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September 12, 2008

Via E-Mail

Carlos Peña, Ph.D.
Office of Science and Health Coordination
Office of the Commissioner (HF–33)
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Re: Comments on the Draft Assessment of Bisphenol A for Use in Food Contact Applications, 73 Fed. Reg. 47957 (Aug. 15, 2008), Docket No. FDA-2008-N-0038

Dear Dr. Peña:

On behalf of the North American Metal Packaging Alliance, Inc. (NAMPA), I am pleased to submit these comments on the United States Food and Drug Administration's (FDA) Draft Assessment of Bisphenol A for Use in Food Contact Applications (Draft Assessment), as noticed in the *Federal Register* on August 15, 2008. This submission compliments the oral comments that I will present at the September 16, 2008, meeting of the BPA Subcommittee of the Science Board to the Food and Drug Administration. NAMPA fully supports the comments of the Polycarbonate/BPA Global Group of the American Chemistry Council (ACC) submitted under separate cover, and urges FDA to adopt ACC's comments in preparing the Draft Assessment in final.

NAMPA is keenly interested in the Draft Assessment because NAMPA members use epoxy resins derived from bisphenol A (BPA) to manufacture protective polymer coatings for the inner surface of metal food and beverage containers. This critical technology helps to assure a safe, wholesome, and nutritious food supply by protecting the contents of food and beverage containers. Compared with other coating technologies, coatings derived from epoxy resins provide superior adhesion to the metal surface, greater durability, and higher resistance to the wide range of chemistries found in foods and beverages. These attributes are essential to protect the packed food from microbiological contamination, which is a significant food safety issue.

The Draft Assessment is a thorough, comprehensive, and objective review of the scientific literature focused on the endpoints of carcinogenesis and reproductive and

developmental toxicity of BPA. NAMPA supports FDA's reliance on published guidance on the conduct of studies to assess which studies could be used to support the safety assessment of BPA. In light of this guidance, not all studies were afforded similar weight. As noted by FDA, "many of the studies cited in the literature failed to control for numerous issues . . . and these shortcomings limit the utility of these studies in an overall safety analysis of the use of BPA in food contact applications."[1] Whether or not a given study was sponsored by industry was afforded appropriately no weight by FDA in its assessment of studies.

The Draft Assessment Critically Assessed Low Dose Studies

FDA's rigorous assessment of studies was particularly critical in evaluating the alleged "low dose" developmental effects attributed to BPA. The challenge in this instance is not a lack of scientific certainty, but rather a lack of scientific rigor and plausibility required to establish a credible scientific basis for concern. Proponents of low dose findings have failed to provide a plausible explanation of the claimed non-monotonic dose-response relationship between the effects reported at low doses and the effects observed in numerous well-conducted studies at higher BPA exposure levels. Comprehensive scientific reviews by the National Institute of Environmental Health Sciences Center for the Evaluation of Risks to Human Reproduction (CERHR),[2] the European Food Safety Authority (EFSA),[3] and FDA[4] do not support the low dose hypothesis.

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1 Draft Assessment at 17.

2 CERHR, NTP-CERHR Expert Panel Report on the Reproductive and Developmental Toxicity of Bisphenol A (Nov. 26, 2007) (CERHR Panel Report), *available at* http://cerhr.niehs.nih.gov/chemicals/bisphenol/BPAFinalEPVF112607.pdf.

3 EFSA, 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), Question number EFSA-Q-2005-100 (adopted on 29 November 2006) (EFSA Panel Report), *available at* http://www.efsa.europa.eu/EFSA/Scientific_Opinion/afc_op_ej428_bpa_op_en,1.pdf.

4 FDA, Letter to Honorable John D. Dingell, Chairman, Committee on Energy and Commerce, U.S. House of Representatives (Feb. 25, 2008) (FDA Statement), *available at* http://energycommerce.house.gov/Investigations/Bisphenol.022508.respto011708.HHS.ltr.pdf.

