Bisphenol A (BPA): Use in Food Contact Application

Update on Bisphenol A (BPA) for Use in Food Contact Applications

January 2010; March 30, 2012; Updated March 2013; July 2014; November 2014

Summary of FDA's Current Perspective on BPA in Food Contact Applications

FDA's current perspective, based on its most recent safety assessment (/media/90124/download), is that BPA is safe at the current levels occurring in foods. Based on FDA's ongoing safety review of scientific evidence, the available information continues to support the safety of BPA for the currently approved uses in food containers and packaging.

Overview of BPA Usage in Food Contact Applications

BPA is a structural component in polycarbonate beverage bottles. It is also a component in metal can coatings, which protect the food from directly contacting metal surfaces. BPA has been used in food packaging since the 1960s.

As is the case when foods are in direct contact with any packaging material, small, measurable amounts of the packaging materials may migrate into food and can be consumed with it. As part of its premarket review of food packaging materials, FDA's food contact regulations and food contact notification program assesses the likely migration from the packaging material to assure that any migration to food occurs at safe levels.

Heightened interest in the safe use of BPA in food packaging has resulted in increased public awareness as well as scientific interest. As a result, many exploratory scientific studies have appeared in the public literature. Some of these studies have raised questions about the safety of ingesting the low levels of BPA that can migrate into food from food contact materials. To address these questions the National Toxicology Program, partnering with FDA's National Center for Toxicological Research is carrying out in-depth studies to answer key questions and clarify uncertainties about BPA.

On the regulatory front, FDA's regulations authorize FDA to amend its food additive regulations to reflect when certain uses of an additive have been abandoned. FDA can take this action on its own initiative or in response to a food additive petition that demonstrates that a use of a food additive has been permanently and completely abandoned. Recently, FDA granted two petitions requesting that FDA amend its food additive regulations to no longer provide for the use of certain BPA-based materials in baby bottles, sippy cups, and infant formula packaging because these uses have been abandoned. As a result, FDA amended its food additive regulations to no longer provide for these uses of BPA.

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Background

BPA is an industrial chemical used to make polycarbonate, a hard, clear plastic, which is used in many consumer products. BPA is also found in epoxy resins, which act as a protective lining on the inside of some metal-based food and beverage cans. Uses of all substances that migrate from packaging into food, including BPA, are subject to premarket approval by FDA as indirect food additives or food contact substances. FDA can make regulatory changes based on new safety or usage information. The original approvals for BPA were issued under FDA's food additive regulations and date from the 1960s.

In 2008 FDA released a document titled *Draft Assessment of Bisphenol A for Use in Food Contact Applications*.[1] This draft assessment was reviewed by a Subcommittee of FDA's Science Board, which released its report at the end of October 2008.[2] Also in 2008, the National Toxicology Program Center for the Evaluation of Risks to Human Reproduction, part of the National Institutes of Health, released the *Monograph on the Potential Human Reproductive and Developmental Effects of Bisphenol A*.[3]

By 2009, FDA released reassessments of studies cited in the NTP *Monograph* in addition to other relevant studies that became available after the Monograph's release. [4] The studies were evaluated for their relevance for regulatory hazard and/or risk assessment. In addition to the FDA review process, FDA's Acting Chief Scientist asked five expert scientists from across the federal government to provide independent scientific review of these documents in the fall of 2009. The results of the independent evaluations were released in April 2010, as FDA made the CFSAN report and other relevant information available for public comment (http://www.regulations.gov/#!docketDetail;D=FDA-2010-N-0100;dct=FR%252BPR%252BN%252BO%252BSR).[5] Although the reassessments indicated a need to further evaluate a number of endpoints or biological outcomes, the analyses did not recommend any adjustments to BPA levels reported in food at that time.

Since that time, the FDA has continued to review additional studies as they became available, including those addressing possible low-dose effects.

In the fall of 2014, FDA experts from across the agency, specializing in toxicology, analytical chemistry, endocrinology, epidemiology, and other fields, completed a four-year review of more than 300 scientific studies. The FDA review has not found any information in the evaluated studies to prompt a revision of FDA's safety assessment of BPA in food packaging at this time.

