



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

The Honorable John D. Dingell
Chairman
Committee on Energy and Commerce
House of Representatives
Washington, D.C. 20515-6115

FEB 25 2008

Dear Mr. Chairman:

Thank you for your letter of January 17, 2008, co-signed by Chairman Bart Stupak, Subcommittee on Oversight and Investigations, Committee on Energy and Commerce, concerning use of the chemical bisphenol A (BPA), particularly in products intended for use by infants and children. You asked questions regarding the effects of exposure to BPA and about the activities of the Food and Drug Administration (FDA or the Agency) regarding the safety assessment of BPA.

By way of background, BPA is used as a monomer in the manufacture of two types of polymers used for food-contact articles (i.e., polycarbonate (PC) polymers regulated in Title 21 of the *Code of Federal Regulations* (CFR) §177.1580 and epoxy-based enamels and coatings regulated in 21 CFR § 175.300 (b)(3)(viii), 21 CFR §177.1440 and 21 CFR §177.2280). Typical uses of PC-based polymers include food processing equipment and water and infant bottles intended to be used multiple times by a consumer prior to disposal. Epoxy-based coatings are used in a variety of canned food and beverage applications.

We have repeated your questions below, in bold type, followed by FDA's responses.

1. Which specific office or division within FDA has the responsibility for determining the agency's policy on BPA, and who is currently in charge of that office?

The Office of Food Additive Safety (OFAS) within the Center for Food Safety and Applied Nutrition (CFSAN) has the responsibility for assessing the safety of food contact substances and for making recommendations concerning FDA policy on BPA. Dr. Laura Tarantino is the current director of OFAS.

2. On what studies is FDA basing the claim that there is no "safety concern at the current exposure level"? If FDA is relying on published studies, please

provide us with the scientific citations from any studies used by FDA in making this determination.

In evaluating the safety of food contact articles or their constituents, such as BPA, FDA's safety assessment relies on evaluating probable consumer exposure as a result of the proposed use and other authorized uses, and ensuring that the probable consumer exposures are supported by the available toxicological information.¹ With regard to consumer exposure, FDA found that the small amounts of BPA that migrated into food from the use of PC-based polymers and BPA-based epoxy coatings result in a cumulative daily intake of 11 micrograms per person per day ($\mu\text{g}/\text{person}/\text{day}$).

This estimate is based on: 1) the migration levels of BPA into food, or into food simulating solvents, under the most severe conditions of use (i.e., time, temperature), and 2) information on the types of food contacted, the fraction of the diet that would come into contact with that type of food contact material, and whether the finished food contact article would be intended for single or repeated use.² FDA's evaluation of the safety of BPA also considered that the use of can enamels in infant formula packaging and the use of PC baby bottles results in an estimated daily intake of 7 $\mu\text{g}/\text{infant}/\text{day}$. These estimates relied on data generated by FDA laboratories or the regulated industry, or that were available in the open literature, on BPA levels in canned food and in food contacting PC articles.

FDA believes that this level of exposure to adults and infants is safe as defined in 21 CFR §170.3(i). This conclusion is based on our most recently completed reviews of two pivotal multigenerational oral studies performed under applicable regulatory guidelines. The studies included the examination of reproductive and some developmental endpoints and a large range of exposures, including low doses. We will provide copies of these studies and their review memoranda as part of our response to Question 4. For your convenience, the specific subjects of these review memoranda are as follows:

- FDA memorandum dated July 24, 2007, Review of Two-Generation Reproductive Toxicity Evaluation of Bisphenol A Administered in the Feed to CD-1® Swiss Mice, RTI Identification Number 65C-09301.000.003/0209301.000.003 submitted to the Agency in Food Master File 580, Volumes I-VIII, referencing the study conducted by Research Triangle Institute (RTI) International, Center for Life Sciences and Toxicology, P.O. Box 12194, 3040 Cornwallis Road, Research Triangle Park, NC 27709 sponsored by American Plastics Council, 1300 Wilson Boulevard, Arlington, VA 22209; completed on March 1, 2007.
- FDA memorandum dated July 18, 2007, Review of study entitled "*Three-generation reproductive toxicity evaluation of Bisphenol A in the feed to CD® (Sprague-Dawley) rats*" submitted to the Agency in Food Master File 580, referencing the study conducted by Research Triangle Institute (RTI), Reproductive and Developmental

