



May 23, 2008

Via E-Mail

Barbara Shane, Ph.D.
Executive Secretary for the NTP BSC
Office of Liaison, Policy and Review
National Toxicology Program
National Institute of Environmental Health Sciences
P.O. Box 12233
MD A3-01
Research Triangle Park, NC 27709

Re: National Toxicology Program; Office of Liaison, Policy and Review; Peer
Review of the Draft NTP Brief on Bisphenol A

Dear Dr. Shane:

The North American Metal Packaging Alliance, Inc. (NAMPA)¹ submits these comments in response to the April 15, 2008, notice announcing availability of, and requesting comment on, the draft National Toxicology Program (NTP) Brief on Bisphenol A.² In addition to these written comments, NAMPA requests an opportunity to provide supplementary oral comments at the meeting of the NTP Board of Scientific Counselors (BSC) at Research Triangle Park, North Carolina, on June 11, 2008.

NAMPA is vitally interested in the subjects addressed in the NTP Brief because NAMPA members use epoxy resins derived from BPA to manufacture protective polymer coatings for the inner surface of light metal food and beverage packaging. This critical

¹ NAMPA was formerly the Inter-Industry Group for Light Metal Packaging. Member companies are committed to the safe and efficient manufacture and distribution of sustainable, wholesome, and nutritious food and beverage products. NAMPA's members manufacture and/or use epoxy resins derived from bisphenol A (BPA) to produce protective polymer coatings for the inner surface of light metal food and beverage containers.

² NTP, DRAFT NTP Brief on Bisphenol A [CAS No. 80-05-7] (Apr. 14, 2008) (NTP Brief), available at http://cerhr.niehs.nih.gov/chemicals/bisphenol/BPADraftBriefVF_04_14_08.pdf.



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technology protects the contents of these containers from aggressive food products, thereby assuring a safe, wholesome, and nutritious food supply. Compared to other coating technologies, coatings derived from epoxy resins provide superior adhesion to the metal surface, greater durability, flexibility, a low taste and odor threshold and higher resistance to the wide range of chemistries found in foods and beverages. These attributes are essential to protect the packed food from leakage and microbiological contamination, which are significant food safety issues.

Epoxy coatings are an enabling technology that has reduced material usage, save energy in production, save petroleum in transportation, reduce GHG emissions, and save the consumer money while providing safe and nutritious food. Today's epoxy coatings are high molecular weight, heat cured epoxy formulations. The very small residual concentrations of BPA that may exist in the metal packaging coating will not increase with time after thermal processing, storage, hydrolysis or damage to the polymer, *i.e.*, denting.

As a preliminary matter, NAMPA wishes to express a general concern regarding the significant confusion that appears to exist regarding the "levels of concern" rating system used by NTP and the Center for the Evaluation of Risks to Human Reproduction (CERHR) Expert Panel in communicating their conclusions. NAMPA appreciates the five levels of concern used by NTP to express in narrative form the conclusions reached by NTP and the Expert Panels tasked with reviewing chemical substances under review by CERHR, and the not insubstantial effort NTP has devoted over the years trying to ensure that these levels of concern are understood for what they are and what they are not.

Despite these efforts, however, there was massive confusion that prevailed immediately following the release of the CERHR Expert Peer Review Report and the more recent release of the NTP Brief. NAMPA is deeply troubled that the five-level rating system is fundamentally misunderstood and, unfortunately, uniquely amenable to media manipulation that can inspire needless fear and widespread confusion. The regrettable consequences of this problem with the rating system were played out with relentless ferocity immediately after the release of the NTP Brief. Countless news reports played off the "some concern" language causing precipitous, irrational, and wholly unnecessary consumer confusion and fear and extensive market disruption. NAMPA urges NTP to consider alternatives to expressing conclusions in this five-level narrative form, or to expand to an even greater extent its efforts to communicate the results of its reviews in a way that presents the five levels of concern in a context that better reflects the meaning of these terms in the rating system as opposed to the everyday use of these very value-laden terms.