The studies reviewed were published or available from November 1, 2009 to July 23, 2013. The review was documented in four memoranda and their attachments:

- *"Final report for the review of literature and data on BPA" (/media/90546/download) – 6/6/2014*
- *"2014 Updated Review of Literature and Data on Bisphenol A" (/media/90582/download) - 6/6/2014*
- *"2012 Updated Review of Literature and Data on Bisphenol A" (/media/90588/download) - 8/22/2013*
- *"Updated Review of the 'Low-Dose' Literature (Data) on Bisphenol A and Response to Charge Questions Regarding the Risk Assessment on Bisphenol" (/media/90596/download) - 5/24/2011*

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Increasing Our Understanding about the Biology and Metabolism of BPA

Strong consumer and scientific interest in the safety of BPA has prompted FDA to support additional studies to provide further information and address apparent inconsistencies in the scientific literature about BPA. Many of these studies addressed how the body disposes of or metabolizes BPA. These studies also addressed questions about how long it takes for the body to dispose of BPA.

FDA's Studies. FDA's regulatory Centers and FDA's National Center for Toxicological Research continue to pursue a set of studies on the fate of BPA in the body from various routes of exposure and the safety of low doses of BPA, including assessing novel endpoints where questions have been raised.

Research studies pursued by FDA's National Center for Toxicological Research have [6]:

- Found evidence in rodent studies that the level of the active form of BPA passed from expectant mothers to their unborn offspring, following oral exposure, was so low it could not be measured. The study orally dosed pregnant rodents with 100-1000 times more BPA than people are exposed to through food, and could not detect the active form of BPA in the fetus 8 hours after the mother's exposure.

- Demonstrated that oral BPA administration results in rapid metabolism of BPA to an inactive form. This results in much lower internal exposure of BPA (i.e., the active form) than what occurs from other routes of exposure such as injection.
- Found that primates (including humans) of all ages effectively metabolize and excrete BPA much more rapidly and efficiently than rodents.
- Developed physiologically based pharmacokinetic models that can be used to predict the level of internal exposure to the active and inactive forms of BPA. Based on the effects of metabolism, internal exposures to the active form of BPA following oral administration are predicted to be below 1% or less of the total BPA level administered.
- Recently completed a rodent subchronic study [7] intended to provide information that would help in designing a long-term study that is now underway (see below). The subchronic study was designed to characterize potential effects of BPA in a wide range of endpoints, including prostate and mammary glands, metabolic changes, and cardiovascular endpoints. The study included an *in utero* phase, direct dosing to pups to mimic bottle feeding in neonates, and employed a dose range covering the low doses where effects have been previously reported in some animal studies, as well as higher doses where estrogenic effects have been measured in guideline oral studies. The results of this study showed no effects of BPA at any dose in the low-dose range.

The FDA's National Center for Toxicological Research is continuing with an additional study:

- **Rodent chronic toxicity study**, which is currently underway. Using the data and design from the rodent subchronic study, the National Toxicology Program/Food and Drug Administration (NTP/FDA) is conducting a long-term toxicity study of BPA in rodents to assess a variety of endpoints, including novel endpoints where questions have been raised. As an addition to this core study, FDA is providing extra animals and tissues to a consortium of grantees [8] selected and funded by the National Institute of Environmental Health Sciences to address other critical questions.

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Food Additive Regulations Amended to No Longer Provide for the Use of BPA-Based Materials in Baby Bottles, Sippy Cups, and Infant Formula Packaging

- **FDA has amended its regulations (https://www.federalregister.gov/articles/2012/07/17/2012-17366/indirect-food-additives-polymers) to no longer provide for the use of BPA-based polycarbonate resins in baby bottles and sippy cups.** In July, 2012, FDA took this action in response to a food additive petition filed by the American

Chemistry Council (ACC) [9]. The ACC petition demonstrated, from publicly available information and information collected from industry sources, that the use of polycarbonate resins in baby bottles and sippy cups had been abandoned.

