

Update on Bisphenol A for Use in Food Contact Applications
U.S. Food and Drug Administration
January 2010

Overview

Bisphenol A (BPA) is an industrial chemical that has been present in many hard plastic bottles and metal-based food and beverage cans since the 1960s.

Studies employing standardized toxicity tests have thus far supported the safety of current low levels of human exposure to BPA. However, on the basis of results from recent studies using novel approaches to test for subtle effects, both the National Toxicology Program at the National Institutes of Health and FDA have some concern about the potential effects of BPA on the brain, behavior, and prostate gland in fetuses, infants, and young children. In cooperation with the National Toxicology Program, FDA's National Center for Toxicological Research is carrying out in-depth studies to answer key questions and clarify uncertainties about the risks of BPA.

In the interim:

- FDA is taking reasonable steps to reduce human exposure to BPA in the food supply. These steps include:
 - supporting the industry's actions to stop producing BPA-containing baby bottles and infant feeding cups for the U.S. market;
 - facilitating the development of alternatives to BPA for the linings of infant formula cans; and
 - supporting efforts to replace BPA or minimize BPA levels in other food can linings.
- FDA is supporting a shift to a more robust regulatory framework for oversight of BPA.
- FDA is seeking further public comment and external input on the science surrounding BPA.

FDA is also supporting recommendations from the Department of Health and Human Services for infant feeding and food preparation to reduce exposure to BPA.

FDA is not recommending that families change the use of infant formula or foods, as the benefit of a stable source of good nutrition outweighs the potential risk from BPA exposure.

Background

BPA is an industrial chemical used to make a hard, clear plastic known as polycarbonate, which has been used in many consumer products, including reusable water bottles and baby bottles. BPA is also found in epoxy resins, which act as a protective lining on the inside of metal-based food and beverage cans. These uses of BPA are subject to premarket approval by FDA as indirect food additives or food contact substances. The original approvals were issued under FDA's food additive regulations and date from the 1960s.

Studies employing standardized toxicity tests used globally for regulatory decision making thus far have supported the safety of current low levels of human exposure to BPA.¹ However, results of recent studies using novel approaches and different endpoints describe BPA effects in laboratory animals at very low doses corresponding to some estimated human exposures.² Many of these new studies evaluated developmental or behavioral effects that are not typically assessed in standardized tests.

The National Toxicology Program Center for the Evaluation of Risks to Human Reproduction, part of the National Institutes of Health, completed a review of BPA in September 2008.³ The National Toxicology Program uses five different terms to describe its level of concern about the different effects of chemicals: negligible concern, minimal concern, some concern, concern, and serious concern.⁴

In its report on BPA, the National Toxicology Program expressed “*some concern* for effects on the brain, behavior, and prostate gland in fetuses, infants, and children at current human exposures to bisphenol A.”⁵ The Program also expressed “*minimal concern* for effects on the mammary gland and an earlier age for puberty for females in fetuses, infants, and children at current human exposures to bisphenol A” and “*negligible concern*” for other outcomes.⁶

The National Toxicology Program does not make regulatory recommendations. With respect to neurological and developmental outcomes of BPA, the Program stated that “additional research is needed to more fully assess the functional, long-term impacts of exposures to bisphenol A on the developing brain and behavior.”⁷ The Program also stated:

Overall, the current literature cannot yet be fully interpreted for biological or experimental consistency or for relevance to human health. Part of the difficulty for evaluating consistency lies in reconciling findings of different studies that use different

¹ See, e.g., European Food Safety Authority. Toxicokinetics of Bisphenol A, Scientific Opinion of the Panel on Food additives, Flavourings, Processing aids and Materials in Contact with Food, Adopted 9 July 2008, *The EFSA Journal* 2008. Available online at http://www.efsa.europa.eu/cs/BlobServer/Scientific_Opinion/afc_ej759_bpa_%20toxicokinetics_op_en.pdf?ssbinary=true.

² See, e.g. vom Saal FS, Akingbemi BT, Belcher SM et al. 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* 2007;24:131-8.

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

⁴ Ibid, page 6.

⁵ Ibid.

⁶ Ibid.

⁷ Ibid, page 20.

experimental designs and different specific behavioral tests to measure the same dimension of behavior.⁸

In August 2008, prior to the release of the final National Toxicology Program report, FDA released a document entitled *Draft Assessment of Bisphenol A for Use in Food Contact Applications*.⁹ This draft assessment was then reviewed by a Subcommittee of FDA's Science Board, which released its report at the end of October 2008.¹⁰

Since that time, the Center for Food Safety and Applied Nutrition within FDA has reviewed additional studies of low-dose toxicity cited by the National Toxicology Program and the Science Board Subcommittee as well as other such studies that have become available. The Center then prepared a document entitled *Bisphenol A (CAS RN. 80-05): Review of Low Dose Studies*, dated August 31, 2009. In the fall of 2009, FDA's Acting Chief Scientist asked five expert scientists from across the federal government to provide independent scientific evaluations of this document.

