FDA SCIENCE BOARD SUBCOMMITTEE ON BISPHENOL A

SCIENTIFIC PEER-REVIEW OF THE DRAFT ASSESSMENT OF BISPHENOL A FOR USE IN FOOD CONTACT APPLICATIONS

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EXECUTIVE SUMMARY

PROCESS

The Science Board provides advice primarily to the Commissioner of the USFDA and other appropriate officials on specific complex and technical issues as well as emerging issues within the scientific community. This temporary Subcommittee was established by the Science Board and consists of two members of the Science Advisory Board and five scientists drawn from academia and government agencies. The focus of this Subcommittee is the scientific peer-review of the draft assessment prepared by the 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 (http://www.fda.gov/ohrms/dockets/ac/08/briefing/2008-0038b1_01_02_FDA%20BPA%20Draft%20Assessment.pdf). 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.

A public meeting (Appendix 1) was held on September 16, 2008 at the Rockville Hilton at which the Subcommittee received from FDA (Drs. Tarantino, Baily and Twaroski) a review of the process and scientific methodologies employed in preparing the draft safety assessment of bisphenol A. Dr. John Bucher, Deputy Director of the National Toxicology Program (NIH-NIEHS) presented the approach used by the NTP in arriving at their own assessment of the safety of bisphenol A (i.e., NTP Brief). The final formal oral presentation by Dr. Frederick vom Saal (University of Missouri-Columbia) provided the Subcommittee with an overview of the conclusions of the Chapel Hill Bisphenol A Expert Panel and of the areas in which that Panel differed from the FDA in its assessment of the toxicity and potential risks from exposure to bisphenol A. Open public hearings were followed by discussion between the Subcommittee and an invited Panel that focused on interpretation of BPA research studies and data gaps related to the draft safety assessment (Appendix 2).

SPECIFIC FINDINGS OF THE SUBCOMMITTEE

- Bisphenol A is present in food contact applications resulting in dietary exposure of BPA to infants, children and adults. The Subcommittee agrees with the focus of the draft assessment on dietary exposures to children, because they are likely to have both greater exposures and susceptibility than adults as a function of food consumption patterns, metabolism, vulnerability of developing systems and other factors. Nevertheless, it is the opinion of the Subcommittee that the FDA assessment would be strengthened by considering cumulative exposures and differential risk in neonates.
- The draft FDA exposure assessment has important limitations including that it lacks an adequate number of infant formula samples and relies on mean values rather than accounting for the variability in samples.

- The draft FDA report does not articulate reasonable and appropriate scientific support for the criteria applied to select data for use in the assessment. Specifically, the Subcommittee does not agree that the large number of non-GLP studies should be excluded from use in the safety assessment.
- Consistent and credible criteria for study inclusion, recommended by the Subcommittee, would be to use those studies that are judged as "adequate" by CERHR in the FDA hazard, dose-response and safety assessment of BPA. In addition, several studies of effects of BPA on adult humans and animal species that were published after the draft assessment was finished should be considered for inclusion in the final assessment.
- The Subcommittee finds that the assessment lacks an adequate characterization of uncertainties in its estimates of both exposure and effects.
- The weight-of-the-evidence, including studies identified by CERHR as adequate and having utility, provides scientific support for use of a point of departure substantially below (i.e., at least one or more orders of magnitude lower than) the 5 mg/kg bw/day level selected in the draft FDA assessment.
- Coupling together the available qualitative and quantitative information (including application of uncertainty factors) provides a sufficient scientific basis to conclude that the Margins of Safety defined by FDA as "adequate" are, in fact, inadequate. This does not mean that the potential exposures are not *"acceptable"*. The latter is the subject of policy that appropriately rests with the Commissioner of the FDA. Any subsequent policy decision would benefit from revisions to the Draft Assessment based on the Subcommittee report and would be informed by other pertinent considerations.
- The weight of the evidence suggests that establishment of a more conservative MOS is indicated for infants.

