions used in the exposure estimate are not well supported (for example, infant formula is no longer consumed after 12 months, bottles are no longer sterilized after two months of age). The Subcommittee suggested that FDA:

- 1) include a wide range of samples for estimating BPA content in food samples;
- 2) use distributions of data values rather than point values;
- 3) conduct sensitivity analysis for values without distributions; and,
- 4) use demographic information to determine the number of individuals that are likely to be exposed at each estimated concentration.

Response:

FDA is revising the exposure section of the Draft Assessment in the following ways:

Concentration of BPA in Food

- X Since January 2009, FDA’s Center for Food Safety and Applied Nutrition (CFSAN) has collected and analyzed more than 100 infant formula samples representing products from four major manufacturers in two geographical regions of the US. Ready-to-feed infant formulas, concentrates, and powders in a variety of package sizes were included in the sampling and analysis.
- X CFSAN has included data from all currently available studies reporting BPA migration from polycarbonate nursing bottles, and information from the 2005-2007 Infant Feeding Practices Study

(IFPS II)¹ to categorize migration data according to anticipated conditions of use. Analyses have been completed reflecting a range of conditions including recommended use conditions, current practices, and “extreme” use conditions.

- X Using data from a recent Health Canada study² that analyzed 122 baby/toddler food products representing seven brands packed in glass jars with metal lids, CFSAN grouped baby foods according to food type (desserts, fruits, meats and vegetables) and calculated BPA concentrations, and estimated potential variability, for each group.
- X Publically available data on BPA concentrations in adult foods have been further categorized according to eleven CFSAN-defined food types. Concentrations of BPA, and its variability were determined for each food type.

Exposure

- X Variability in exposure due to individual differences in food consumption and body mass for various age groups was obtained using consumption data from the food consumption database of the National Health and Nutrition Examination Survey (combined NHANES 1999-2006, 1 day data) and from Exponent’s Food Analysis and Residue Evaluation (FARE) software (Version 8.50). Ranges of eater-only exposures for infants (<1 year of age in monthly increments), babies/toddlers (1-2 years of age) and children/adults (>2 years of age) have been estimated and will be included in a revised Assessment.

Comment 3: Inter-individual differences in systemic internal exposures following a standardized exposure to environmental BPA were not taken into account.

Response:

The pharmacokinetics of BPA have been studied extensively in mice, rats, primates, and humans (reviewed in Willhite et al., 2008). Orally administered BPA is extensively absorbed from the GI tract in rodents and primates, including humans. However, the design of previous investigations of BPA pharmacokinetics resulted in data of limited value for the assessment of risks associated with low-level oral human exposures, particularly during the perinatal period. The limitations in these studies arise mainly from the use of analytical methodology (e.g., use of total radioactivity) or protocols that did not measure BPA and its Phase II conjugates separately. Other studies quantified BPA and its conjugated forms separately, but used either high oral doses (> 10 mg/kg bw) or non-oral routes of administration. Consequently, reliable relationships between external doses of BPA and systemic internal exposures at low doses were not developed for the Draft Assessment.

To address this issue, the National Center for Toxicological Research (NCTR) is currently developing physiologically based pharmacokinetic (PBPK) models for both rodents and primates. These pharmacokinetic (PK) studies are designed to develop a model for the prediction of internal exposure of BPA in both the free and conjugated forms, and may yield reliable data on the magnitude of inter-individual differences. Depending on the quality of the results, data from these studies might be useful for estimating an internal dose from a variety of exposure scenarios; to facilitate comparisons of

¹ Grummer-Strawn, L. M.; Scanlon, K. S.; Fein, S. B. Infant feeding and feeding transitions during the first year of life. *Pediatrics* 2008, 122 Suppl 2, S36-S42.

² Bureau of Chemical Safety; Food Directorate; Health Products and Food Branch . Survey of bisphenol A in baby food products prepackaged in glass jars with metal lids. http://www.hc-sc.gc.ca/fn-an/pubs/securit/bpa_survey-enquete-eng.php, 2009.

exposure across all stages of perinatal development; and, to develop relationships between the results of rodent and primate feeding studies. In addition, these data may allow the agency to assess the magnitude of the potential differential risk in neonates.

