DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration

Memorandum

Date: June 17, 2014

From: Jason Aungst, Ph.D.
Division of Food Contact Notifications, Office of Food Additive Safety (OFAS),
Center for Food Safety and Applied Nutrition (CFSAN, HFS-275)

Subject: 2014 Updated safety assessment of Bisphenol A (BPA) for use in food contact applications.

To: Michael Landa, J.D.
Director, CFSAN (HFS-001)

Through: Francis Lin, Ph.D. Francis S. Lin -S Digitally signed by Francis S Lin S DN: c=US o=U S Government ou=HHS ou=FDA ou=People cn=Francis S Lin S 0 9 2342 19200300 100 1 1=1300002125 Date: 2014 08 06 14:58:38 04'00'
Director, DFCN, OFAS, CFSAN (HFS-275)

Through: Dennis Keefe, Ph.D. Dennis M. Keefe -S Digitally signed by Dennis M. Keefe -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300072773, cn=Dennis M. Keefe -S Date: 2014.08.11 15:08:01 -04'00'
Director, OFAS, CFSAN (HFS-200)

INTRODUCTION

The most recent FDA safety assessment on BPA for use in food contact applications was released in 2008[1] with additional updates on "low-dose" studies in 2009.[2] These documents are available at:

http://www.regulations.gov/#!docketBrowser;rpp=25;po=0;dct=SR;D=FDA-2010-N-0100.

Since January 2011, the FDA BPA Joint Emerging Science Working Group (Working Group) conducted iterative reviews of the newly available toxicological and scientific studies.[3] The Working Group reviewed studies employing various routes of administration for purpose of

1 FDA, 8/14/2008, *Draft Assessment of Bisphenol A for use in Food Contact Applications*
2 Aungst and Twaroski/Goodman, 8/31/2009, *Bisphenol A (CAS RN. 80-05-7): Review of Low Dose Studies.* Aungst and Twaroski/Administrative File: Food Additive Petition (FAP) 8T4773, 11/24/2009. *Bisphenol A (CAS RN. 80-05-7): Update regarding studies added to 'Review of Low Dose Studies' assessment.*
3 Bisphenol A Joint Emerging Science Working Group to FDA Chemical and Environmental Science Council, memoranda dated 5/24/2011, 8/22/2013, 6/9/2014: *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; 2012 Updated Review of Literature and Data on Bisphenol A (CAS RN 80-05-7); 2014 Updated Review of Literature and Data on Bisphenol A (CAS RN 80-05-7).*

hazard assessment determination, as well as identifying information relevant to risk and safety assessments applicable to FDA's product Centers. Information and conclusions from the Working Group memoranda relevant to the safety evaluation of BPA dietary intake are discussed herein.

EXPOSURES

Chemists from the Division of Food Contact Notifications and the Division of Biotechnology and GRAS Notice Review collaborated to provide an updated exposure assessment (Attachment 1).[4] The exposure assessment was conducted using a probabilistic approach in evaluating exposures and resulted in an updated estimate of 0.2 µg/kg-bw/day (mean) and 0.5 µg/kg-bw/day (90th percentile) for the adult US population aged 2 years and older.

Previous FDA exposure assessments estimated exposures[5] for infants and toddlers less than 2 years old with mean and 90th percentile estimates as follows (age, µg/kg-bw/d): 0-1 year, 0.3, 0.6; 1-2 years, 0.5, 1.1. In the current 2014 memorandum, the exposure assessment did not include updated values for these groups but did note that exposure is expected to decrease based on recent amendments to the food additive regulations that no longer authorize the use of polycarbonate resins in infant feeding bottles and spill-proof cups designed to help train babies and toddlers to drink from cups (77 FR 41899, July 17, 2012) and to no longer provide for the use of BPA-based epoxy resins as coatings in packaging for infant formula (78 FR 41840, July 12, 2013), as well as an increase in effective notifications for "BPA-free" materials including can coatings.