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CHARGE QUESTIONS AND FINDINGS

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?**

The draft FDA *Assessment of Bisphenol A for Use in Food Contact Applications* identifies the data and methods used to develop an exposure assessment and a toxicological profile. The exposure assessment and qualitative and quantitative information from the toxicological profile are brought together in the Margins of Safety section of the draft report to support conclusions as to the safety of food contact applications.

Exposure Assessment: The exposure assessment is focused on food contact applications only and does not consider the potential cumulative and interactive effects of non-food contact exposures to BPA. Thus, this approach to assessing the risk of exposure to BPA is intrinsically limited by its use of data from food contact sources alone. On this point, FDA decided *a priori* to leave out biomonitoring studies that could have shed light on cumulative exposures and inter-individual variability in internal exposure. Furthermore, the updated exposure assessment itself was limited both in size (14 cans of infant formula), geographical and temporal distribution, and thus did not adequately account for variability in potential exposures, which the invited Panel (September 16, 2008 public meeting) noted could be very large. Inter-individual differences in systemic internal exposure following a standardized exposure to environmental BPA were not taken into account. Table 1 and the accompanying text portray a reasonable approach to estimate age-specific BPA exposure, but the data are point estimates (e.g., a mean of 2.5 ppb BPA in formula from epoxy can coatings is used rather than a 95th percentile [not provided] or the maximum value of 6.6 ppb from a sample of 14 cans). Other assumptions are not well supported (e.g., that by 12 months of age a high percentage of infants have stopped consuming liquid formula and that PC bottles are not sterilized for infants above 2 months of age) or addressed (e.g., that microwave heating of formula in infant bottles may alter BPA exposures).

Arguments that the exposure estimates in Table 1 are conservative (i.e., represent likely maximum values, rather than averages) are provided in the FDA Draft. These arguments provide some reassurance; nevertheless, the approach would be strengthened by (1) including a wider range of samples for estimating BPA content in food products; (2) using distributions of data values (rather than point estimates to describe exposure); (3) a sensitivity analysis for data values without distributions; and (4) demographic information to determine the numbers of individuals likely to be exposed at each estimated concentration which would yield a more robust basis for informing the safety assessment by producing characterizations such as “5% of children < 1 y.o. are exposed to BPA from food contact above [xx] µg/kg bw/day”.

Toxicological Profile: Criteria for selection of data are mentioned in the Toxicological profile section, and a link to the FDA 'Redbook 2000' protocols is provided. However, the criteria themselves are not given in the assessment, except by mention of characteristics that disqualified studies from consideration. In addition, the summary data tables in Appendix 1 and the reviews of selected studies in Appendix 2 list study characteristics that were cause for excluding studies from the assessment. A clearer and more specific description of the criteria and decision rules for acceptance for both exposure and effects studies would strengthen the assessment. For example, was a small sample size considered an equivalent limitation for both positive studies (where statistical power is not as much of a concern) and negative studies? The logic required to proceed from listing study limitations to justification for exclusion is more complex than the draft report would suggest. The Subcommittee finds that the draft FDA report does not articulate reasonable and appropriate scientific support for the criteria and methods employed in the draft assessment and the Subcommittee does not agree that the large number of non-GLP studies should be excluded from use in the safety assessment.

As shown in Appendix 2, the scientific evaluation and utility of studies is summarized for several organizations (FDA, CERHR, EU RAR, EFSA). The draft FDA report dismisses many studies that were judged by the CERHR as being "adequate" [in terms of scientific strength] and of either "limited" or "high utility"[1,2]. The exclusion of studies judged by CERHR as adequate and of high utility diminishes the weight of evidence judgments on hazard, dose-response and safety of BPA food contact applications. The Subcommittee finds 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 the FDA hazard, dose-response and safety assessment. Those studies judged by CERHR as "adequate" and of "limited" utility also provide useful information on the potential hazards posed by exposure to BPA.