Comment 4: The Subcommittee found that the draft assessment does not provide appropriate support for the criteria and methods employed for acceptance of both exposure and effects studies, and that consistent and credible criteria for study inclusion would include accepting those studies judged by CERHR as adequate and of high utility as directly relevant to FDA's hazard, dose-response, and safety assessment. The Subcommittee also found that studies judged by CERHR as adequate and of limited utility also provide useful information on potential hazards posed by exposure to BPA.

Response:

CFSAN has recently completed a comprehensive re-review of those studies that were considered adequate by NTP/CERHR for the endpoints identified in the NTP draft brief as cause for some concern. This review includes the conclusions of many reviews conducted by FDA's toxicology reviewers, pharmacologists, and pathologists. Also included in this review are studies examining those same endpoints, and other endpoints mentioned in the Science Board report, that became available to the Agency between April 2008, when the NTP bulletin was released, and June 2009.

Each of these studies was subjected to a set of eight criteria that were derived from a compilation of FDA's Redbook 2000, the Organization for Economic Co-operation and Development (OECD), and Environmental Protection Agency (EPA) guidelines. These organizations are in general agreement concerning toxicity testing and criteria necessary for data to be useful in a regulatory safety assessment. These criteria are explicitly identified and explained in the review document.

CFSAN has historically accepted studies performed under Redbook, OECD, or EPA guidelines for evaluating endpoints of toxicity. OECD and EPA guidelines regarding the evaluation of developmental neurotoxicity and potential endocrine disruption were consulted to address additional endpoints for inclusion in the quantitative safety assessment. The degree to which each study conformed to the eight criteria determined the weight and confidence of its inclusion, and influence on the quantitative safety assessment.

FDA has made CFSAN's assessment of these low-dose studies available for public review and comment along with the comments of five non-FDA, government experts who were requested by FDA to review CFSAN's assessment of these studies. In the same docket, FDA has also made three related documents available: 1) CFSAN's review and summary of several studies on potential health effects of BPA exposure that became available after its assessment of low-dose studies was complete; 2) an updated dietary exposure estimate for the food-contact uses of BPA in packaging for infant formula, baby and adult foods, and polycarbonate nursing bottles; and, 3) CFSAN's review of the available biomonitoring data on BPA. These documents, and instructions for commenting on them, may be obtained by searching www.regulations.gov for Docket Number FDA-2010-N-0100. The comment period closed on June 4, 2010.

Question 2 Are uncertainties in the assessment objectively and transparently identified and characterized?

Comment 1: For the exposure Assessment, the Subcommittee found that the Draft Assessment discusses ranges of exposure values, but does not adequately quantify the uncertainties associated with the sampling variability within the FDA samples used to obtain estimates of exposure.

Response:

As described in our response to Question 1, Comment 2, above, CFSAN has collected and analyzed about 100 new infant formula samples in the past year. The analysis of these samples included an analysis of the variability of the BPA concentration in a given sample, and across lots, brands, and between geographical regions. In addition, variability in exposure due to individual differences in food consumption and body mass for various age groups was obtained using consumption data from the food consumption database of the National Health and Nutrition Examination Survey (combined NHANES 1999-2006, 1 day data, eaters only) and from Exponent's Food Analysis and Residue Evaluation (FARE) software (Version 8.50). Ranges of exposure estimates were thereby developed for an age stratified group of consumers. Additional work towards quantifying the uncertainty at various points in the exposure assessment is ongoing.

Comment 2: The uncertainties regarding the potential effects of BPA on neurodevelopmental, prostate, mammary gland, the acceleration of puberty and specifically, the potential gender dependant distinctions among neurobehavioral phenotypes are described qualitatively but there has been no attempt to quantify those uncertainties.

