BISPHENOL A PEER REVIEW COMMENTS AND NTP RESPONSE

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National Toxicology Program

National Institute of Environmental Health Sciences
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In December 2005, The National Toxicology Program (NTP) Center for the Evaluation of Risks to Human Reproduction (CERHR) announced its intention to conduct an evaluation of the potential for bisphenol A (BPA) to cause adverse effects on reproduction and development in humans. CERHR selected BPA for evaluation because of its widespread human exposure, public concern for possible health effects from human exposures, high production volume, and evidence of reproductive and developmental toxicity in laboratory animal studies.

CERHR follows a formal process for review and evaluation of nominated chemicals that includes multiple opportunities for public comment (*http://cerhr.niehs.nih.gov/aboutCERHR/index.html*). As part of that process, the NTP prepared a draft Brief on BPA. The goal of the NTP Brief is to provide the public, as well as government health, regulatory, and research agencies, with the NTP's conclusions regarding the potential for BPA to adversely affect human reproductive health or children's development. The draft NTP brief on was released for public comment in April 2008. The NTP Board of Scientific Counselors (BSC), supplemented with several non-voting *ad hoc* reviewers, conducted a peer review of the draft NTP Brief on BPA on June 11, 2008.

NTP BSC members in attendance
Christopher Bradfield, University of Wisconsin
Tracie Bunton, Eicarte LLC
Russell Cattley, Amgen
Kenny Crump, Louisiana Technical University
Katharine Hammond, University of California Berkeley
William Janzen, Independent Consultant
Nancy Kerkvliet, Oregon State University
Gail McCarver, Medical College of Wisconsin (chair)
Jon Mirsalis, SRI International
Raymond Novak, Wayne State University
Michael Pino, Sanofi-Aventis
Jim Riviere, North Carolina State University (present during only part of the peer review; not present for the voting)
Diane Robins, University of Michigan Medical School
Keith Soper, Merck & Company

***Ad hoc* reviewers**
Michael Baum, Boston University
Robert Cardiff, University of California, Davis (via teleconference)
J. Steven Leeder, Children's Mercy Hospitals and Clinics
Ruth Ann Rudel, Silent Sprint Institute
Richard Sharpe, The University of Edinburgh Academic Centre
Barry Timms, The University of South Dakota
Jorma Toppari, University of Turku

The NTP provided BSC members and *ad hoc* reviewers with this charge:

> To determine whether the scientific information cited in the draft NTP Brief on BPA is technically correct, clearly stated, and supports the NTP's conclusions regarding the potential for BPA to cause adverse reproductive and developmental effects in exposed humans.

This report contains a summary of the peer review comments as well as NTP's response to major comments and recommendations made during the peer review. Summary minutes of the June 11, 2008 BSC meeting are available at *http://ntp.niehs.nih.gov/go/9741*. The final NTP-CERHR Monograph on BPA is available at *http://cerhr.niehs.nih.gov/evals/bisphenol/bisphenol.html.*

The following comments, grouped by topic (in bold type), were presented during the peer review meeting. The NTP's responses to the comments (in italic type) follow each set of comments:

Exposure

- The NTP Brief should state that exposure to BPA occurs frequently during the course of day.
- The NTP Brief should have more discussion of occupational exposures.
- Table 2 should include the maximum detected urinary concentration and corresponding estimated daily intake to better present the upper end of the exposure range.
- The NTP Brief should note that the limited data available indicates fetal exposure to BPA.

The NTP agrees with and accepts these suggestions. Additional text related to these issues has been added to the final NTP Brief. In addition, the maximum detected urinary concentrations of BPA and the corresponding estimated daily intakes for each demographic category have been added to Table 2. The NTP calculated the maximum estimated daily intakes by multiplying the maximum detected urine concentration for each category by the default urine output volume used by Lakind et al. (2008) and then dividing this number by the individual body weight provided in the NHANES data files. However, the NTP notes that the maximum detected value is based on a single individual and this value is difficult to interpret at the population level. Calculating valid and reliable exposure estimates for high percentiles, such as the 99th, requires very large sample sizes (CDC 1994). In the NHANES dataset the sample size for each demographic group is ~ 500 to 600. For this reason, estimates above the 95th percentile may not be reliable.

