DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

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Dear Dr. McNeil:

I want to express my sincere appreciation for 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 Bisphenol A for Use in Food Contact Applications* (draft assessment). The Science Board considered and accepted the recommendations of the Subcommittee, with modifications, and formally transmitted the Peer Review Report to FDA on October 31, 2008. FDA requested this review by the Science Board to obtain an independent, expert review of our draft assessment of the use of BPA in food contact applications. We recognize that the Subcommittee and Board members have applied their knowledge and experience to evaluate a large volume of data, and to consider very complex scientific questions as part of their consideration of FDA's draft assessment. This letter provides FDA's initial response to the Board's Peer Review Report (the Report). FDA will further respond to the Report in the future.

The Report acknowledges several areas of agreement with FDA's draft assessment. Perhaps most important, the Report agreed that the main focus of the assessment should be on infants and children due to the likelihood of both greater exposures and greater susceptibility to potential health effects. In addition, the Report agreed with FDA's use of the results of animal studies published by Tyl *et al.* in the quantitative assessment of certain potential health effects. The Report also agreed with FDA's assessment that available data indicate a need for additional research to assess more clearly potential health effects of BPA on certain other developmental endpoints, and agreed that the studies proposed by FDA in the draft assessment would yield valuable information.

The Report also identified several limitations of the draft assessment and raised some important questions that underscore the need for additional work. The Report made recommendations in three main areas: exposure, health effects, and proposed research. FDA has been pursuing, or is planning for, additional information and analysis in these areas as described below.

Exposure

Peer Review Report: The Report stated that the exposure estimate in the final safety assessment should account for the totality of BPA exposures from other routes. Focusing primarily on the data relating to infant formula exposures, the Report suggested that the estimate of BPA exposure originating from food-contact materials could be strengthened by explaining criteria used in acceptance of studies, by expanding the number of samples, and in particular, expanding the geographic and temporal range of samples analyzed, by discussing the variability and

exposure assessment by obtaining a better understanding of the ranges of exposures in various populations.

FDA Response: FDA agrees with the Report that the exposure estimate in the final safety assessment should account for the totality of BPA exposures from all FDA-regulated products and that the current exposure estimate from food-contact uses can be strengthened. As stated in the draft assessment, FDA's plan has been to focus the initial assessment on dietary exposures and, when better data are available, to publish an assessment of BPA exposures resulting from the use of BPA in the manufacture of drugs, biologics, cosmetics, and medical devices and the materials used for packaging such products. Accordingly, FDA has published a request for information on potential BPA exposures from non-dietary sources on October 15, 2008 (73 FR 61135).

FDA plans on further strengthening the dietary exposure assessment by expanding the discussion of biomonitoring data in comparison to exposure estimates, and, to the extent possible, to reconcile the total exposure estimate with such data. Where applicable and supported, we intend to quantify and to expand the discussion of the uncertainties present in the analysis, and to employ demographic information to stratify exposure estimates by age group.

FDA is re-evaluating available data, and planning for the acquisition of additional data that will strengthen the exposure estimates from all dietary sources of BPA, with particular attention to dietary sources relevant to infants and children. Our initial efforts are focused primarily on exposures resulting from the use of epoxy coatings in infant formula packaging. FDA has already initiated expanded sampling of infant formula products marketed in epoxy-lined cans, with a view towards assessing the variability of the most important parameters contributing to BPA exposure such as can types and manufacturers, formula processing and filling conditions, shelf life and storage conditions, and variability of the cans and formula over time and geographic region.

In addition, FDA has engaged packaging manufacturers in the design of experiments intended to lead to the development of codes of practice that identify control points for the optimization of packaging manufacturing processes. Should industry desire to utilize alternative packaging materials, FDA is prepared to assist industry in determining whether alternative packaging materials are already authorized by FDA for food contact use (a requirement) and facilitate access to safe alternatives by working with industry to meet the requirements of infant formula notifications for changes in packaging. If new materials have not been authorized, FDA will provide guidance to industry regarding what data may be required to establish the safety of new materials.