Response:

As described more fully below, CFSAN has reviewed the studies deemed adequate by NTP/CERHR, for the endpoints identified in the NTP draft brief as cause for some concern, and concluded that, based on the criteria selected for data inclusion, they do not collectively provide sufficient support for a lower point of departure. CFSAN does not agree that the available data may be aggregated in a quantitative manner to determine a numerical NOAEL, or even a numerical lowest observed adverse effect level (LOAEL) at this time. CFSAN concludes that the reported studies raise questions regarding developmental neurotoxicity that require further investigation before the potential toxicity of BPA may be quantified.

Comment 3: The Science Board suggested that the section of the draft assessment dealing with margins of safety be revised to include a more complete discussion of the basis for the selection of uncertainty factors. The committee referenced EPA discussions of uncertainty factors in recent IRIS assessments.

Response:

FDA uses uncertainty factors to extrapolate the highest dose where no effects are found in animal studies to the highest hypothetical exposure levels where no effects are expected to be found in humans. The margin of safety is the difference between this hypothetical exposure and the actual estimated exposure in humans. For this review, FDA considered a number of uncertainty factors when developing a margin of safety based on animal data including: intra- and inter-species variability; duration of the study (subchronic-to-chronic uncertainty); and, the availability of non-rodent data.

Of the data for which a no observed adverse effect level (NOAEL) could be determined, the lowest, 5 mg/kg bw/day for systemic toxicity, was observed in both the rat and mouse multigenerational studies (Tyl et al. 2002, 2008). For reproductive and developmental toxicity, the lowest NOAEL is 50 mg/kg bw/day. Because the NOAEL for reproductive and developmental toxicity is 10 times higher than that for systemic toxicity, and the maximum uncertainty factor for reproductive and developmental toxicity is 1000, the critical endpoint for establishing the margin of safety is the lower NOAEL of 5 mg/kg bw/day

for systemic toxicity. Therefore, we describe here the application of an uncertainty factor to the systemic toxicity endpoint.

Inter-species variability (animal variation): The current data in rodent models suggests that rodents may have increased sensitivity to BPA, either through enterohepatic recirculation, or through alternative metabolites. This information suggests that an uncertainty factor for inter-species variability of less than 10 may be applicable. However, given the continued debate on the sensitivity of the different animal models to estrogens in general, and how these models relate to humans, FDA employed a default uncertainty factor of 10 to account for this unknown variability.

Intraspecies variability (human variation): Data currently available suggests that glucuronidating capability is low at birth and develops with age due to the low expression of glucuronosyltransferases. Therefore, based on the possibility of decreased neonatal metabolism, as well as individuals who may be compromised in enzyme activity, or renal clearance, there appear to be susceptible populations that indicate the need for the application of a 10-fold uncertainty factor to account for this kind of variability.

Study duration: Although a chronic study is available, it is somewhat antiquated in design, and more applicable to cancer assessment than to chronic toxicity. The NOAEL of 5 mg/kg bw/day used by FDA was for systemic toxicity and was derived from studies of less than chronic duration. Therefore, FDA used an uncertainty factor of 10 to adjust for the less than chronic duration of the NOAEL.

Availability of non-rodent data: CFSAN may use an additional factor of 2 when only rodent data are available to assess the safety of a particular chemical. Since systemic toxicity of BPA was evaluated in a non-rodent species (dog), the use of the additional factor of 2 is not warranted.

FDA has expanded and clarified the discussion of its use of uncertainty factors in an updated revision of the Draft Assessment. Included in this discussion is a more detailed explanation of the basis for the selection of the uncertainty factors used.

Question 3 Are there additional scientific/technical studies relevant to the endpoints examined and the route of exposure that should have been considered?