TOXICOLOGY

The 2008 FDA *Draft Assessment of Bisphenol A for Use in Food Contact Applications* reviewed the available data on the toxicity of BPA, including additional focus on studies evaluating developmental toxicity endpoints identified in the 2008 *NTP-CERHR Monograph on the Potential Human Reproductive and Developmental Effects of Bisphenol A*. Based on the studies reviewed for the 2008 FDA draft assessment, FDA concluded the appropriate no observed adverse effect level (NOAEL) to be the NOAEL for systemic toxicity of 5 mg/kg bw/day (5000 µg/kg bw/day) derived from two multigenerational rodent studies. FDA's 2008 draft assessment noted that the available data and information were insufficient to support other endpoints, such as developmental prostate gland toxicology, developmental neural or behavioral toxicology, as a point of departure for estimating margins of safety. The 2008 draft assessment concluded that an adequate margin of safety existed for BPA at previously estimated levels of exposure from food contact uses.

The 2009 CFSAN low-dose updates and 2011, 2012, 2014 Working Group assessments constitute a progressive series of evaluations with each subsequent memorandum building on

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4 Memorandum dated 3/18/2014, Hatwell/Mihalov to Aungst, *Updated exposure assessment for Bisphenol A (BPA) from the consumption of adult (canned) food – new data on canned food and beverages*.

5 Memorandum dated 5/4/ 2011, Bailey/Hatwell/Mihalov to Twaroski, *Updated exposure to Bisphenol A (BPA) from the consumption of infant formula, toddler food and adult (canned) food-new data on canned food and beverages.*

the conclusions from the previous memoranda. The 2009 CFSAN low-dose updates[6] included review of studies not reviewed in the 2008 FDA assessment, but were deemed adequate by NTP/CERHR[7] for the endpoints of 'some concern.' The CFSAN low-dose updates also included review studies available from April 2008 through July 2009. Regarding the Working Group reports, the 2011 report[8] reviewed literature published from November, 2009 through January, 2011 that had not been reviewed in previous assessments. The 2012 report[9] reviewed literature published from February 2011 through October 24, 2011, and the third report[10] evaluated the literature available October 24, 2011 to July 23, 2013 including available NCTR studies. Studies included for review were conducted with doses ≤5mg/kg bw/d and satisfied appropriate hazard identification and/or risk assessment criteria as defined in the CFSAN low-dose and Working Group assessments. Therefore, the conclusions of the 2014 Working Group report are based on all reviewed literature published on or available prior to July 23, 2013, and can be considered as the current state of the science evaluation for use in Center specific product assessments.

The Working Group did identify information relevant to hazard identification according to the Working Group review criteria; however, the Working Group qualified these hazard endpoints as "maintained with low confidence due to study limitations, conflicting reports, and current understanding of potential for unintended exposure or contamination."

From risk assessment-quality studies, the Working Group identified multiple NOAELs, and, based on a weight-of-evidence evaluation, concluded that the NOAEL of 5 mg/kg bw/day from oral dosing studies should be maintained for risk or safety assessments.

The margin of exposure (MOE) is the dose at which a NOAEL in animals was defined divided by the dose (exposure level) to which humans will be exposed (estimated dietary intake or EDI). The MOE is compared to uncertainty factors typically used for the associated endpoint, study, or available data in deeming if the substance is safe for use at the expected exposure. A MOE larger than the relevant uncertainty factors indicates that the MOE is "adequate." An uncertainty factor of 1000 is traditionally applicable in the case of a NOAEL derived for systemic toxicity in a subchronic rodent study (10x10x10; 10 for intraspecies variability, 10 for interspecies variability, and 10 to extrapolate from subchronic to chronic exposure).[11] FDA

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6 Aungst and Twaroski/Goodman: 8/31/2009 Bisphenol A (CAS RN. 80-05-7): Review of Low-Dose studies, and 11/10/2009 Bisphenol A (CAS RN. 80-05-7): Response to reviewers of 'Review of Low Dose Studies' and update of the assessment.

7 NTP-CERHR Monograph on the Potential Human Reproductive and Developmental Effects of BPA; 09/2008, accessible at http://cerhr niehs.nih.gov/chemicals/bisphenol/bisphenol.pdf

8 Bisphenol A (BPA) Joint Emerging Science Working Group to FDA Chemical and Environmental Science Council (CESC), 5/24/2011, 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.