2. ARE UNCERTAINTIES IN THE ASSESSMENT OBJECTIVELY AND TRANSPARENTLY IDENTIFIED AND CHARACTERIZED?

Uncertainty has both qualitative aspects (e.g., are the correct studies identified, are the studies correctly interpreted) and quantitative aspects (e.g., are quantitative data fully displayed, analyzed and communicated). Assumptions regarding the conclusions of the assessment are provided that suggest uncertainties, but they are not systematically presented as uncertainties. For example, the assessment discusses ranges of exposure values but does not adequately quantify the uncertainties associated with the estimates of exposure that are used to determine the margins of safety. Rather than appropriately characterizing the sampling variability within the FDA samples used to obtain exposure estimates, and the estimates of exposure given by others, the document appears to appeal to a set of assumptions based on scenarios related to packaging and usage practices that the FDA feels are conservative.

Uncertainties regarding potential effects of BPA on neuro-developmental, prostate, mammary gland and acceleration of puberty health endpoints are described qualitatively, but no attempt is made to quantify or characterize those uncertainties. A similar ambiguity exists with the limited available information that indicates a role for BPA in the disturbance of some gender-dependent distinctions among neurobehavioral phenotypes, e.g., the ablation of sexual

dimorphism in open field anxiety. Uncertainty regarding the selection of critical studies (e.g., the exclusion of studies judged by CERHR as adequate and of limited or high utility) and the critical effect (e.g., neurobehavioral, prostate) is not provided since the other studies are dismissed, yet such a discussion of uncertainty is an essential element to informed decision making. The Subcommittee finds that this is a major omission in the characterization of uncertainty.

Within the section on Margins of Safety is the statement "A MOS higher than the relevant UF indicates that the margin of safety is "adequate"". The margin of safety (MOS) analysis compares the NOAELs from the Tyl studies to age-stratified estimates of exposure[3,4]. This analysis assumes "typical" uncertainty factors of 10 for intra-species variability and inter-species variability for reversible effects (combined UF = 100); an additional factor of 10 is applied for irreversible reproductive or developmental effects, yielding a combined UF of 1000. A further factor of 10 for "systemic" toxicity from less-than-chronic exposure is also used to extrapolate to chronic exposure. The combined UF is then stated to be 10^3 = 1,000, when it appears that with four areas of uncertainty it should be greater than 1,000. This paragraph requires clarification including a more complete discussion of the basis for selection of uncertainty factors (see, for example, how EPA discusses uncertainty factors in recent IRIS assessments www.epa.gov/iris).

3. **ARE THERE ADDITIONAL SCIENTIFIC/ TECHNICAL STUDIES RELEVANT TO THE ENDPOINTS EXAMINED AND THE ROUTE OF EXPOSURE THAT SHOULD HAVE BEEN CONSIDERED?**

The draft assessment considered, but rejected for various reasons, a number of potentially relevant studies as described in the Appendices. The Subcommittee finds that the CERHR evaluated studies in an appropriate manner and this evaluation can provide a consistent and coherent basis for FDA evaluation. The studies identified by CERHR as "adequate" should be considered as alternatives for the qualitative and/or quantitative assessment in the body of the assessment. In addition, consideration should be given to several studies of effects of BPA on adult humans and animal species that were published after the assessment was finished or that were identified by the Subcommittee, as described below.

(1) An epidemiologic study that correlated biomonitoring data, e.g., urinary BPA levels, with the prevalence of several diseases in humans should be examined to guide experimental investigation of the BPA hazard to adult humans using animal models to shed light on the biological plausibility of the associations that were observed[5]. Limitations of this study are recognized, such as (i) the cross-sectional nature of the study (exposure did not precede the development of disease); (ii) the uncertainty as to whether the single measurements of BPA levels in urine could adequately represent chronic BPA exposure; (iii) the lack of internal consistency amongst signals of chronic toxicity – i.e., there was a signal for "coronary heart disease" [defined only by history] but no signal with respect to effects on lipids or blood pressure or stroke and (iv) the uncertain plausibility for an association with diabetes, as reflected by the biphasic in

vitro relationships with adiponectin and antioxidant enzyme levels; the absence of any insulin clamp/BPA data in any species and the generally weak evidence of insulin resistance (3 out of 4 estimates of HOMA). Nevertheless, given the nature of the investigation and the well-recognized research value of the study population (NHANES), the study's findings are of concern, and the Subcommittee concludes that consideration of this study is warranted.