Comment 1: The subcommittee stated that studies identified by CERHR as adequate should be considered as alternatives for FDA's qualitative/quantitative assessment of risk. In addition, the subcommittee recommended including several studies of the effects of BPA on adult humans and on animals that were published after the assessment was prepared, including:

- X Lang, I.A., Galloway, T.S., Scarlett, A., Henley, W.E., Depledge, M., Wallace, R.B., and Melzer, D. (2008) Association of urinary bisphenol A concentration with medical disorders and laboratory abnormalities in adults. *Journal of the American Medical Association* 300(11):1303-1310;
- X Leranath, C., Hajszan, T., Szigeti-Buck, K., Bober, J., and MacLusky, N.J. (2008) Bisphenol A prevents the synaptogenic response to estradiol in hippocampus and prefrontal cortex of ovariectomized nonhuman primates. *Proceedings of the National Academy of Sciences (USA)* 105(37):14187-14191;
- X Leranath, C., Szigeti-Buck, K., MacLusky, N.J., and Hajszan, T. (2008) Bisphenol A prevents the synaptogenic response to testosterone in the brain of adult male rats. *Endocrinology* 149:988-994;

- X Dolinoy, D.C., Huang, D., and Jirte, R.L. (2007) Maternal nutrient supplementation counteracts bisphenol A-induced DNA hypomethylation in early development. *Proceedings of the National Academy Sciences* 104:13056-13061; and,
- X Fein, S.B., and Falci, C.D. (1999) Infant formula preparation, handling, and related practices in the United States. *Journal of the American Dietetic Association* 99(10): 1234-1240.

Response:

As stated in the response to Question 1, Comment 4, CFSAN has recently completed a comprehensive re-review of those studies that were considered adequate by NTP/CERHR for the endpoints identified in the NTP draft brief as cause for some concern. Also included are studies examining those same endpoints, and other endpoints mentioned in the Science Board report, that became available to the Agency between April 2008, when the NTP Bulletin was released, and June 2009. Included in these reviews are the first four of the studies cited by the Science Board, above. The fifth was reviewed as part of the analysis of migration of BPA from polycarbonate baby bottles described in our response to Question 1, Comment 2.

Comment 2: The subcommittee disagreed with the Agency's decision to dismiss the results of studies that were not amenable to the construction of a dose-response relationship, but that were otherwise scientifically sound, inclusive of more advanced and sensitive endpoints, and that were often indicative of BPA impacts that could portend significant risks to health at much lower levels than observed in the guideline studies used by FDA. The subcommittee felt that the inclusion of these studies in the hazard identification phase of the assessment will indicate additional endpoints of concern (prostate, neurobehavioral, and mammary) and that in the dose response phase, health effects are identified at levels substantially below the 5 mg/kg bw/day identified by the guideline studies.

Response:

As stated in our response to Question 1, Comment 4, CFSAN has completed a comprehensive re-review of those studies that were considered adequate by NTP/CERHR for the endpoints identified in the NTP draft brief as cause for some concern: *i.e.* neurotoxicity, prostate, mammary; and early onset of puberty in females. Also included, were studies examining those same endpoints, and other endpoints mentioned in the Science Board report, that became available to the Agency between April 2008, when the NTP Bulletin was released, and June 2009.

Neurodevelopmental Toxicity: Three studies were determined to be of utility for this endpoint. Stump *et al.*, 2009, assayed sensory and motor endpoints (surface righting response, auditory startle test, and motor activity test) and learning and memory endpoints (Biel swimming maze) at a wide range of exposures including low doses in rats. A NOAEL of 164 mg/kg/day for these neurotoxicity endpoints can be established based on this study. In addition, Ryan *et al.* 2009, addressed some sexually dimorphic endpoints using female rats. Sensory (saccharin preference), spontaneous motor activity (Figure-8 maze) and sexual behavior (lordosis) were tested. No low-dose effects were noted for these neurotoxicity endpoints between 2 and 200 µg/kg/day. Finally, Ema *et al.*, 2001, examined developmental toxicity endpoints in a 2-generation study conducted in rats, concluding that the changes observed were slight, not dose dependant, and inconsistent across generations. The study was well-controlled, examined the low dose range, and included a large treatment group. The authors examined validated markers of behavior without positive findings at low doses; their results suggest a lack of effect for this endpoint at low doses of BPA. For effects on developmental, sexually dimorphic (*i.e.* changes in anxiety, learning and behavior between the sexes), and neuroanatomical endpoints, CFSAN has determined that a NOAEL for neurotoxicity cannot be established. The data available in which CFSAN has high confidence did not adequately examine or model these endpoints. The more exploratory studies in the literature do not sufficiently link the reported findings to adverse endpoints, or sufficient information is unavailable on the