The CERHR Panel Report, issued in 2007 by a scientific panel composed of independent experts, concluded that studies reporting "low dose" effects of BPA have not been replicated nor corroborated. Thus, the CERHR Panel declined to assign these reported effects any weight:

> Hence, the failure of BPA to produce reproducible adverse effects via a relevant route of exposure, coupled with the lack of robustness of the many . . . low dose studies (sample size, dose range, statistical analyses and experimental design, GLP) and the inability to reproduce many of these effects of any adverse effect strains the credibility of some of these study results. They need to be replicated using appropriate routes of exposures, adequate experimental designs and statistical analyses and linked to higher dose adverse effects if they are to elevate our concerns about the effects of BPA on human health.[5]

In its critical review of low dose studies of developmental effects, the CERHR Panel also noted that in some low dose studies the researchers failed to detect "*some* manifestation of toxicity (e.g., altered weight, histopathology)" at higher BPA doses.[6] As the CERHR Panel observed:

> Every chemical that produces low dose cellular and molecular alterations of endocrine function also produces a cascade of effects increasing in severity resulting in clearly adverse alterations at higher doses, albeit the effects can be different from those seen at low doses.[7]

Similarly, the EFSA Panel derived a No Observed Adverse Effect Level (NOAEL) from well-conducted multi-generation reproduction studies in mice and in rats, rather than on questionable "low dose" studies. Like the CERHR Panel, the EFSA Panel was reluctant to assign any weight to the developmental effects reported in the "low dose" studies:

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5 CERHR Panel Report at 352.

6 *Id*. (emphasis in original).

7 *Id*.

> The Panel considered that low-dose effects of BPA in rodents have not been demonstrated in a robust and reproducible way, such that they could be used as pivotal studies for risk assessment. Moreover, the species differences in toxicokinetics, whereby BPA as parent compound is less bioavailable in humans than in rodents, raise considerable doubts about the relevance of any low-dose observations in rodents for humans.[8]

The EFSA Panel also questioned the plausibility of the claimed non-monotonic dose-response relationship:

> [T]he Panel notes that toxicologists are familiar with U-shaped and inverted U-shaped dose-response curves for hormonal activities, but the presence of a response at one dose level only does not necessarily indicate a causal relationship between the administration of a substance and an observed change. To demonstrate U-shaped dose responses in a robust way, it is necessary to have reasonably spaced dose intervals, usually of less than 10-fold, and not steps of 1000-fold as in some recent studies.[9]

NAMPA recognizes that Health Canada has adopted a precautionary approach in recommending reduced BPA exposures to infants based on low dose studies in animals. Importantly, however, according to a Government of Canada Q&A, "*current exposures from canned foods and drinks represent a negligible health risk to the general population. Health Canada does not recommend any changes in eating habits. . . . Exposure to bisphenol A through canned formula is low, and the nutritional benefits of infant formula far outweigh possible risk.*"[10]

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8 EFSA Panel Report at 4.

9 *Id.*

10 Government of Canada, *Questions and Answers for Action on Bisphenol A Under the Chemicals Management Plan* (emphasis added), available at http://www.chemicalsubstanceschimiques.gc.ca/faq/bisphenol_a_qa-qr_e.html.

Residue Data Overestimate BPA Levels

Epoxy coatings are an enabling technology that protects public health by assuring food safety. BPA, however, is not a coating material itself. Rather, BPA is a building block for creating the high molecular weight epoxy resin components that are used in metal food packaging coatings. Today's epoxy coatings are cured at high temperatures to form highly cross-linked inert polymeric films on the metal. BPA may remain in trace quantities after the polymerization and thermal curing steps used to form the liquid coating and convert it into a cured dry film on the metal packaging. Significantly, the very small residual concentrations of BPA that may exist in the film will not increase with time after thermal processing, storage, hydrolysis, or even damage to the polymer, *i.e.*, scratching or denting.