(2) An experimental study in monkeys that showed that BPA blocked estrogen-mediated synaptogenesis in hippocampus[6] confirms effects previously reported from this group in adult rodent models[7]. It is recognized that feeding estradiol chronically to ovarectomized animals may not simulate the effects of phasic alterations in endogenous insulin and that a functional phenotype has not been related directly to the hippocampal phenotype. Nonetheless, these studies deserve consideration because of the significance of the effect and consistency across species. The single dose of BPA used in the monkey study and the subcutaneous route of administration will complicate its utility in any risk assessment, however.

(3) A 2007 study in mice published in the Proceedings of the National Academy of Sciences on the impact of maternal exposure to BPA on DNA methylation at metastable loci with resultant changes in offspring phenotype deserves consideration, even though the study was not designed to ascertain dose-response relationships, in so far as stable epigenetic changes during early life are emerging as a major potential mechanism for the development of adult chronic disease[8].

(4) A study summarizing the FDA Infant Feeding Practices Study was reported by Fein SB and Falci, CD[9]. This report of a national longitudinal study of food handling practices for infants at 2, 5 and 7 months of age, found that a large percentage of mothers heat baby bottles with formula in a microwave oven. The effect of microwave heating on BPA release from baby bottles is an unexplored limitation in the FDA assessment.

Finally, although the Subcommittee can appreciate the FDA's decision to focus the quantitative risk assessment process on the large Tyl studies, it disagrees with the decision by FDA to dismiss many other studies on BPA that were less amenable to the construction of dose-response relationships but that were otherwise scientifically sound, inclusive of more advanced and sensitive endpoints, and that were often indicative of BPA impacts that could potentially portend significant risks to health at lower levels of exposure than observed in the Tyl studies. Thus, this Subcommittee finds that these other studies deserve more consideration (and discussion) in the assessment, despite the fact that these other studies may not be as amenable to quantitative analysis of dose response. Specifically, the effect of including additional studies now relegated to the Appendices and the studies mentioned above is that in the hazard identification phase of risk assessment, additional endpoints are identified (e.g., prostate, neurobehavioral, mammary) and, in the dose-response evaluation phase, health effects are identified at levels substantially lower (at least an order of magnitude lower) than the 5 mg/kg

bw/day NOAEL identified in the Tyl et al studies[3,4]. This makes these studies highly relevant to this assessment. (Discussed again below).

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?**

The Subcommittee finds that the draft risk assessment did not sufficiently consider alternative studies in the identification of the point of departure for calculating the margins of safety. Many studies were excluded from the quantitative risk assessment due to a variety of specific, individual deficiencies. However, the large number of positive findings in the areas of neurobehavioral development, prostate gland, mammary gland and puberty in females, as identified in the NTP Brief, raises the possibility that BPA interacts importantly with gonadal hormone receptors during development, and that these interactions may induce adverse effects in offspring of exposed mothers at levels at least an order of magnitude below the 5 mg/kg bw/day NOAEL identified in the draft assessment. Using applied dose (in the absence of internal dose) the effects of these interactions can be systematized and quantified into coherent dose-effect relationships (e.g., the data could be portrayed on a simple diagram showing how various effect measures compare quantitatively), and they point to a lower NOAEL or a LOAEL.

EPA has developed ways to use internal dose to conduct meta-analysis for organic solvents[10,11]. The approach requires knowledge of the dose metric (e.g., concentration of the proximal toxicant in the target organ), a viable PBPK model for estimating that dose from a variety of exposure scenarios, and ways to convert effects on a variety of endpoints to a common scale ('Effect magnitude' in the study terminology). This may be applicable to BPA, given what is known about its binding to ERs, the organs of concern, the amount of information about the kinetics of BPA already available, and the wealth of effects that have been reported, and may provide more confidence in identification of a point of departure.