endpoint measured to adequately characterize the change observed. As the brain is a highly plastic system incorporating multiple compensatory mechanisms, the ability to link molecular, hormonal, or subtle findings to adverse outcomes is extremely important in characterizing the hazard. Furthermore, it is unclear that certain of the results observed in the rodent studies are relatable to human adverse outcomes. Based on these data gaps and the various limitations of the studies, a NOAEL based on the reported observations cannot be determined with confidence. However, collectively the available studies, though uncertain, indicate that developmental BPA exposure may influence certain sexually dimorphic behaviors and anxiety and neuroanatomical endpoints.

Prostate Gland Toxicity: CFSAN concludes that the available data are insufficient to establish a NOAEL for prostate findings, or to influence the existing NOAELs. These data are limited in interpretation due to the route of administration, the plausibility of the findings (these studies do not demonstrate findings that are clearly relatable to adverse findings in humans and do not demonstrate progression to tumors), and the lack of repeatability. No studies have demonstrated tumors following BPA treatment. Although BPA was negative in the NTP bioassay, the questions regarding appropriateness of the animal model and the lack of *in utero* exposure lessen our confidence in the bioassay results. Additionally, the techniques used in many of the low-dose studies examined changes at the molecular and morphological level that would not have been discernible in the guideline studies. Although the reported findings are relevant to the knowledge base of carcinogenic mechanisms, the data are not sufficiently complete, or accompanied with accessory findings, to support the conclusion of toxicity. These factors, combined with a lack of data demonstrating effects following oral exposure, limit this endpoint to hazard identification. Due to the lack of a sufficient animal model, BPA's potential effects on the prostate remain uncharacterized.

Mammary Gland Toxicity: Studies suggesting low-dose findings with respect to predisposition of the mammary gland to cancer were conducted using non-oral administration to dams. Studies using gavage (oral) administration are less remarkable at low doses. Data currently available in adult pregnant animals receiving BPA orally suggest that the level of free BPA available for the fetus would be a minor fraction of the dose; this is especially true for primates. As such, the plausibility of the findings from subcutaneous dam exposure has low confidence with regard to mammary gland effects as compared to oral pregnant human exposure. Although the NTP bioassay lacked an *in utero* exposure period, CFSAN notes that its negative findings also support a lack of effect on this tissue. The weight of evidence suggests that oral BPA exposure does not affect the mammary gland.

Early Onset of Puberty: Onset of puberty has been measured in numerous studies, including several that were well conducted and documented. The weight of evidence suggests that BPA does not affect the onset of puberty.

Other Endpoints:

Based on the available data, other endpoints examined in the low-dose review (metabolic homeostasis and potential epigenetic changes) did not indicate a concern at the current level of exposure.

CFSAN has reviewed the studies deemed adequate by NTP/CERHR for the endpoints identified in the NTP draft brief as cause for some concern, and concluded that, based on the criteria selected for data inclusion, they do not collectively provide sufficient support for a lower point of departure. As noted above, the neurotoxicity studies appear to suggest effects on developmental, sexually dimorphic (*i.e.* changes in anxiety, learning and behavior between the sexes), and neuroanatomical endpoints. However, the significance of these limited rodent data to human health outcomes is not clear. CFSAN does not believe that the available data may be aggregated in a quantitative manner to determine a numerical NOAEL, or even

a numerical LOAEL at this time. CFSAN concludes that the reported studies raise questions regarding developmental neurotoxicity that require further investigation before the potential toxicity of BPA may be quantified.

Question 4 Is the no observed adverse effect level (NOAEL) used in this assessment the appropriate point of departure for calculating the margins of safety (MOS), for purposes of this safety assessment, or do data support the use of an alternative endpoint? In selecting the NOAEL, did FDA make the best scientific choice based on the available data and information?