Health Effects

Peer Review Report: With respect to the health effects evaluation, the Report found that the FDA's draft assessment did not articulate reasonable and appropriate scientific support for the criteria used in the selection or elimination of the available data, in particular, with regard to the exclusion of certain studies that CERHR found to be "adequate." The Report also stated that certain mechanistic studies may portend risks at lower doses than those examined in the studies published by Tyl *et al.*, and that such studies indicate additional hazard end points at these lower doses that should be discussed. Additionally, the Report found that the description of FDA's application of uncertainty factors to the safety data analyzed in the draft assessment was ambiguous and indicated that clarification was necessary with regard to the margin of safety discussion.

The Report suggested that more sophisticated analyses, such as benchmark dose modeling on the studies published by Tyl *et al.*, and the development of meta-analytical methods for the mechanistic studies, might more fully exploit the available data, and that the uncertainty regarding possible health effects may be better characterized. In addition, the Report states that evidence suggests that the metabolism of BPA may be less efficient in neonate than in adult animal models, possibly resulting in a greater risk for neonates. Finally, the Report recommended that additional studies, including studies published after the draft assessment was made available, should be considered regarding potential toxicity in adults.

FDA Response: FDA is reevaluating the studies currently listed in Appendix 2 of the Draft Assessment to characterize more clearly the weight-of-evidence approach for the four endpoints (neurotoxicity, prostate and mammary gland toxicity, and early onset of puberty) highlighted by the Report. We are re-considering these studies for expanded inclusion in the assessment and will define more clearly criteria for data inclusion, or exclusion, for both hazard identification analysis and quantitative assessment. Additionally, FDA will more clearly characterize the uncertainty in these data, and the conclusions drawn from these data. Further, FDA will clarify its discussion regarding the use of uncertainty factors in the assessment of the margins of safety.

Benchmark dose modeling has been conducted, as suggested in the Report, on the Tyl *et al.* studies, by both the CERHR panel and in a review authored by Whillhite *et al.* We have analyzed these results for inclusion in an updated assessment and are considering if, and how, Benchmark dose modeling may be used to evaluate other end points that were of interest to the Subcommittee.

FDA considers the suggestion of a meta-analysis a more global issue, beyond that of the current safety assessment of BPA. We are interested in exploring the use of meta-analysis for safety assessment; however, the current techniques have not been utilized previously for regulatory decisions and require more investigation at this time. Accordingly, we are approaching counterparts in and outside of the Department of Health and Human Services to assist in exploring the feasibility of approaches to meta-analysis suitable for regulatory decisions.

FDA is revising the draft assessment to articulate better our assumptions and conclusions regarding metabolism of BPA during development. As discussed further below, FDA's research plan anticipates the development of additional data to address this question. BPA research is an extremely active area with a number of studies having been published since the draft assessment was released. FDA has actively searched for newer data on BPA and had already begun reviewing two of the studies identified by the Subcommittee. All relevant and recently published, or acquired, studies will also be reviewed and when appropriate, included in the final assessment.

Proposed Research

Peer Review Report: With respect to the development of additional data, the Report agreed with FDA's draft assessment that human biomonitoring data could inform the exposure assessment, and that experimental animal biomonitoring data would be useful for an analysis of the existing data with regard to differential risk in neonates and in other vulnerable populations. Furthermore, the Report agreed with FDA's proposed pharmacokinetic studies, stating that physiologically-based pharmacokinetic models are essential for integrating data from studies employing non-oral exposure routes and to inform cross-species analysis.

The Report also recommended that a large rodent study be considered to address the central question of the developmental toxicity of BPA, and should be designed to address the endocrine mechanism-based concerns using models validated for the study of such developmental processes. The Report suggested that a rodent study would be an appropriate way to seek plausibility of the reported observations in the cross-sectional study with BPA in a recent study using NHANES data (Lang *et al.*). The Report noted that studies in non-human primates should be limited and driven by the need to answer specific questions.