Further, the draft assessment did not attempt to model the applied dose-response relationships found in the Tyl studies nor any other study using the readily available Benchmark Dose (BMD) software (www.epa.gov/NCEA/BMDS/). The advantage of BMD modeling is that confidence intervals on dose (e.g., $BMDL_{10}$) are used as the point of departure, better representing the power of various studies and providing a consistent basis as point of departure. The Tyl data, and data from other studies, likely are sufficient and available to support BMD modeling, and this approach is preferred to the NOAEL/LOAEL approach.

The Subcommittee finds that the weight-of-the-evidence provides scientific support for including studies by CERHR as "adequate" in the identification of a point of departure (as described above). Though these studies individually have limitations, taken together they provide sufficient support for a point of departure evaluation at levels of exposure at least an order of magnitude lower than the 5 mg/kg bw/day level selected by FDA. Notwithstanding concerns expressed above, taking the BPA exposure assessment in the FDA draft assessment at

face value, in which 0-2 month old infants are estimated to have BPA exposure at the 2.3-2.4 µg/kg bw/day level, the identification of a point of departure at least an order of magnitude lower than the 5 mg/kg bw/day NOAEL selected by FDA suggests that the margins of safety from food contact applications are minimal.

5. WERE SCIENTIFIC ASSUMPTIONS THAT ARE NOT STRICTLY LINKED TO THE DATA EXPLAINED AND APPROPRIATE FOR THE PURPOSES OF THIS SAFETY ASSESSMENT?

As noted elsewhere in this Subcommittee's report, the draft assessment does not include a discussion of cumulative exposures and risk, and the biomonitoring data were not evaluated; hence these topics were not well explored in the assessment. The human health risks of the food contact applications may be understated when only a single source of exposure is considered and limited data are available regarding other food contact exposures (e.g., PC sippy cups, PC sport bottles). Assumptions of no biological activity of bisphenol A glucuronide appear to be reasonable based on data for other glucuronide metabolites. However, the basis for assuming other metabolites are of no effect is unclear. Moreover, evidence presented in the NTP brief suggests that even though fetal and neonatal rats have the ability to metabolize bisphenol A, their metabolic pathways are less efficient than those of adult rats. However, infants' and neonates' ability to metabolize bisphenol A are not explained in the FDA assessment, although the rat studies referred to in the NTP brief suggest higher risks for neonates than is assumed in the draft assessment.

6. ARE THE SCENARIOS ADDRESSED REPRESENTATIVE, COMPREHENSIVE, AND SCIENTIFICALLY SOUND, CONSIDERING THE PUBLIC HEALTH RISK EVALUATED?

The Subcommittee assumed that this question refers to *exposure* scenarios. At the September 16 meeting, the invited Panel suggested stratifying exposure to BPA through milk ingestion and defining exposure not as a mean value but at a number of levels. This approach would be particularly useful if ingestion could be related to the number of children exposed at each ingestion level, to improve estimates of exposure on a population basis. Given the limited number and limited geographic dispersion of the FDA samples analyzed, it is difficult to assess the representativeness of the samples. [Data are lacking to assess the representativeness of the scenarios employed in the assessment.]

An important problem is the marked paucity of data on internal exposure of any kind in the most vulnerable population, especially as some of these infants might have additional exposure from devices if in an ICU setting. This again speaks to the need to consider cumulative exposures and differential risk in neonates.

7. **ARE THE RECOMMENDED STUDIES IN THE TIERED TESTING STRATEGY PRESENTED APPROPRIATE IN RELATION TO BISPHENOL A 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.**

Pharmacokinetic studies will be essential for integrating findings from the many studies that used non-oral routes of exposure. Emphasis should be placed on developing physiologically-based pharmacokinetic (PBPK) models for model species and humans, so that comparisons of dose can be made across species in a rational, quantitative manner. In addition, methods to quantitatively compare disparate endpoints should be explored, so that effects in different systems can be placed on common axes (see response to question 4, above). These approaches may enable quantitative synthesis of dose-effect functions across endpoints that currently are not comparable.