Comment 1: The FDA Science Board requested that FDA re-analyze the results of studies in the areas of neurobehavioral development, prostate gland, mammary gland, and acceleration of puberty in females, as identified in the NTP Brief, in three ways:

- X diagram the effect magnitude against the applied dose;
- X use available information to convert the magnitude of effects on a variety of endpoints to a common scale and then graph those results against an internal dose (concentration in the target organ) developed from what is already known of BPA binding to estrogen receptors and kinetics of BPA; and,
- X analyze the applied dose-response relationships in the Tyl studies using a benchmark dose model.

Response:

Among the specific endpoints observed in the studies that examined the areas of neurobehavioral development, prostate gland, mammary gland, and acceleration of puberty in females, as identified in the NTP Brief, many are not relatable to one another. Nevertheless, it may be possible to sub-group such studies according to similar observations of related effects and plot those against an applied dose for orally administered doses. CFSAN expects that the uncertainties associated with this approach would exceed those expected from plotting such grouped observations of effect against an internal dose in the target organ, but both approaches will be explored.

The normalization of related effects data to a common magnitude scale and then plotting them against an internal dose in a target organ forms the basis of the meta-analytical method. Meta analysis is the process of re-analyzing results that have been aggregated from a set of studies that all employ similar methods and procedures to measure a common endpoint. It is often used to overcome the problem of reduced statistical power in studies with small sample sizes. CFSAN will examine the applicability of the meta analytical method to the studies that examined the areas of neurobehavioral development, prostate gland, mammary gland, and acceleration of puberty in females, as identified in the NTP Brief. The studies included in this analysis will be subjected to data quality criteria as well as criteria to assure a valid data aggregation. CFSAN expects that the internal dose data now being developed by NCTR will enhance the ability to perform such an analysis.

Various benchmark dose modeling analyses have already been conducted on the Tyl. et al. (2002, 2008) studies using EPA's software.³ FDA had previously approached its analysis of BPA using the NOAEL

³ a) Willhite CC, Ball GL and McLellan CJ. (2008). Derivation of a bisphenol A oral reference dose (RfD) and drinking-water equivalent concentration. *Journal of Toxicology and Environmental Health, Part B*, 11(2): 69 – 146.
b) CERHR final report NTP-CERHR Expert Panel Report on the Reproductive and Developmental Toxicity of Bisphenol A, dated November 2007 (accessible at <http://cerhr.niehs.nih.gov/chemicals/bisphenol/BPAFinalEPVF112607.pdf>) and published as Chapin et al. (2008) NTP-CERHR Expert Panel Report on the Reproductive and Developmental Toxicity of Bisphenol A Birth Defects Research (Part B) 83:157–395.

as the point of departure. An examination of the various benchmark dose modeling analyses reported leads to the conclusion that using the same information (Tyl et al. 2002, 2008) and the EPA software would produce an equivalent result if conducted by FDA independently. Moreover, for effects deemed treatment related, none of these analyses indicate a more sensitive endpoint or a lower point of departure than application of the NOAEL approach. As discussed in the draft Assessment, several potential endpoints of BPA toxicity are not examined in these two multigenerational studies. It is noteworthy that this analysis is limited to the endpoints examined in the Tyl et al (2002, 2008) studies. Based on the examination of the benchmark dose approach, a more conservative approach is to utilize the existing point of departure, the NOAELs, for the endpoints analyzed in these studies.

Comment 2: The Science Board asserts that, though individually the studies deemed adequate by CERHR have limitations, taken together they provide sufficient support for a point of departure at least an order of magnitude below the 5 mg/kg bw/day selected by FDA.

Response:

CFSAN has reviewed the studies deemed adequate by NTP/CERHR for the endpoints identified in the NTP draft brief as cause for some concern, and concluded that, based on the criteria selected for data inclusion, they do not collectively provide sufficient support for a lower point of departure. As stated above, CFSAN acknowledges that the neurotoxicity studies appear to suggest effects on anxiety, learning and memory between the sexes, and neuroanatomical endpoints. However, CFSAN does not agree that the available data may, at this time, be aggregated in a quantitative manner to determine a numerical NOAEL or even a numerical LOAEL. CFSAN concludes that the reported studies raise questions regarding developmental neurotoxicity that require further investigation before the potential toxicity of BPA may be quantified. A detailed response to this comment is provided in the response to Question 3, Comment 2.

