



Memorandum

Date: June 6, 2014

From: Jason Aungst, Ph.D. and Steven Anderson, Ph.D., M.P.P.
Chairs, FDA Bisphenol A Joint Emerging Science Working Group

Subject: Final report for the review of literature and data on BPA.

To: FDA Chemical and Environmental Science Council (CESC)
Office of the Commissioner
Attn: Stephen M. Ostroff MD

The FDA Bisphenol A Joint Emerging Science Working Group submits the following three memoranda with attachments as completion of the Working Group charge issued January 2011 and in response to FDA Science Board subcommittee recommendations of September 6, 2008.

- *2014 Updated Review of Literature and Data on Bisphenol A (CAS RN 80-05-7) dated 6/6/2014*
 - Attachment 1: Y.Gu and R.Mitkus/J.Aungst, 8/2/2013. *Review of a specialized oral developmental toxicity study on bisphenol A (BPA), entitled "Evaluation of the toxicity of bisphenol A (BPA) in male and female Sprague-Dawley rats exposed orally from gestation day 6 through postnatal day 90"*
 - Attachment 2: S.Mog and S.Francke-Carroll/J.Aungst, 7/19/2013. *Request for CFSAN Pathology comments on mammary gland hyperplasia in the NCTR subchronic (PND 21 and 90) oral rat study with BPA*
 - Attachment 3: *NCTR GLP/NTP Technical Report Project No. E2176.01: Evaluation of the toxicity of bisphenol A (BPA) in male and female Sprague-Dawley rats exposed orally from gestation day 6 through postnatal day 90*
- *2012 Updated Review of Literature and Data on Bisphenol A (CAS RN 80-05-7) dated 8/22/2013*
- *Updated Review of the 'Low-Dose' Literature (Data) on Bisphenol A (CAS RN 80-05-7) and Response to Charge Questions Regarding the Risk Assessment on Bisphenol A dated 5/24/2011*

The memoranda constitute a comprehensive review of approximately 300 studies published or available from November 1, 2009 to July 23, 2013. The conclusions in the memoranda are an extension and update from previous reviews and assessments conducted by CFSAN in 2008 and 2009. In the past few years, advances in BPA research in the areas of analytical methodology, biomonitoring, and pharmacokinetics have increased our understanding of the fate of BPA following human exposure as well as the potential for inadvertent exposure and background contamination in research studies. Data from these studies have proven useful in

interpretation of toxicological studies and increasing confidence in hazard and risk characterization.

The Working Group conclusions from *2014 Updated Review of Literature and Data on Bisphenol A (CAS RN 80-05-7)* memorandum represent the most current evaluation and hazard characterization of BPA. The major conclusions are summarized below.

Studies reviewed support the need for strict criteria in hazard identification and risk assessment in building weight-of-evidence evaluations. The high potential for inadvertent exposure or contamination by native BPA, confounding due to high or variable environmental estrogenic contamination or background, and methodological limitations in dose preparation significantly limits interpretation of studies that do not address these issues, leading to a high degree of uncertainty when trying to incorporate a given study's findings into an overall assessment.

Pharmacokinetic and biomonitoring data continue to support our understanding that BPA is quickly and efficiently metabolism once ingested. Presystemic metabolism of low-dose BPA in the gastrointestinal tract and liver of adults of all species attenuates internal exposures to aglycone BPA following oral administration to <1% of total. However, there are neonatal species differences with rodents being the more sensitive species. Neonatal rodent metabolic and excretory capacities are immature as compared to adult rodents, whereas neonatal monkeys are very near adult metabolic competence. The same oral BPA low-dose would produce approximately 10-fold higher aglycone BPA levels in a newborn rodent vs. a newborn monkey. Aglycone BPA does not accumulate in serum or tissues including fetal tissues due to the prominent effect of maternal metabolism augmented by the fetal metabolism that increases throughout gestation. Due to the efficiency of presystemic metabolism, internal exposures to aglycone BPA following parenteral administration (IV and subcutaneous injection) will be substantially greater than following oral exposure. Physiologically-based pharmacokinetic models for extrapolation between ages, species, and routes of exposure have been developed or are currently being developed at NCTR.

The Working Group identified three endpoints as potential hazards although with low confidence due to study limitations, conflicting reports, and current understanding of potential for unintended exposure or contamination. The hazard identification endpoints are developmental neurotoxicity related to molecular or neuroanatomical endpoints with varying routes of administration, cardiovascular disease-related factors based on human epidemiology studies, and sperm/testicular/hormone related parameters based on very limited supporting animal data. Hazard identification endpoints identified in this and previous reviews are currently being investigated in a NCTR GLP / NTP chronic oral toxicity study, and the results of this study should further address risk assessment issues.

The Working Group identified multiple studies relevant to a safety or risk assessment. The results of these new toxicity data and studies do not affect the dose-effect level and the existing NOAEL (5 mg/kg bw/day; oral exposure).