- **FDA has amended its regulations (https://www.federalregister.gov/articles/2013/07/12/2013-16684/indirect-food-additives-adhesives-and-components-of-coatings) to no longer provide for the use of BPA-based epoxy resins as coatings in packaging for infant formula.** In July, 2013, FDA took this action in response to a food additive petition filed by Congressman Edward Markey [10] of Massachusetts. This petition demonstrated, from publicly available information and information collected from industry sources, that the use of BPA-based epoxy resins as coatings in packaging for infant formula had been abandoned.

An amendment of the food additive regulations based on abandonment is *not* based on safety, but is based on the fact that the regulatory authorization is no longer necessary for the specific use of the food additive because that use has been permanently and completely abandoned. The safety of a food additive is not relevant to FDA's determination regarding whether a certain use of that food additive has been abandoned.

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Next Steps and Collaborations

FDA continues to review the available information and studies on BPA. FDA will update its assessment of BPA and will take additional action if warranted. Based on FDA's ongoing safety review of scientific evidence, the available information continues to support the safety of BPA for the currently approved uses in food containers and packaging.

FDA will also continue to consult with other expert agencies in the federal government, including the National Institutes of Health (and the National Toxicology Program), the Environmental Protection Agency, the Consumer Product Safety Commission, and the Centers for Disease Control and Prevention.

FDA will continue to participate in discussions with our international regulatory and public health counterparts who are also engaged in assessing the safety of BPA.

For example, FDA has participated with Health Canada in encouraging industry efforts to refine their manufacturing methods for the production of infant formula can linings to minimize migration of BPA into the formula.

In addition, FDA actively supported and participated in the Expert Consultation on BPA convened by World Health Organization and the Food and Agriculture Organization of the United Nations on November 2-5, 2010, in Ottawa, Canada. Information about this expert

consultation and the report of the meeting is available from the WHO web site. [11]

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[1]U.S. Food and Drug Administration, *Draft Assessment of Bisphenol A for Use in Food Contact Applications (http://wayback.archive-it.org/7993/20180424053047/http://www.fda.gov/ohrms/dockets/AC/08/briefing/2008-0038b1_01_02_FDA%20BPA%20Draft%20Assessment.pdf) (http://www.fda.gov/about-fda/website-policies/website-disclaimer)*, 14 August 2008.

[2]FDA Science Board Subcommittee on Bisphenol A. Scientific Peer-Review of the Draft Assessment of Bisphenol A for Use in Food Contact Applications (http://wayback.archive-it.org/7993/20180424053047/http://www.fda.gov/ohrms/dockets/ac/08/briefing/2008-4386b1-05.pdf) (http://www.fda.gov/about-fda/website-policies/website-disclaimer), 31 October 2008.

[3]NTP-CERHR Monograph on the Potential Human Reproductive and Developmental Effects of Bisphenol A, NIH Publication No. 08-5994, September 2008.

[4] http://www.regulations.gov/#!documentDetail;D=FDA-2010-N-0100-0006.

[5] http://www.regulations.gov/#!docketDetail;D=FDA-2010-N-0100;dct=FR%252BPR%252BN%252BO%252BSR (http://www.regulations.gov/#!docketDetail;D=FDA-2010-N-0100;dct=FR%252BPR%252BN%252BO%252BSR)

[6]

a) Churchwell MI, Camacho L, Vanlandingham MM, Twaddle NC, Sepehr E, Delclos KB, Fisher JW, Doerge DR. Comparison of life-stage-dependent internal dosimetry for bisphenol a, ethinyl estradiol, a reference estrogen, and endogenous estradiol to test an estrogenic mode of action in Sprague Dawley rats. (http://www.ncbi.nlm.nih.gov/pubmed/24496641) *Toxicol Sci.* 2014 May;139(1):4-20. doi: 10.1093/toxsci/kfu021. Epub 2014 Feb 4.

b) Delclos KB, Camacho L, Lewis SM, Vanlandingham MM, Latendresse JR, Olson GR, Davis KJ, Patton RE, Gamboa da Costa G, Woodling KA, Bryant MS, Chidambaram M, Trbojevich R, Juliar BE, Felton RP, Thorn BT. Toxicity evaluation of bisphenol a administered by gavage to sprague dawley rats from gestation day 6 through postnatal day 90. (http://www.ncbi.nlm.nih.gov/pubmed/24496637) *Toxicol Sci.* 2014 May;139(1):174-97. doi: 10.1093/toxsci/kfu022. Epub 2014 Feb 4.