Question 5 Were scientific assumptions that are not strictly linked to the data explained and appropriate for the purposes of this safety assessment?

Comment 1: Evidence presented in the NTP Brief suggests that even though fetal and neonatal rats have the ability to metabolize BPA, their metabolic pathways are less efficient than those of adult rats, suggesting higher risks for neonates than is assumed in the draft assessment. The Subcommittee suggested that the FDA Assessment discuss the ability of infants and neonates to metabolize BPA.

Response:

As stated in the response to Question 1, Comment 3, NCTR is currently conducting PK studies in both rodents and primates. These PK studies are designed to develop a PBPK model for the prediction of internal exposure of BPA in both the free and conjugated forms, and may yield reliable data on the magnitude of inter-individual differences. Data from these studies may be used to estimate an internal dose from a variety of exposure scenarios; to facilitate comparisons of exposure across all stages of perinatal development; and to develop relationships between the results of rodent and primate feeding studies. More to the point, these data may allow the agency to assess the magnitude of the potential differential risk in neonates. Such information and analysis will be included in an updated Assessment.

Question 6 Are the scenarios addressed representative, comprehensive, and scientifically sound, considering the public health risk evaluated?

Comment 1: The Subcommittee suggested that the exposure estimate be stratified at a number of levels rather than reporting a mean value across all ages. Of particular concern is the lack of data on internal dose in light of the potential for exposure from medical devices if in an ICU setting.

Response:

Please see our response to Question 1, Comments 1 and 2.

Question 7 Are the recommended studies in the tiered testing strategy presented appropriate in relation to BPA exposure through the use of food contact applications, and will those studies reduce the uncertainties associated with the assessment? Please suggest any other recommended studies and/or endpoints that you think would be useful for future assessments.

Comment 1: Pharmacokinetic studies are needed to integrate the many studies that employed non-oral routes of exposure. Methods to quantitatively compare disparate endpoints should be explored so that effects in different systems can be compared.

Response:

FDA agrees that the results of PK studies are needed to explore methods by which many of the available studies that employed non-oral routes of exposure might be integrated into the quantitative safety assessment. Please refer to our response to Question 1, Comment 3.

Comment 2: The Subcommittee suggested that rodent studies be performed to seek plausibility for the findings in the JAMA study. For example, does BPA exposure affect insulin resistance, elevate blood pressure or enhance response to thrombogenic stimuli, or accelerate atherosclerosis in predisposed mice in a dose dependent manner?

Response:

Rodent subchronic studies are in progress to characterize the dose-response in the prostate and mammary glands for orally administered BPA. In addition, these studies will explore metabolic and cardiovascular endpoint changes identified in the JAMA study (Lang et al. JAMA 300(11):1303-1310), and more recent studies. These studies will include an *in utero* phase, mimic bottle feeding in neonates, and employ a dose range that will cover the low doses where effects have been previously reported, as well as higher doses where estrogenic effects have been measured in guideline oral studies.

Findings in this study will allow for a safety assessment based on a more thorough and controlled analysis of the endpoints identified in the literature as raising questions. Additionally, this information will be used to determine the need for a 2-year carcinogenicity study with an *in utero* phase, and to select doses for such a study.

Comment 3: The Science Board recommended a large rodent study to address the central question of developmental toxicity of BPA and specifically to:

- X meet criteria for acceptance established by the FDA, or reasonable criteria applied by the scientific community for study evaluation that FDA should adopt,
- X address the endocrine mechanism-based concerns of the scientific community, and
- X use endpoints and models validated for the study of endocrine-mediated developmental processes.