NAMPA questions the reliability of much of the residue data reporting BPA in foods. NAMPA believes that the levels of BPA reported in food, and attributed to migration of residual monomer from the epoxy coating on metal food and beverage containers, are often significantly overstated. Unless an analytical methodology suitable for measuring very low BPA levels in complex matrices is utilized, the reported results can be influenced by interferences from other food constituents. As the CERHR Panel Report documents,[11] much of the sampling to date has been done utilizing Gas Chromatography with Mass Spectrometry (GC/MS) or High Performance Liquid Chromatography with fluorescence detection, that are prone to interferences from other substances naturally present in food products. High Performance Liquid Chromatography in tandem with Mass Spectrometry (HPLC/MS) is a more reliable approach, but has seldom been used for monitoring BPA levels in food because of the high cost of equipment and operation.

In one GC/MS study, BPA levels in raw agricultural produce were "equal to or higher than those found in canned foods."[12] Although it is conceivable that these reported BPA residues were attributable to BPA from another source, it is highly probable that the researchers incorrectly reported other phenolic substances naturally present in the commodities as BPA. In any case, these data challenge the general presumption in most BPA studies of metal packaged foods that all of the *reported BPA* is from residual monomer migrating from the epoxy lining.

NAMPA believes that BPA exposure estimates would be more reliable if the residue data utilized to develop such estimates are collected with more robust and defensible analytical technologies and protocols, such as HPLC/MS.

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11 CERHR Panel Report at 14.

12 *Id.*

NAMPA fully concurs with FDA's conclusion "that safety assessments . . . should be based on laboratory animal studies using oral routes of exposure since this is the most relevant route of human exposure for food contact materials. Studies based on other routes of exposure . . . are likely not comparable to typical human exposures to food contact materials and will not produce results relevant to safety assessments of food contact materials."[13] Moreover, the importance of selecting appropriate routes of exposure has been recognized increasingly by toxicologists. For example, Rory Conolly, *et al*., observed, "[g]iven that a major, and possibly *the* major, application of toxicological data today is protection of the public health *via* its application of risk assessment, use of routes of exposure . . . set primarily for purposes of experimental conveniences, should be avoided."[14]

NAMPA is committed to the safety of the metal packaging products its members produce. In this regard, NAMPA welcomes FDA's conclusion in the Draft Assessment that "an adequate margin of safety exists for BPA at current levels of exposure from food contact uses, for infants and adults."[15] Importantly, in reaching this conclusion, FDA "used unmodified, typical study type UFs [uncertainty factors] and considers them conservative based on the large body of knowledge for BPA and the findings observed in the pivotal studies,"[16] and thoroughly reviewed data "on endpoints highlighted as of potential concern in recent reports, such as developmental effects on the prostate gland and developmental neural and behavioral toxicity...."[17]

To the extent scientific uncertainties surrounding the Draft Assessment exist, NAMPA supports FDA's proposed tiered testing strategy to decrease these uncertainties. We

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13 Draft Assessment at 19.

14 Conolly, R.B., *et al*. (1999). Stimulating Research to Improve the Scientific Basis of Risk Assessment. *Toxicol. Sci*. 49:1-4 (emphasis in original); *see also* Carmichael, N.G., *et al.* (2006). Agricultural Chemical Safety Assessment: A Multisector Approach to the Modernization of Human Safety Requirements. *Crit. Rev. Toxicol*. 36:1-7 ("Data from kinetic studies coupled with pharmacokinetic modeling allows conversion of administered dose into an 'internal' dose that can be extrapolated from animals to humans.").

15 Draft Assessment at 36.

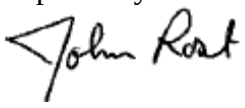
16 *Id.* at 34.

17 *Id.* at 36.

note, however, that in the Draft Assessment, FDA introduces an additional level of conservatism into its weight of evidence safety assessment by assuming infant exposure to BPA that is likely higher than actual exposure levels. For example, FDA assumed the maximum exposure for the full exposure period (0 - 12 months of age), even though infant formula consumption and BPA exposure decrease with age.

NAMPA looks forward to presenting additional information on the issues discussed in these comments to the BPA Subcommittee on September 16, 2008. If you have any questions regarding this submission, please feel free to e-mail me at rost@metal-pack.org.

Respectfully submitted,



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