FDA is continuing to consider the low dose toxicity studies of BPA as well as other recent peer-reviewed studies related to BPA. At this stage, FDA is explaining its current perspective on BPA, its support for further studies, its intent to solicit and consider public comment before revising its assessment of BPA use in food contact applications, its interim public health recommendations, its view of the appropriate regulatory framework for BPA use in food contact applications, and our planned collaborations with international partners.

FDA's Current Perspective on BPA

At this interim stage, FDA shares the perspective of the National Toxicology Program that recent studies provide reason for some concern about the potential effects of BPA on the brain, behavior, and prostate gland of fetuses, infants and children. FDA also recognizes substantial uncertainties with respect to the overall interpretation of these studies and their potential implications for human health effects of BPA exposure. These uncertainties relate to issues such as the routes of exposure employed, the lack of consistency among some of the measured endpoints or results between studies, the relevance of some animal models to human health, differences in the metabolism (and detoxification) of and responses to BPA both at different ages and in different species, and limited or absent dose response information for some studies.

⁸ Ibid.

⁹ U.S. Food and Drug Administration, *Draft Assessment of Bisphenol A for Use in Food Contact Applications*, 14 August 2008 (Available online at http://www.fda.gov/ohrms/dockets/AC/08/briefing/2008-0038b1_01_02_FDA%20BPA%20Draft%20Assessment.pdf).

¹⁰ FDA Science Board Subcommittee on Bisphenol A. *Scientific Peer-Review of the Draft Assessment of Bisphenol A for Use in Food Contact Applications*, 31 October 2008 (Available online at <http://www.fda.gov/ohrms/dockets/ac/08/briefing/2008-4386b1-05.pdf>).

FDA is pursuing additional studies to address the uncertainties in the findings, seeking public input and input from other expert agencies, and supporting a shift to a more robust regulatory framework for oversight of BPA to be able to respond quickly, if necessary, to protect the public.

In addition, FDA is supporting reasonable steps to reduce human exposure to BPA, including actions by industry and recommendations to consumers on food preparation. At this time, FDA is not recommending that families change the use of infant formula or foods, as the benefit of a stable source of good nutrition outweighs the potential risk of BPA exposure.

Additional Studies

FDA supports additional studies, by both governmental and non-governmental entities, to provide additional information and address uncertainties about the safety of BPA.

FDA's Studies. FDA's National Center for Toxicological Research is pursuing a set of studies on the safety of low doses of BPA, including assessment of the novel endpoints where concerns have been raised. These include studies pursued in collaboration with the National Toxicology Program and with support and input from the National Institute for Environmental Health Sciences. Depending on the results, each could influence regulatory decisions about BPA.

FDA's studies include:

- Physiologically based pharmacokinetic modeling studies in both rodents and nonhuman primates are under way to predict internal exposure of BPA in both the free and conjugated forms, and to provide data on the magnitude of inter-individual differences. These data will facilitate comparisons of exposure across all stages of development and development of relationships between the results of rodent and nonhuman primate feeding studies, and will allow comparisons of internal doses of BPA when given by oral and intravenous routes. This approach has been identified as critical in order to fully evaluate the potential human health implications of studies that have used novel endpoints or non-oral dosing, particularly in rodents, which may metabolize BPA differently than humans. These data will also allow the agency to assess the magnitude of the potential differential exposure (and risk) to neonates. Results from this study are expected to be available to FDA to inform the agency's decisionmaking starting in spring 2010.
- Rodent subchronic studies are in progress to characterize potential effects, and, where observed, the dose-response relationship in the prostate and mammary glands for orally administered BPA. In addition, these studies will explore other issues including potential effects of BPA on metabolic changes and cardiovascular endpoints. These studies will include an *in utero* phase, mimic bottle feeding in neonates, and employ a dose range that will cover 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. Results from this study are expected to be available to FDA to inform the agency's decisionmaking starting in 2012.

- Rodent behavioral/neuroanatomical pilot studies are also already in progress as part of the sub-chronic study to characterize dose levels at which behavioral, neuroanatomical, neurochemical and hormonal endpoints may be affected by developmental exposure to BPA. These data are intended to evaluate possible effects of exposure to BPA during development that have been reported in some published studies on sexually dimorphic behavioral endpoints such as anxiety, as well as on standard developmental neurotoxicity tests. Results from this study are expected to be available to FDA to inform the agency's decisionmaking starting in 2012.

Other Studies. Other studies on the safety of BPA are also underway. For example, the National Institute of Environmental Health Sciences has recently announced that it is providing \$30 million in funding to study BPA, which includes support both for FDA studies and external grants.

Public Comment and Next Steps for FDA's Assessment of BPA

FDA will open a public docket for comment on BPA. The docket will contain the Center for Food Safety and Applied Nutrition's review of the low dose toxicity studies and recently published studies, the five expert reviews, and other relevant material. The agency welcomes comments on these documents, other available evidence, and the agency's regulatory options. This docket will be open for public comment for 60 days.