¹ Detailed information regarding guidance on food contact notifications is available at <http://www.cfsan.fda.gov/~dms/opa-notf.html>

² Detailed information regarding calculations can be accessed at <http://www.cfsan.fda.gov/~dms/opa2pmnc.html>, Guidance for Industry, Preparation of Food Contact Notifications and Food Additive Petitions for Food Contact Substances: Chemistry Recommendations

Toxicology Laboratory, Center for Life Sciences and Toxicology, 3040 Cornwallis Road, Research Triangle Park, NC 27709 sponsored by American Plastics Council, 1300 Wilson Boulevard, Arlington, VA 22209; completed on 10/05/2000; study # 656-07036-000 [Note this study is also available published: Tyl. et al., *Toxicological Sciences* 68, 121-146 (2002)].

In addition, FDA has completed a compact summary of the pharmacokinetic data on BPA in multiple species. FDA has determined that understanding the species differences and the differences in how metabolic systems handle BPA administered via various routes of exposure, such as oral versus subcutaneous, are pivotal to examining the safety of BPA. We will provide copies of these studies and the review memoranda as part of the response to Question 4. For your convenience, the specific subject of the review memorandum is as follows:

- FDA memorandum dated June 1, 2007, Compact Summary of Bisphenol A (BPA) Pharmacokinetics. The memorandum includes references cited therein.

FDA has compared the “no observed effect” levels of the data reviewed to the estimated daily intake values and considers that an adequate margin of exposure exists for the conclusion of reasonable certainty of no harm under the intended conditions of use.

FDA is aware of multiple safety assessments recently performed on BPA, including those conducted by the European Food Safety Authority’s (EFSA) Scientific Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food³ and the Japanese National Institute of Advanced Industrial Science and Technology.⁴ Neither of these risk assessments disagrees with FDA’s current position of the safe use of BPA at the current exposure level.

FDA is also aware of the conclusions of the National Toxicology Program’s (NTP) Center for the Evaluation of Risks to Human Reproduction (CERHR)⁵ expert panel review of BPA. It concluded that, based on current BPA exposure levels, for pregnant women and fetuses and infants and children some concern exists for exposure to BPA (including *in utero*) causing neural and behavioral effects. In addition, FDA is aware of reports from the Environmental Working Group (EWG)⁶ and the “Chapel Hill” Bisphenol A Expert Panel⁷ detailing exposure data and summarizing the current literature, which have concluded that a safety concern exists at the current exposure levels. FDA considers the findings of all such analyses seriously and will continue to monitor these data, acting on them as appropriate.

3 Opinion of the Scientific Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food on a request from the Commission related to 2,2-bis(4-hydroxyphenyl)propane (Bisphenol A)

4 Bisphenol A Risk Assessment Document, (AIST Risk Assessment Document Series No. 4), New Energy and Industrial Technology Development Organization (NEDO) and Research Center for Chemical Risk Management (CRM), National Institute of Advanced Industrial Science and Technology (AIST), completed November 2005. Accessible at http://unit.aist.go.jp/crm/mainmenu/e_1-10.html

5 NTP-Center for the Evaluation of Risks to Human Reproduction, Report on the Reproductive and Developmental Toxicity of Bisphenol A DRAFT 11/2006 and Final DRAFT (available for comments) of 11/26/2007 accessible at <http://cerhr.niehs.nih.gov/chemicals/bisphenol/bisphenol-eval.html>

6 Accessible at <http://www.ewg.org/node/20936> and <http://www.ewg.org/reports/bpaformula>.

7 Chapel Hill Bisphenol A Expert Panel Consensus Statement: Integration of Mechanisms, Effects in Animals and Potential to Impact Human Health at Current Levels of Exposure. *Reproductive Toxicology* 24(2) 2007

3. Please provide the Committee with a summary of any tests that FDA scientists have conducted to determine levels of BPA in canned food or migrating from baby bottles. Indicate for each test the specific product tested, the methodology used (e.g., gas chromatography-mass spectrometry, liquid chromatography-mass spectrometry, high performance liquid chromatography, or enzyme linked immunosorbent assay), as well as the detection limit for the assay used.

