



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

JUN 05 2008

Dear Mr. Chairman:

Thank you for your letter of April 4, 2008, co-signed by Chairman Bart Stupak, Subcommittee on Oversight and Investigations, Committee on Energy and Commerce, concerning the chemical bisphenol A (BPA), particularly as used in products intended for use by infants and children. Your letter posed questions regarding the activities of the Food and Drug Administration (FDA or the Agency) regarding the safety assessment of BPA.

In light of recent reports and statements from the National Toxicology Program (NTP), Health Canada and Environment Canada, as well as interested public health advocates, Commissioner of Food and Drugs Andrew von Eschenbach has formed an Agency-wide BPA Task Force to conduct a review, encompassing all FDA-regulated product lines, of the concerns raised about BPA. The task force is undertaking a broad review of current research and information on BPA. In addition to looking at the food and beverage containers that have been the focus of recent concerns as well as our regulatory efforts over the years, the task force is conducting an inventory of all products regulated by FDA's food and medical products centers to better understand other potential routes of exposure.

At this time, FDA is not recommending that consumers discontinue using food contact materials that contain BPA. Although our review of the NTP and other reports are ongoing, a large body of available evidence indicates that food contact materials containing BPA currently on the market are safe, and that exposure levels to BPA from these materials, including exposure to infants and children, are below those that may cause health effects. We also acknowledge that BPA research is an extremely active area, and we assure you that if FDA's review of data leads us to a determination that uses of BPA are not safe, the Agency will take action to protect the public health.

BPA is used in the manufacture of two types of polymers used in food contact articles, specifically, polycarbonate polymers and epoxy-based enamels and coatings. These food contact substances have been regulated for many years pursuant to regulations published in Title 21 of the *Code of Federal Regulations* (CFR). Polycarbonate (PC) polymers are regulated in 21 CFR §177.1580 and epoxy-based enamels and coatings are regulated in 21

CFR §175.300 (b) (3) (viii), 21 CFR §177.1440 and 21 CFR §177.2280. Typical food-contact uses for PC polymers include food processing equipment, such as popcorn makers, and water and infant bottles. Epoxy-based coatings manufactured with BPA are used in a variety of canned food and beverage applications.

Because polymerization reactions do not go entirely to completion, small residual amounts of BPA can remain in polymers. Although BPA is not itself a food contact substance, these small residual amounts of BPA may migrate out into food during use. For this reason, FDA's safety assessments include a consideration of likely consumer exposure. The Agency has determined that dietary exposure to BPA is in the very low parts per billion range from these uses. Further, it is important to emphasize that as new data and reviews of BPA become available, FDA's review of the safety of BPA is continual.

We have repeated your questions below, in bold type, followed by our responses. We have provided a consolidated response to questions 1 and 2. We have also provided additional details to expand upon and clarify our responses to the questions you asked in your letter of January 17, 2008, concerning the review of BPA.<sup>1</sup>

- 1. Please provide in writing the names of those who specifically made the decision to base FDA's assessment of BPA's safety on these two studies.**
- 2. Please provide in writing the names of those who specifically made the determination of BPA's safety based on these two studies.**

As stated in our response to question 1 of your letter of January 17, 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 and has responsibility for the decisions of that office as well as recommendations that may be made to the director of CFSAN or the FDA Commissioner.

OFAS continually monitors the safety of the products it regulates. When new information that may affect the safety determination of a previously regulated food additive becomes available, OFAS typically forms multidisciplinary working groups to reexamine the actual use and estimated intake of the substance and to review the new safety information. These working groups are assigned to perform safety assessments, comparing the estimated human exposure to the substance with all relevant safety information to determine if a conclusion of reasonable certainty of no harm, the standard for food additive approval defined in 21 CFR §170.3(i), remains valid in light of the new information.

In the case of BPA, these groups include regulatory scientists, chemists, toxicologists, reproductive and developmental toxicologists, pharmacologists, and interdisciplinary scientists. The risk managers are staff involved in policy and administrative decisions and may hold

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<sup>1</sup> See FDA response letter dated February 25, 2008.

academic credentials in various relevant scientific areas. After performing the safety assessment, these scientists report their findings and recommendations to managers at the Office, Center, and Agency level, to help determine the appropriate action, if any, to be taken by FDA. While the expertise and analysis of these risk managers are vital to making the safety determinations on food contact substances, these individuals do not have final decision-making authority.

Additional details about the process and reviews undertaken on BPA, including the determination of pivotal studies, are included below.