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

Based on this outside input and the results of new studies, FDA will update its assessment of BPA and will be prepared to take additional action if warranted. As the scientific field is evolving rapidly, FDA anticipates providing further updates on BPA to the public as significant new information becomes available.

Interim Public Health Recommendations

At this interim stage, FDA supports reasonable steps to reduce exposure of infants to BPA in the food supply. In addition, FDA will work with industry to support and evaluate manufacturing practices and alternative substances that could reduce exposure to other populations.

Given that these are preliminary steps being taken as a precaution, it is important that no harmful changes be made in food packaging or consumption, whether by industry or consumers, that could jeopardize either food safety or reduce access to and intake of food needed to provide good nutrition, particularly for infants.

Infants. Infants are a potentially sensitive population for BPA because (1) their neurological and endocrine systems are developing; and (2) their hepatic system for detoxification and elimination of such substances as BPA is immature.

- FDA is supporting the industry’s actions to stop producing BPA-containing bottles and infant feeding cups for the U.S. market. FDA understands that over the past year, the major manufacturers of these products have stopped selling new BPA-containing bottles and infant feeding cups for the U.S. market. Glass and polypropylene bottles and plastic disposable “bag” liners have long been alternatives to polycarbonate nursing bottles.
- FDA is facilitating the development of alternatives to BPA for the linings of infant formula cans. FDA has already noted increased interest on the part of infant formula manufacturers to explore alternatives to BPA-containing can linings, and has received notifications for alternative packaging. The agency is supporting efforts to develop and use alternatives by (1) working with manufacturers regarding the regulatory status and safety of alternative liners; (2) giving technical assistance to those wishing to prepare applications for approval of alternatives; and (3) expeditiously reviewing any such new applications for alternatives. Because reliable can lining materials are a critical factor in ensuring the quality of heat processed liquid infant formula, safe replacement of such materials requires not only that they both be safe for food contact but also allow for processing that is fully functional in protecting the safety and quality of the infant formula itself.

The American Academy of Pediatrics and other health authorities recommend breastfeeding as the optimal nutrition for infants. Infant formula, including infant formula packaged in cans, is a safe and acceptable alternative that provides known nutritional benefits and prevents life-threatening nutritional deficiencies.

FDA is not recommending that families change the use of infant formula or foods, as the benefit of a stable source of good nutrition outweighs the potential risk of BPA exposure.

Other Populations. With respect to uses of BPA in packaging of food intended for other populations, FDA will support changes in food can linings and manufacturing to replace BPA or minimize BPA levels where the changes can be accomplished while still protecting food safety and quality. FDA will support efforts to develop alternatives for other can lining applications similar to those which are already being tested for liquid infant formula packaging. Reliable can lining materials are a critical factor in ensuring the quality of heat processed foods. Therefore, FDA will work to encourage and facilitate changes that minimize exposure to BPA and avoid other adverse impacts on food safety or quality.

Other Advice. FDA is supporting recommendations by the Department of Health and Human Services for infant feeding and food preparation to reduce exposure to BPA

The Regulatory Framework for BPA

Current BPA food contact uses were approved under food additive regulations issued more than 40 years ago. This regulatory structure limits the oversight and flexibility of FDA. Once a food additive is approved, any manufacturer of food or food packaging may use the food additive in accordance with the regulation. There is no requirement to notify FDA of that use. For example,

today there exist hundreds of different formulations for BPA-containing epoxy linings, which have varying characteristics. As currently regulated, manufacturers are not required to disclose to FDA the existence or nature of these formulations. Furthermore, if FDA were to decide to revoke one or more approved uses, FDA would need to undertake what could be a lengthy process of rulemaking to accomplish this goal.

Since 2000, FDA has regulated new food contact substances through the Food Contact Notification Program. Under this program:

- FDA receives notification from each manufacturer of the basis for the safe use of a food contact substance, detailing the conditions of the substance's use, allowing the agency and public to know how much is being used, and for what applications;
- FDA can work with individual manufacturers to minimize exposure if a potential or actual safety concern is identified after approval;
- FDA can require the submission of additional safety and exposure data from individual manufacturers to address a significant safety concern;
- FDA can require additional studies by individual manufacturers to address a significant safety concern; and
- If FDA were to reach a conclusion that revocation of one or more approved uses is justified, FDA could quickly protect the public by revoking the use through a notice published in the Federal Register.

Given concern about BPA, and the ongoing evaluation of and studies on its safety, FDA believes that the more modern framework is more robust and appropriate for oversight of BPA than the current one.

FDA will encourage manufacturers to voluntarily submit a food contact notification for their currently marketed uses of BPA-containing materials.

In addition, FDA will explore additional options to regulate BPA under the more modern framework.

Collaboration with International Partners

FDA will continue to participate in discussions with our International regulatory and public health counterparts who have also been 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 is planning to support and participate in an upcoming planned Expert Consultation on BPA to be convened by World Health Organization and the Food and Agriculture Organization of the United Nations. Information about this expert consultation is available from the WHO web site:

http://www.who.int/foodsafety/fs_management/infosan_archives/en/