Studies conducted by FDA laboratories in the early 1990s focused on BPA migration from PC infant bottles and BPA levels in vegetables⁸ and infant formula⁹ packed in epoxy-coated cans. Migration studies were conducted on reusable PC infant bottles under conditions simulating actual household use in the preparation of infant formula. In addition, FDA laboratories surveyed selected canned vegetables and infant formula for levels of BPA.

Residual levels of BPA in commercially available PC infant bottles were reported to range from 7 to 30 parts per million (ppm). PC bottles were tested according to two migration protocols designed to model “common” and “worst case” use scenarios in the preparation of infant formula. The results are as follows:

- Common Protocol: PC bottles were sterilized for 5 minutes in boiling water, filled with water or 10% ethanol,¹⁰ and stored at room temperature for up to 72 hours. The test solutions were then analyzed for BPA by high performance liquid chromatography (HPLC) with fluorescence detection at a limit of detection (LOD) of 5 parts per billion (ppb). BPA was not detected in any sample. As detailed in the attached documents, using the LOD as the measured value, this corresponds to a BPA migration to food of less than 1.7 ppb.
- Worst-Case Protocol: PC bottles were sterilized for 5 minutes in boiling water, filled with water or 10% ethanol, heated to 100° Celsius (C) for 30 minutes, cooled to room temperature, and stored in the refrigerator for 72 hours. The test solutions were analyzed for BPA by HPLC with fluorescence detection at a limit of detection (LOD) of 5 ppb. BPA was not detected in any sample. As detailed in the attached documents, using the LOD as the measured value, this corresponds to a BPA migration to food of less than 1.7 ppb.

FDA used the worst-case protocol value to estimate infant exposure to BPA from the use of PC infant bottles.

Additionally, BPA levels were determined in select canned vegetables purchased in Washington, D.C. area supermarkets and packed in imported and domestic manufactured cans containing

⁸ A summary of studies by CFSAN's Chemistry Methods Branch (CMB) on BPA migration from PC infant bottles and BPA level in vegetables was provided to the Chemistry Review Board (CRB) on 9-26-95 by CMB (Henry Hollifield) in a draft report entitled “Bisphenol-A: Status Summary Report.”

⁹ CMB's studies on BPA levels in infant formula are described in a CMB memorandum dated 3-5-96 (J. Biles to G. Diachenko).

¹⁰ These solutions are used to simulate food as described in Guidance for Industry Preparation of Food Contact Notifications and Food Additive Petitions for Food Contact Substances: Chemistry Recommendations, accessible at <http://www.cfsan.fda.gov/~dms/opa2pmnc.html>.

epoxy-based coating enamels. The test samples consisted of canned mushrooms (3 samples), tomatoes, artichokes, and mixed vegetables (1 sample each) and included both the pureed vegetable and liquid. The test samples were analyzed for BPA by HPLC. BPA levels ranged from 5-39 ppb in vegetables, with an average value of 16 ppb for all 6 samples. FDA used the value of 22 ppb to estimate adult exposure to BPA from the use of BPA-based container coatings.

BPA levels were determined in both milk-based and soy-based infant formula (liquid concentrate) distributed by five different manufacturers and purchased in Washington, D.C. area supermarkets. The samples consisted of both two-piece and three-piece cans with epoxy, modified-epoxy, and/or PVC-based side and lid coatings. Several lots from each manufacturer were tested in triplicate (for a total of 42 analyses). Aliquots of each test sample were loaded onto a solid-phase extraction column and the retained BPA eluted with chloroform. The organic phase was evaporated to near dryness, redissolved in acetonitrile:methanol:water (1:1:1), and analyzed by HPLC with fluorescence detection. BPA recoveries were reported to range from 67-106%. BPA levels ranged from 0.1-13.2 ppb in infant formula (liquid concentrate). The average BPA level for all 14 concentrate samples was 5 ppb. Accounting for dilution on use, BPA levels in prepared formula ranged from 0.05-6.6 ppb, with an average of level of 2.5 ppb. Given that an infant's diet may consist of exclusively one type (or brand) of infant formula, the highest BPA level in prepared formula (i.e., 6.6 ppb) was used in developing an estimate of infant exposure to BPA from epoxy-based can enamels.