FDA Response: FDA appreciates the recommendations in the Report and is modifying its current research plan to address these suggestions. FDA's National Center for Toxicological Research (NCTR) has been actively working with the FDA's product review Centers to develop protocols to address these issues regarding BPA safety. These efforts have included the following work:

- FDA has finalized a study protocol designed to analyze pharmacokinetic properties of BPA. This study will examine the absorption, distribution, metabolism and elimination of BPA in adult, neonatal, and fetal rats administered low doses of BPA either directly or through maternal transfer via intravenous (IV), oral, or subcutaneous routes. Pharmacokinetic parameters will also be measured in adult and neonatal rhesus monkeys following BPA administration via IV or oral routes. Data gathered in these studies as well as appropriate data from the literature in multiple species, including humans, will be used in developing a physiologically-based pharmacokinetic model.

- FDA has approved the concept development of a sub-chronic rodent study to be completed as part of a tiered approach towards a 2-year bioassay. Specifically, this study will be designed to examine Sprague-Dawley rats for mammary gland and prostate gland findings following *in utero* and direct exposure to BPA. The sub-chronic study will examine endocrine target tissues for a number of endpoints reported in the literature (i.e. apoptosis, proliferation, DNA methylation patterns, histopathology, molecular markers) at multiple termination times. Unlike the existing large studies, this study will also examine developmental endpoints following direct administration to pups (via gavage); a method chosen by FDA to mimic more directly BPA exposure from bottle feeding and to ensure accurate dose delivery. Additionally, and as suggested by the Subcommittee, this protocol has been expanded to include endpoints related to cardiotoxicity, liver function (clinical chemistry), and metabolic changes (i.e. insulin, glucose) following treatment by BPA. Doses and findings of this sub-chronic study will be used to plan a 2-year bioassay on BPA which contains an *in utero* exposure period.

- FDA is currently developing a protocol for a neurodevelopmental study in rodents. The rodent study is planned to run concurrent with the aforementioned sub-chronic study. The aims of this study are to evaluate the effects of BPA on standard developmental neurotoxicity endpoints and sexually dimorphic endpoints. In addition, this study will examine directly effects of BPA treatment on the sexually dimorphic nuclei and quantify adult levels of hormones.

- FDA is currently developing a protocol to examine the effects of BPA on growth and cognitive and pubertal development in rhesus monkeys chronically exposed to BPA from birth. Likely endpoints for this study include the operant test battery and measurements of growth and sex hormones, bone markers and secondary sexual characteristics.

FDA is planning to conduct these studies in its laboratories using representative dose ranges and multiple animal models. In addition, although these studies are being planned to support FDA's product safety assessments, some are being reviewed by Toxicology Study Selection and Review Committee, a collaborative committee with the National Toxicology Program (NTP).

Accordingly, members of NTP's Committee for the Evaluation of Risks to Human Reproduction staff have and will continue to be a part of the research planning, implementation, and discussion of results. These studies represent a large research effort and FDA will weigh the public health need with ethical concerns as noted by the Subcommittee with regard to non-human primate studies.

With regard to improving our exposure assessment and as noted in the draft assessment, FDA is planning to collaborate with CDC and other interested parties in the development of additional biomonitoring data; data which considers infants and children. Additionally, FDA is initiating its own sampling plan and collaborating with multiple parties to improve our assessment of BPA exposures from infant formula packaging. As noted above, FDA is currently re-evaluating the existing exposure data on polycarbonate bottles and food cans based on suggestions in the Report; where necessary, FDA plans to initiate additional sampling and analytical work to test assumptions and to otherwise strengthen the exposure estimate.

Again, I would like to thank the members of the FDA Science Board and its BPA Subcommittee for their hard work in conducting a peer review of FDA's Draft Assessment.

Sincerely,

/s/

Norris Alderson, Ph.D.
Associate Commissioner for Science
Food and Drug Administration