**3. Please describe the process by which FDA may reconsider their decision regarding the safety of BPA.**

OFAS monitors exposure and safety information on a continuing basis for products it regulates. In investigating a potential post-market safety concern related to a regulated food additive, FDA may take certain actions to revoke or amend a food additive regulation, either by the Agency acting on its own initiative or in response to citizen-prompted actions such as a Citizen's Petition. Regarding BPA, if the Agency found that current levels of exposure to BPA were unsafe, one course of action would be to propose revocation or amendment of the relevant food additive regulations by means of rulemaking.

It is important to emphasize that as new data and reviews of BPA are generated, our review of the safety of this substance is continuing. In determining what, if any, safety concerns exist on a regulated product, OFAS has several options for gathering the information necessary to decide whether to propose to revoke or amend a regulation. Some examples of actions OFAS has taken or is taking in the case of BPA include:

- CFSAN laboratory scientists have examined the actual use of BPA in food contact materials, thereby allowing OFAS to more accurately determine current exposure. In our letter of February 25, 2008, we elaborated on FDA's method for determining the current exposure to BPA, and provided our current estimate that the cumulative daily intake for adults is 11 micrograms BPA per person per day and for infants, 7 micrograms BPA per infant per day.
- OFAS continues to monitor all available safety data on BPA, having individual scientists or multidisciplinary groups gather information and deliberate on the potential concerns and perform a new, formal safety assessment, as deemed appropriate. For example, in addition to information previously reviewed, FDA is currently reviewing multiple studies that include examination of neural and behavioral effects following BPA administration.
- OFAS is continuing to gather human biomonitoring data on BPA through the Center for Disease Control and Prevention as part of the National Health and Nutrition Examination Survey (NHANES).

In gathering this information on BPA, FDA's scientists report their findings and recommendations to Agency managers who then determine the appropriate Agency action(s). As noted previously, although FDA has completed an analysis on the exposure and some of the toxicological endpoints for BPA, FDA is still examining the data that continue to be gathered on BPA.

In your letter, you state that "it appears FDA's position on BPA's safety is entirely dependent on two studies, both of which are funded by the American Plastics Council (APC), and one of which has not been published or peer-reviewed. Given that there are dozens of published, peer-reviewed studies related to BPA, your development of critical public health policy in this manner, especially related to infants and children, seems highly questionable." It is important to clarify that FDA's position on BPA is based on the consideration of hundreds of studies and is not derived solely from the review of these two studies. However, FDA has concluded that these two studies are pivotal to the safety assessment of BPA, due to the design of the studies and the quality of the data. While we have used these studies in determining the current "no observed effect level" (NOEL) for BPA, this is not the same as stating that our position is entirely dependent on consideration of only these two studies.

It may be helpful to summarize a brief chronology of our activities regarding BPA. After the majority of BPA uses were regulated, it was determined that BPA is a weakly estrogenic compound. Since these initial findings, which were reported in the late 1990s, OFAS has continuously monitored the new data on BPA. Specifically, Vom Saal et al reported findings concerning "low dose" effects of BPA administered to mice on endocrine organs and behavior. These studies were reviewed by OFAS scientists in a comparison to a study submitted by industry in 1999, (the MPI Study) which attempted to replicate the findings of this group.<sup>2</sup> As the concerning data could not be replicated, these studies were in conflict and no clear conclusions could be drawn. In addition to these studies, OFAS reviewed various studies conducted by NTP or by industry, designed to test the endpoints of carcinogenicity, systemic toxicity, and reproductive and developmental toxicity. None of these studies indicated a concern; however, they also did not involve testing protocols that included "low doses."

In the late 1990s, OFAS formed an internal working group to gather information on "endocrine disruptors." This group attended scientific meetings convened by international scientific groups on the subjects of endocrine disruptors and "low dose" effects and monitored the literature in this field. During this time, OFAS scientists continued to evaluate the scientific literature on BPA and discuss internally with FDA management the relevance and findings of published studies. Discussions were also conducted with the regulated industry.

In addition to monitoring the publicly available literature, OFAS received regular updates from stakeholders on BPA research and analysis, including the submission, in full, of safety studies. In March 2007, OFAS formed a task group specifically to review these data on BPA, beginning with a review of the pharmacokinetic (PK) data and the two good laboratory practice (GLP) animal feeding studies using low doses of BPA in their protocol.

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<sup>2</sup> These documents were included in FDA's February 25, 2008 response to Question #4.

Many of the studies reviewed by OFAS are those conducted by or on behalf of NTP or industry. It is not unusual for the Agency to rely on studies submitted by the interested industry. In fact, industry-gathered data serve as the basis for most of FDA's product approvals, because the regulated industry is responsible for developing and gathering the data that support the safety of its products and for reporting to FDA all relevant data on the safety of those products prior to being marketed.