The previously described studies were later published by FDA scientists^{11,12} in two journal articles.

In the first article, supplemental migration studies (in addition to those described above) were conducted with cut-up bottle strips or intact bottles in contact with water; 8%, 10%, 50% or 95% ethanol; food oil; infant formula or juice under various time and temperature conditions. The four migration protocols employed were deemed to represent typical, repeat, exaggerated and extreme use. Two of the four protocols simulated normal use of the baby bottles. The details and results of the two typical use protocols are summarized below:

- Intact bottles were held in boiling water for 5 minutes, filled with apple juice or formula, and refrigerated at 4° C for 24 hours. BPA was not detected in the juice or formula at a LOD of 100 nanograms per milliliter (ng/mL) (100 ppb);
- Bottle pieces were placed in the food simulants, heated at 100° C for 30 minutes, and refrigerated for 72 hrs. The BPA level in the 10% ethanol and water was 2 micrograms per kilogram (µg/kg) (2 ppb), after correction for the food mass-to-surface area typical of baby bottles. The LOD for BPA in these simulants was 2 ng/mL (2 ppb). The higher LOD for BPA in juice and formula was attributed to matrix effects of real foods.

11 Biles, J.E., T.P. McNeal, T.H. Begley, and H.C. Hollifield, "Determination of Bisphenol-A in Reusable Polycarbonate Food-Contact Plastics and Migration to Food-Simulating Liquids, *Journal of Agricultural and Food Chemistry*, Vol. 45, No. 9, 1997, pp. 3541-3544.

12 Biles, J.E., T.P. McNeal, and T.H. Begley, "Determination of Bisphenol A Migrating from Epoxy Can Coatings to Infant Formula Liquid Concentrates," *Journal of Agricultural and Food Chemistry*, Vol. 45, 1997, pp. 4697-4700.

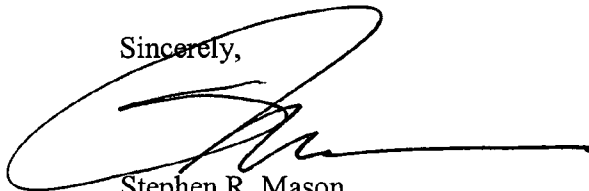
The second article provides the details of analysis of BPA levels in both milk-based and soy-based infant formula (liquid concentrate) described above. The samples consisted of three cans (liquid concentrates) each from four manufacturers of infant formula, plus one single can of ready-to-feed formula that was three years old. The identities of the interior coatings, including body and end, were determined by infrared spectroscopy. For those cans found to contain epoxy coatings, the extracts were concentrated by solid phase extraction (SPE) and BPA levels determined by HPLC with fluorescence detection. BPA was confirmed in selected formula extracts by gas chromatography with mass selective detection (GC-MS).

4. Please provide all records relating to BPA that FDA employees and consultants have produced since 1998.

We are continuing to examine our files to collect documents relating to BPA from 1998 to the present and will provide them to the Committee in a subsequent submission.

Thank you again for contacting us concerning this matter. A similar response has been sent to Chairman Stupak. If you have any further questions, please let us know.

Sincerely,

A handwritten signature in black ink, appearing to be 'S. Mason', written over a large, stylized circular flourish.

Stephen R. Mason
Acting Assistant Commissioner
for Legislation

cc: The Honorable Joe Barton, Ranking Member
Committee on Energy and Commerce

The Honorable John Shimkus, Ranking Member
Subcommittee on Oversight and Investigations
Committee on Energy and Commerce