Response:

Rodent neuroanatomy and behavioral studies are in progress as part of the subchronic study to determine if behavioral/neuroanatomical/neurochemical or hormonal endpoints are altered by developmental exposure to low doses of BPA. This study will include a wide range of doses, *in utero* exposure, exposure mimicking bottle feeding, and a large variety of neurological and developmental endpoints. These data are intended to resolve inconsistencies described in the published literature regarding sexually dimorphic endpoints as well as the standard developmental neurotoxicity resulting from developmental exposure to BPA. Findings in this study may allow for a safety assessment based on more a thorough and controlled analysis of the endpoints identified in the published literature as raising questions.

Question 8: Do the assessment results objectively and transparently support the conclusions? Are they supported by the available data and science?

Comment 1: The Science Board requested that the selection of data used to estimate exposure be better justified, that the variability in the data be analyzed and that information on an age stratified distribution of exposures be developed, rather than relying on an average value.

Response:

Please see our response to Question 1, Comment 2.

Comment 2: Regarding the safety data, the Science Board stated that consistent and credible criteria for study inclusion would be to use the studies judged as adequate by CERHR, as well as the previously identified studies of the effects of BPA on adult humans that were published after the draft assessment was finished. The Science Board concludes that the inclusion of these studies in the assessment provides a basis for concluding that the margins of safety are far less than those defined by FDA as adequate.

Response:

Please see our response to Question 1, Comment 4, and Question 3, Comment 2.

Question 9 Do you have any additional comments that would assist FDA in refining the assessment?

Comment 1: Either a meta analysis for systematizing disparate results, or a more comprehensive *weight-of-the-evidence* evaluation including a sensitivity analysis would facilitate the use of relevant information obtained for academic purposes.

Response:

A properly conducted meta analysis requires knowledge of the internal dose in the target tissue as well as several reliable measures of data on reliable end points. As stated in our response to Question 1, Comment 3, the data required to develop reliable relationships between external doses of BPA and systemic internal exposures at low doses are not yet available. NCTR is currently conducting PK studies in both rodents and primates to address this need for data. FDA will be in a better position to further explore methods to quantitatively compare related endpoints from different studies when these data become available.

Consequently, a comprehensive weight-of-evidence approach suggested by the Science Board was used in CFSAN's re-review of those studies considered adequate by NTP/CERHR for the endpoints identified in the NTP draft brief as cause for some concern including prostate, mammary, developmental neurotoxicity, and early onset of puberty in females. These results are briefly summarized in our response to Question 3, Comment 2, and will be included in a revised Assessment.

Question 10 Does the information and data in Appendices 1 and 2 support the underlying assumptions used in the interim assessment?

Comment 1: The Appendices describe the limitations of individual studies and FDA's rationale for excluding them from the risk assessment, however, it is not clear that the information supports the assumptions discussed in the draft Assessment.

Response:

As stated in Question 1, Comment 4, CFSAN has recently completed a comprehensive re-review of the studies cited in the Appendices of the Draft Assessment that correspond to studies that were considered adequate by NTP/CERHR for the endpoints identified in the NTP draft brief as cause for some concern, as well as studies released after FDA's draft assessment became available relating to the same endpoints, and studies examining other endpoints mentioned in the Science Board report. As a part of this review, CFSAN described in detail the criteria used for the inclusion of data in the quantitative part of the assessment. The utility of the studies that were re-examined was established by comparison to these criteria.

As stated above, FDA has made CFSAN's assessment of these studies available for public review and comment along with the comments of five non-FDA, government experts who were requested by FDA to review CFSAN's assessment of these low-dose studies. In the same docket, FDA has also made three related documents available: 1) CFSAN's review and summary of several studies on potential health effects of BPA exposure that became available after its assessment of low-dose studies was complete; 2) an updated dietary exposure estimate for the food-contact uses of BPA in packaging for infant formula, baby and adult foods, and polycarbonate nursing bottles; and, 3) CFSAN's review of the available biomonitoring data on BPA. These documents, and instructions for commenting on them, may be obtained by searching www.regulations.gov for Docket Number FDA-2010-N-0100. The comment period closed on June 4, 2010.