c) Doerge DR, Twaddle NC, Vanlandingham M, Fisher JW. Pharmacokinetics of bisphenol A in neonatal and adult Sprague-Dawley rats. *Toxicol Appl Pharmacol.* 2010 Sep 1;247(2):158-65.

d) Doerge DR, Twaddle NC, Vanlandingham M, Brown RP, Fisher JW. Distribution of bisphenol A into tissues of adult, neonatal, and fetal Sprague-Dawley rats. *Toxicol Appl Pharmacol*. 2011 Sep 15;255(3):261-70.

e) Doerge DR, Twaddle NC, Vanlandingham M, Fisher JW. Pharmacokinetics of bisphenol A in neonatal and adult CD-1 mice: inter-species comparisons with Sprague-Dawley rats and rhesus monkeys. *Toxicol Lett*. 2011 Dec 15;207(3):298-305.

f) Doerge DR, Twaddle NC, Vanlandingham M, Fisher JW. Pharmacokinetics of bisphenol A in serum and adipose tissue following intravenous administration to adult female CD-1 mice. *Toxicol Lett*. 2012 Jun 1;211(2):114-9.

g) Doerge DR, Twaddle NC, Woodling KA, Fisher JW. Pharmacokinetics of bisphenol A in neonatal and adult rhesus monkeys. *Toxicol Appl Pharmacol*. 2010 Oct 1;248(1):1-11.

h) 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.

i) Doerge DR, Vanlandingham M, Twaddle NC, Delclos KB. Lactational transfer of bisphenol A in Sprague-Dawley rats. *Toxicol Lett*. 2010 Dec 15;199(3):372-6.

j) Ferguson SA, Law CD Jr, Abshire JS. Developmental treatment with bisphenol A or ethinyl estradiol causes few alterations on early preweaning measures. *Toxicol Sci*. 2011 Nov;124(1):149-60.

k) He Z, Paule MG, Ferguson SA. Low oral doses of bisphenol A increase volume of the sexually dimorphic nucleus of the preoptic area in male, but not female, rats at postnatal day 21. *Neurotoxicol Teratol*. 2012 May-Jun;34(3):331-7.

l) Patterson TA, Twaddle NC, Roegge CS, Callicott RJ, Fisher JW, Doerge DR. Concurrent determination of bisphenol A pharmacokinetics in maternal and fetal rhesus monkeys. *Toxicol Appl Pharmacol*. 2013 Feb 15;267(1):41-8.

m) Twaddle NC, Churchwell MI, Vanlandingham M, Doerge DR. Quantification of deuterated bisphenol A in serum, tissues, and excreta from adult Sprague-Dawley rats using liquid chromatography with tandem mass spectrometry. *Rapid Commun Mass Spectrom*. 2010 Oct 30;24(20):3011-20.

n) Yang X, Doerge DR, Fisher JW. Prediction and evaluation of route dependent dosimetry of BPA in rats at different life stages using a physiologically based pharmacokinetic model. *Toxicol Appl Pharmacol*. 2013 Jul 1;270(1):45-59.

[7] Study available upon request.

[8] Schug et al. (2013) A new approach to synergize academic and guideline-compliant research: the CLARITY-BPA research program. *Reprod Toxicol*. 40:35-40.

[9] 77 Fed. Reg. 41,899

[10] 78 Fed. Reg. 41,840

[11] www.who.int/foodsafety/areas_work/chemical-risks/bisphenol/en/ (http://www.who.int/foodsafety/areas_work/chemical-risks/bisphenol/en/) (http://www.fda.gov/about-fda/website-policies/website-disclaimer)

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Resources For You

- Questions & Answers on Bisphenol A Use in Food Contact Applications (/food/food-additives-ingredients/questions-answers-bisphenol-bpa-use-food-contact-applications)
- Bisphenol A Overview & Response to Petitions (/food/food-additives-ingredients/bisphenol-bpa)
- European Food Safety Authority Information on Bisphenol A (http://www.efsa.europa.eu/en/topics/topic/bisphenol) (http://www.fda.gov/about-fda/website-policies/website-disclaimer)