The biomonitoring recommended by FDA in the draft assessment (both in humans and in experimental animals) will be very useful for improving estimates of exposure, which is a weakness of the current assessment.

Studies in non-human primates would be valuable, but should be limited due to expense and ethical concerns. Well-parameterized PBPK models can address the issues of species-specific metabolism of BPA, and should enable accurate extrapolation from rodents to humans. Uncertainty related to species-specific endocrine-dependent development will be reduced through research in primates.

Rodent studies could be performed to seek plausibility for the JAMA study[5]. Does BPA exposure actually influence insulin resistance in vivo and is this influenced by deletion of the adiponectin receptor? Does BPA exposure elevate blood pressure or enhance the response to thrombogenic stimuli in vivo in a dose dependent manner and how does this relate to urinary ("total") BPA? Does BPA exposure accelerate atherogenesis in predisposed mice in a dose dependent manner? Are any of these effects influenced by gender? The areas of research identified above, i.e., biomonitoring studies, PBPK models, rodent and non-human primate studies will provide a large amount of useful information. However, except for classification into "tiers" there is no priority assigned to the tasks. From a public health perspective one might select first to identify areas that are most likely to contradict the conclusion of the draft FDA report to take no regulatory action.

In addition to the recommendations in the assessment, a large rodent study should be considered to address the central question of the developmental toxicity of BPA. To this end, the study must be designed (1) to meet criteria for acceptance established by the FDA or reasonable criteria applied by the scientific community for study evaluation that FDA should adopt, (2) to address the endocrine mechanism-based concerns of the scientific community, and (3) to use endpoints and models validated for the study of endocrine-mediated developmental processes. Appropriate endpoints have been developed to address questions of

development of structure and function of the nervous system (and other endpoints of concern), and experimental designs and statistical analyses exist that can optimize the study for purposes of risk assessment[12]. Finally, akin to the case with the pharmaceutical industry, any data generated subsequent to the initial approval of a product should be released to the FDA in a timely fashion for review by an independent body.

8. DO THE ASSESSMENT RESULTS OBJECTIVELY AND TRANSPARENTLY SUPPORT THE CONCLUSIONS? ARE THEY SUPPORTED BY THE AVAILABLE DATA AND SCIENCE?

The Subcommittee finds that the draft assessment conclusions are not supported by the available data and science unless the arguments for excluding all work on effects of BPA except the Tyl studies are accepted. While these may be the only available studies designed to address questions immediately pertinent to regulatory science, the studies excluded from the quantitative analysis raise additional and unsettling concern about potential effects from exposure to BPA, as indicated by the NTP Brief and the comments from the invited Panel that were received by the Subcommittee. For example, the new evidence on associations of urinary BPA with disease[5] and on estrogen-mediated synaptogenesis[6,7], limited as they are, indicate the need for further consideration of the potential toxicity of BPA in adults.

In regard to the exposure data, the report would be strengthened if the selection of the data used to estimate exposure were better justified, data variability were more appropriately summarized and information on the distribution of exposure values (rather than average value) were considered in the assessment.

Consistent and credible criteria for study inclusion, recommended by the Subcommittee, would be to use those studies that are judged as "adequate" by CERHR in the FDA hazard, dose-response and safety assessment of BPA. In addition, several studies of effects of BPA on adult humans and animal species that were published after the draft assessment was finished should be considered for inclusion in the final assessment. Combining qualitative and quantitative information from the CERHR-identified studies with the draft FDA exposure assessment (which may or may not be "conservative"), provides a basis for the Subcommittee to reasonably conclude that the Margins of Safety are far less than those defined by FDA as "adequate".