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Increased “Concern” Level for Certain Developmental Effects

The draft NTP Brief is based on a prior report on the potential developmental toxicity of BPA prepared by an expert panel of the CERHR.³ Notwithstanding NTP’s principal reliance on this report, the draft NTP Brief disregards the CERHR Panel’s conclusion that there is “minimal concern” for developmental effects on the prostate and mammary gland and for accelerated puberty among pregnant women, fetuses, and infants at BPA exposure levels for the general population in the United States.⁴ Instead, the NTP Brief concludes that there should be “some concern” for these same effects.⁵

NTP’s departure from the recommended findings of its own highly qualified expert panel is not explicitly acknowledged and is without rational basis. The CERHR Panel did state “some concern” with respect to potential neural and behavioral effects for pregnant women, fetuses, and infants exposed to BPA, but the Panel explicitly stated that this is because the literature indicating neural and behavioral effects following low dose exposure to BPA is “more consistent.” In contrast, the CERHR Panel assigned less credibility to the other developmental effects reported in low dose studies because it correctly found that those studies are not biologically plausible and that the results have not been successfully replicated. The CERHR Panel stated:

Hence, the failure of BPA to produce reproducible adverse effects via a relevant route of exposure, coupled with the lack of robustness of many of the 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 exposure, adequate experimental designs and statistical analyses and linked to higher

³ 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>.

⁴ CERHR Panel Report at 352-353.

⁵ NTP Brief at 37.

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dose adverse effects if they are to elevate our concerns about the effects of BPA on human health.⁶

The language used in the NTP Brief stresses areas of agreement with the recommendations of the CERHR Panel, but NTP has actually adopted an elevated concern level for a number of developmental effects without production, let alone consideration, of any of the new data the CERHR Panel indicated would be needed to trigger a higher level of concern. NTP does not clearly acknowledge that it has departed from the recommendations of its own experts, nor does NTP give any persuasive rationale for doing so.

Plausibility of Non-Monotonic Dose Response for Developmental Effects

It appears that NTP gives higher credibility to some of the developmental effects reported in low dose studies with BPA, notwithstanding the absence of any consistent effects at higher doses, based in part on the general observation that “[e]ffects that have biphasic, or non-monotonic dose response curves, are well documented in toxicology, endocrinology, and other scientific disciplines...”⁷ The CERHR Panel stated that it did not afford greater credibility to the developmental effects reported in some low dose studies because of the failure of other researchers to detect “some manifestation of toxicity (e.g., altered weight, histopathology)” at higher BPA doses. Assigning scientific credibility to a non-monotonic dose response relationship in these circumstances, as NTP now appears to be doing, is unprecedented. 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.⁸

NTP has not supported its position by providing any example of another substance for which endocrine effects appear at lower doses and diminish as the dose increases, yet there are no

⁶ CERHR Panel Report at 352.

⁷ NTP Brief at 11.

⁸ CERHR Panel Report at 352.

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observed adverse effects of any kind at higher doses. Without such an example, NTP is at a direct conflict with the CERHR expert panel's report.

Reliability of Food Residue Data Used for Exposure Estimates

NAMPA questions the reliability of much of the residue data reporting BPA in foods upon which the exposure estimates for the general population are predicated. 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,⁹ much of the sampling to date has been done utilizing Gas Chromatography with Mass Spectrometry (GC/MS), an approach prone to interferences from other substances that are naturally present in food products. High Performance Liquid Chromatography with tandem MS (HPLC/MS/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.

Questions concerning the accuracy of BPA residue levels in food that have been attributed to excess monomer from the epoxy lining of containers are underscored by one GC/MS study that found levels "equal to or higher than those found in canned foods" in raw agricultural produce.¹⁰ While it is possible 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 call into question the general presumption utilized in most BPA studies of metal packaged foods that all of the reported BPA is from excess 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.

⁹ CERHR Panel Report at 14.

¹⁰ *Id.*



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NAMPA appreciates this opportunity to comment on the draft NTP Brief for
BPA.

Respectfully submitted,

John M. Rost, Ph.D.
Chair, NAMPA