In the case of BPA, the two rodent studies that were considered pivotal were sponsored by the APC and the Society of the Plastics Industry and were conducted by RTI International, Research Triangle Park, NC. Due to the ongoing controversy with regard to the low dose effects of BPA on endpoints of concern at that time, the industry briefed FDA and our European counterparts on the two studies during the planning and execution phases. These studies were considered pivotal in our review of the existing data for a number of reasons, including the following: (1) they were conducted in a manner that OFAS would recommend to a stakeholder seeking an approval for a new use (i.e., they follow Agency guidelines) and included additional protocol considerations allowing for the examining of issues that were controversial to BPA at the time planned; (2) they were submitted to the Agency with supporting information (raw data) allowing for our independent evaluation of the findings; and (3) they both included a large range of exposures, including a range of high and low doses which allowed for the examination of dose response curves. With regard to FDA's evaluation of BPA, these studies have been given more weight compared to publications in the public literature that examine the same endpoints because the publications often lack details and supporting data that would allow Agency scientists to make an independent evaluation of the underlying data. In addition, many of the published studies on BPA have numerous protocol limitations, including the animal model utilized, the method of BPA measurement, the statistical analysis of the data, the failure to use multiple or correctly spaced doses in the experimental protocol, and the route of administration.

As noted in our February 25, 2008, letter, OFAS is aware that, in addition to the studies and reviews already referenced, multiple safety assessments have become available on BPA, including those conducted by the European Food Safety Authority's Scientific Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food<sup>3</sup> and by the Japanese National Institute of Advanced Industrial Science and Technology.<sup>4</sup> The conclusions of the safety assessments by these regulatory bodies have not indicated a concern for the current regulated exposure levels to BPA. We are aware that other assessments of BPA by regulatory counterparts are ongoing and we will fully consider any forthcoming assessments by these regulatory bodies.

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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](http://unit.aist.go.jp/crm/mainmenu/e_1-10.html)

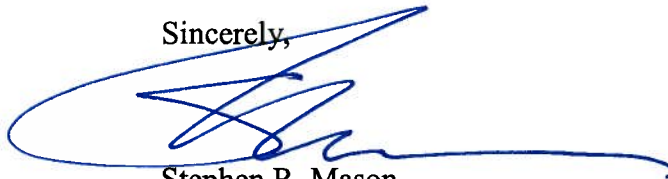
FDA is reviewing the conclusions of the National Toxicology Program's (NTP) Center for the Evaluation of Risks to Human Reproduction (CERHR) expert panel review, the Health Canada and Environment Canada's (HC/EC) Draft Screening Assessment of BPA, and of NTP's Draft Brief. The opinion reached by the CERHR expert panel concluded that, based on current BPA exposure levels, for pregnant women, fetuses, infants and children "some concern"<sup>5</sup> exists for exposure to BPA causing neural and behavioral effects. The panel also concluded that there was "minimal concern" for BPA exposure in these populations for effects in the prostate gland, mammary gland, and an earlier age for puberty in females. HC/EC's draft also indicates a concern for neural and behavioral effects. NTP's Draft Brief reiterates the conclusions of the CERHR expert panel with regard to neural and behavioral effects, but departed from the panel in concluding that "some concern" exists for BPA exposure to fetuses, infants and children for effects in the prostate gland, mammary gland, and an earlier age for puberty in females. These analyses emphasized relatively new data and emerging or difficult-to-interpret endpoints in toxicology and considered the fact that the studies currently available provide limited evidence and contain numerous uncertainties. It is noteworthy that the increase from "minimal concern" in the NTP's CERHR expert panel report to "some concern" in the NTP's Draft Brief reflects numerous studies that have appeared in the literature only in the past several months.

Finally, as noted in our February 25, 2008, response, we are also aware of, and considering the findings of, two other recent reports detailing exposure data or summarizing the current literature, specifically, an Environmental Working Group (EWG) report and the "Chapel Hill" Bisphenol A Expert Panel report, both released in 2007.

In summary, we are actively reviewing the data on BPA and will continue to consider the relevancy of new data and studies as they appear. If our continuing review of all available data leads us to a determination that the current levels of exposure to BPA are not safe, we will take appropriate regulatory action.

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,



Stephen R. Mason  
Acting Assistant Commissioner  
for Legislation

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<sup>5</sup> The likelihood of an adverse reproductive or developmental effect in humans resulting from exposure is expressed as a level of concern. The five levels of concern used by NTP are, from highest to lowest: Serious Concern, Concern, Some Concern, Minimal Concern, and Negligible Concern.

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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