9. DO YOU HAVE ANY ADDITIONAL COMMENTS THAT WOULD ASSIST FDA IN REFINING THE ASSESSMENT?

The approach of requiring guideline-worthy studies (e.g., large N, GLP protocols) perforce eliminates a great deal of relevant information from consideration in the risk assessment, and begs the question of the utility of data collected for academic and other purposes. Development of meta-analytical methods for systematizing these disparate data sets would facilitate their use in quantitative risk assessments in general or, in the absence of a meta-analysis, a more comprehensive weight-of-the-evidence evaluation. In particular, a limited sensitivity analysis summarizing the impact of inclusion of appropriately selected alternative studies on the conclusions of the report would be useful.

10. **DOES THE INFORMATION AND DATA IN APPENDICES 1 AND 2 SUPPORT THE UNDERLYING ASSUMPTIONS USED IN THE INTERIM ASSESSMENT?**

The information and data in Appendices 1 and 2 provide the limitations of individual studies and discuss the FDA's rationale for excluding each of them from the formal risk assessment. This approach creates a false sense of security about the information that *is* used in the assessment, however, as it overlooks a wide range of potentially-serious findings. It is not clear that the information in the Appendices supports the assumptions discussed in the draft assessment.

SUMMARY

The Subcommittee appreciates the clarity of the draft safety assessment of bisphenol A in food contact applications. The literature review was thorough and the criteria for reliance on the Tyl studies in the generation of a quantitative risk/safety assessment were made amply clear. The strengths of the draft safety assessment notwithstanding, the Subcommittee identified several significant concerns with the assessment in its current form. The exposure assessment lacks an adequate number of infant formula samples and relies on mean values rather than accounting for the variability in samples. The draft lacks a clear description of the criteria for eliminating an increasing number of non-GLP studies that indicate the possibility of toxic effects that are not mediated by interaction of BPA with the estrogen receptor, and the Subcommittee does not agree with the exclusion of the non-GLP studies in the safety assessment. Additional concern is expressed with the calculation of the NOAEL and specifically whether the exposure assessment to 'at risk' infants with minimal or impaired metabolic function and exposures from medical devices and procedures is as conservative as the assessment claims. In fact, it is the judgment of the Subcommittee that lack of consideration of the totality of exposures from other sources severely limits the usefulness of the safety assessment with respect to food contact applications. The final assessment should also include evaluation of a number of studies that appeared after the completion of the current draft or were otherwise identified by the Subcommittee.

The Subcommittee identified a need for application of state-of-the-art risk assessment methods in this assessment, which will enable utilizing all appropriate scientific information available on the potential toxicity of BPA. For example, methods developed at the EPA could expand the range of data sources used in the assessment to include academic and government-sponsored studies that are not necessarily GLP-compliant. This approach would be consistent with the opinions of the NTP regarding studies that it judged to be adequate and having utility for the BPA safety assessment. Finally, research is needed to develop and improve methods for quantitative evaluation of existing data to incorporate mechanistic studies into the risk assessment of BPA and other chemicals.

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ABBREVIATIONS

BMD	Benchmark Dose
$BMDL_{10}$	95% lower confidence limit on the Benchmark Dose at the 10% response level
BPA	Bisphenol A
CERHR	Center for the Evaluation of Risks to Human Reproduction
EFSA	European Food Safety Authority
EPA	U.S. Environmental Protection Agency
EU RAR	European Union Risk Assessment Report
FDA	Food and Drug Administration
GLP	Good Laboratory Practice
HOMA	Homeostasis Model Assessment
ICU	Intensive Care Unit
JAMA	Journal of the American Medical Association
LOAEL	Lowest Observed Adverse Effect Level
MOS	Margin of Safety
NHANES	National Health and Nutrition Examination Survey
NIH	National Institutes of Health
NIEHS	National Institute of Environmental Health Sciences
NOAEL	No Observed Adverse Effect Level
NTP	National Toxicology Program
PBPK	Physiologically-Based Pharmacokinetic
PC	Polycarbonate
UF	Uncertainty Factor
USFDA	United States Food and Drug Administration

APPENDIX 1: PUBLIC MEETING NOTICE

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA–2008–N–0038]

Bisphenol A Subcommittee of the Science Board to the Food and Drug Administration; Notice of Meeting