9 Bisphenol A (BPA) Joint Emerging Science Working Group to FDA Chemical and Environmental Science Council (CESC), 8/22/2013, 2012 Updated Review of Literature and Data on Bisphenol A (CAS RN 80-05-7).

10 Bisphenol A (BPA) Joint Emerging Science Working Group to FDA Chemical and Environmental Science Council (CESC), 6/6/2014, 2014 Updated Review of Literature and Data on Bisphenol A (CAS RN 80-05-7).

11 Twaroski ML, Batarseh LI, and Bailey AB. The Regulation of Food Contact Substances in the United States. Chemical Migration and Food Contact Materials. Woodhead Publishing (2007) Barnes, Sinclair, and Watson (Eds.).

considers the use of these typical uncertainty factors as sufficiently protective.

Recent pharmacokinetic data and physiologically-based pharmacokinetic models as evaluated by the Working Group suggest that the magnitude of the uncertainty factors as stated provide an overly-conservative safety margin in extrapolating from a rat study to the human scenario. For interspecies variability, rats and especially neonatal rodents have been shown to metabolize BPA much less efficiently than primates. The available data suggest that all ages of primates have multiple forms of enzymes capable of metabolizing BPA; Physiologically Based Pharmacokinetic (PBPK) models predict and biomonitoring data support the conclusion that resulting serum levels of the active form of BPA in primates (including humans) of all ages will be approximately 1000-fold less than the ingested dose. The decreased metabolic capacity in rodents with a minor impact of rodent enterohepatic recirculation results in higher internal exposure levels in rodents than primates when given the same oral dose. This suggests the rat as the more "sensitive" species, thus diminishing the support for the full interspecies variability factor of 10x. However, as an additional conservative measure in deference to hazard endpoints identified by the Working Group, the interspecies uncertainty factor was not modified herein.

CONCLUSIONS

The 2014 hazard assessment by the FDA's BPA Joint Emerging Science Working Group reconfirms the previously identified NOAEL of 5 mg/kg bw/day for systemic toxicity from subchronic/multigenerational studies using rodents as the most appropriate NOAEL for a safety assessment of oral or dietary exposures.[12] Available pharmacokinetic data and comparisons between ages and species further support use of this NOAEL as very conservative in extrapolating to humans. Compared to the 90th percentile exposures cited above for populations of <2 years old and ≥2 years old, the margins of safety exceed the uncertainty factor of 1000. The conclusion of this report is that an adequate margin of safety exists for BPA at current levels of exposure from food contact uses.

Table 1: Margins of Safety for BPA

Populations (age in years)	NOAEL (mg/kg bw/day)	EDI (µg/kg bw/day)	Margin of exposure	Uncertainty factor
<2	5	1.1	4545	1000
≥2	5	0.5	10000	1000

A number of additional research studies are currently in progress, e.g., NCTR two year rodent chronic toxicity study on BPA,[13] NCTR development of PBPK models,[14] and NIEHS human

12 Based on the lowest NOAELs for systemic toxicity which were observed in the RTI studies (Tyl et al. 2002 and 2008) for which liver and body weight effects were observed in animals administered BPA in utero and ~ 3 months (subchronic duration). See 2008 FDA Draft Assessment of Bisphenol A for Use in Food Contact Notifications.

13 NTP testing Bisphenol A - 10034-Y at http://ntp.niehs nih.gov/?objectid=BC9825E3-123F-7908-7BF465F9E25681B0

14 Examples of recent models:

Yang X, Doerge DR, Fisher JW. Prediction and evaluation of route dependent dosimetry of BPA in rats at

pharmacokinetic studies.[15] This safety assessment may be revised accordingly pending completion, review, and identification of data from these or other studies relevant to a dietary safety assessment.

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different life stages using a physiologically based pharmacokinetic model. Toxicol Appl Pharmacol. 2013 Jul 1;270(1):45-59

Fisher JW, Twaddle NC, Vanlandingham M, Doerge DR. Pharmacokinetic modeling: prediction and evaluation of route dependent dosimetry of bisphenol A in monkeys with extrapolation to humans. Toxicol Appl Pharmacol. 2011 Nov 15;257(1):122-36.

15 NIH Study number 12-E-0089, Clinical Trial NCT01573429 at http://clinicaltrials.gov/ct2/show/NCT01573429