Consideration of Non-Oral Route of Administration

The NTP should include more discussion on the sulfation metabolism pathway for BPA.

The NTP agrees and included more text on sulfation metabolism in the final NTP Brief. In addition, the NTP added discussion of several research needs related to the metabolism of BPA that were identified during the peer review meeting.

Behavior

No specific recommendations related to this section of the draft NTP Brief were presented during the peer review. However, the primary *ad hoc* reviewer for this topic considered the literature on behavior to be more consistent than indicated in the draft NTP Brief. The BSC agreed with the

NTP's conclusions of "some" concern for neural and behavioral effects from BPA exposure in fetuses, infants, and children.

The NTP added text to this section of the final NTP Brief to address a number of points raised during the peer review, including:

- *Several of the rodent studies show some degree of consistency for specific examples of a loss of sexual dimorphism from BPA exposure.*
- *The translation of the more consistent rodent findings related to a loss of sexual dimorphism to primates and humans is unclear.*
- *Several of the "low" dose behavior studies are considered to be of high experimental quality.*
- *Future studies should include androgen receptor-mediated sexual dimorphisms and be designed experimentally to distinguish between "organizational" and "activational" effects of hormone action.*

The NTP did not modify the draft conclusion of "some" concern for BPA exposures to fetuses, infants, and children based on neural and behavioral effects because the NTP BSC voted to accept this conclusion.

Mammary Gland

No specific suggestions to modify the text for this section of the draft NTP Brief were presented during the peer review although the primary *ad hoc* reviewer for this topic was not convinced of the diagnostic classification of the reported lesions.

The NTP BSC recommended modifying the level of concern from "some" to "minimal" for BPA exposures to fetuses, infants, and children based on effects in the mammary gland.

The NTP accepted the BSC recommendation of "minimal" concern for the mammary gland and changed the level of concern in the final NTP Brief. In addition, a technical note was added to the "Mammary Gland" section of the final NTP Brief to reflect the peer review discussion on diagnostic classification.

Puberty

No specific suggestions to modify the text for this section of the draft NTP Brief were presented during the peer review.

The NTP BSC recommended modifying the level of concern from "some" to "minimal" for BPA exposures to fetuses, infants, and children based on an earlier age of puberty in females.

The NTP accepted the BSC recommendation of "minimal" concern for an earlier age of puberty in females and changed the level of concern in the Brief. In addition, the NTP revised the text to the "Puberty" section of the Brief to more thoroughly discuss the specifics of the key mouse studies and to address differences in the "low" dose puberty literature in rats and mice.

Prostate

No specific suggestions to modify the text for this section of the draft NTP Brief were presented during the peer review.

The BSC agreed with the NTP's conclusions of "some" concern for BPA exposure in fetuses, infants, and children at current human exposures based on effects in the prostate gland.

The NTP added text to this section of the final NTP Brief to address a number of points that were made during the peer review meeting regarding the classification of prostate intraepithelial neoplastic (PIN) lesions in the laboratory animal studies and the relevance of these lesions for humans. The NTP did not modify the draft conclusion of "some" concern for BPA exposures to fetuses, infants, and children based on effects on the prostate gland because the NTP BSC voted to accept this conclusion.

General Comments

A comment was made during the peer review that the concept of biological plausibility should be more clearly presented in the NTP Brief.

The NTP agrees that this issue could be more clearly addressed in the NTP Brief. The issue of biological plausibility in relation to estrogen receptor activity was discussed in the draft NTP Brief in the context of appropriate use of positive controls. The NTP moved this discussion to the section titled "Are the in vivo effects biologically plausible?" The NTP agrees with the opinion of several peer reviewers that the potential biological activity of BPA should not be considered solely in relation to it's binding to ERα or ERβ.

The NTP BSC agreed with the NTP's conclusions regarding concern for non-occupationally exposed adults and workers and offspring of pregnant women exposed to BPA.

The NTP did not modify the draft conclusions, "minimal" concern for workers exposed to BPA and "negligible" concern for BPA exposures to non-occupationally exposed adults and offspring of pregnant women, because the NTP BSC voted to accept these conclusions.