AGENCY: Food and Drug Administration, HHS. **ACTION:** Notice. This notice announces the following meeting: Bisphenol A (BPA) Subcommittee of the Science Board to the Food and Drug Administration (FDA) meeting. The topic to be discussed is the draft assessment of BPA for use in food contact applications. The Subcommittee will hear and discuss the draft assessment of BPA for use in food contact applications, including oral presentations from the public. *Date and Time*: The meeting will be held on September 16, 2008, at 9 a.m. to 3:30 p.m. *Location*: Hilton Washington, WashingtonDC/Rockville Executive Meeting Center, Plaza Ballroom, 1750 Rockville Pike, Rockville, MD 20852. *Contact Person*: Carlos Pen˜ a, Office of Science and Health Coordination, Office of the Commissioner (HF–33), Food and Drug Administration, 5600 Fishers Lane, (for express delivery, rm. 14B–08) Rockville, MD 20857, 301–827–3340, or by e-mail: *Carlos.Pena@fda.hhs.gov* or FDA Advisory Committee Information Line, 1–800–741–8138 (301–443–0572 in the Washington, DC area), code 3014512603. Please call the Information Line for up-to-date information on this meeting. A notice in the **Federal Register** about last minute modifications that impact a previously announced advisory committee meeting cannot always be published quickly enough to provide timely notice. Therefore, you should always check the agency's Web site and call the appropriate advisory committee hot line/phone line to learn about possible modifications before coming to the meeting. *Agenda*: The Subcommittee will hear and discuss the draft assessment of BPA for use in food contact applications, including oral presentations from the public. FDA's draft assessment of BPA and FDA's charge to the Subcommittee will be posted on or after August 15, 2008, on FDA's Web site at *http:// www.fda.gov/ohrms/dockets/ac/ acmenu.htm*, click on the year 2008 and scroll down to the appropriate advisory committee link. FDA intends to make background material available to the public no later than 2 business days before the meeting. If FDA is unable to post the background material on its Web site prior to the meeting, the background material will be made publicly available at the location of the advisory committee meeting, and the background material will be posted on FDA's Web site after the meeting. Background material is available at *http://www.fda.gov/ohrms/ dockets/ac/acmenu.htm*, click on the year 2008 and scroll down to the appropriate advisory committee link. *Procedure*: Interested persons may present data, information, or views, orally or in writing, on issues pending before the Subcommittee. Written submissions may be made to the contact person on or before September 12, 2008. Oral presentations from the public will be scheduled between approximately 11 a.m. and 12 noon and between approximately 1 p.m. and 2 p.m. on September 16, 2008. Those desiring to make formal oral presentations should notify the contact person and submit a brief statement of the general nature of the evidence or arguments they wish to present, the names and addresses of proposed participants, and an indication of the approximate time requested to make their presentation on or before September 4, 2008. Time allotted for each presentation may be limited. If the number of registrants requesting to speak is greater than can be reasonably accommodated during the scheduled open public hearing session, FDA may conduct a lottery to determine the speakers for the scheduled open public hearing session. The contact person will notify interested persons regarding their request to speak by September 5, 2008. Persons attending FDA's advisory committee meetings are advised that the agency is not responsible for providing access to electrical outlets. FDA welcomes the attendance of the public at its advisory committee meetings and will make every effort to accommodate persons with physical disabilities or special needs. If you require special accommodations due to a disability, please contact Dr. Carlos Pen˜ a at least 7 days in advance of the meeting. FDA is committed to the orderly conduct of its advisory committee meetings. Please visit our Web site at *http://www.fda.gov/oc/advisory/ default.htm* for procedures on public conduct during advisory committee meetings. Notice of this meeting is given under the Federal Advisory Committee Act (5 U.S.C. app. 2). Dated: August 11, 2008. **Jeffrey Shuren,** *Associate Commissioner for Policy and Planning.* [FR Doc. E8–18864 Filed 8–14–08; 8:45 am] **BILLING CODE 4160–01–S**

APPENDIX 2: INVITED PANEL ROSTER

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