May 23, 2008

Dr. Barbara Shane
Executive Secretary for the NTP Board of Scientific Counselors
NTP Office of Liaison, Policy and Review
National Institute of Environmental Health and Safety
P.O. Box 12233
MD A3–01
Research Triangle Park, NC 27709

PEOPLE FOR THE ETHICAL TREATMENT OF ANIMALS

HEADQUARTERS
501 FRONT STREET
NORFOLK, VA 23510
TEL 757-622-PETA
FAX 757-622-0457

Via email to: shane@niehs.nih.gov

Dear Dr. Shane,

The following comments on the draft NTP brief on bisphenol A are submitted on behalf of the more than 2 million members and supporters of People for the Ethical Treatment of Animals (PETA). PETA is committed to using the best available science and promotes the acceptance of human-relevant methods for risk assessment.

In response to the draft NTP brief, Senators Dianne Feinstein (D-Calif.) and Charles Schumer (D-N.Y.) introduced the *BPA-Free Kids Act of 2008* to prohibit the use of bisphenol A in children's products. The bill would also require the Centers for Disease Control and Prevention to submit a plan to Congress to study the health effects of bisphenol A exposure in all age groups and in pregnant women. When Senator Feinstein announced the legislation on April 29th, she remarked: "We cannot let the health of our children hang in the balance while we wait for more studies, which could take several years."[1] We applaud this precautionary approach to regulation and human-relevant approach to risk assessment, both of which we consistently promote. This legislation follows Reps. John D. Dingell's (D-Mich.) and Bart Stupack's (D-Mich.) April 15th call for the FDA to reconsider its determination that bisphenol A can be used safely to line infant formula cans.[2] It also follows Canadian Health Minister Tony Clement's April 18th announcement that Canada will ban the use of bisphenol A in polycarbonate baby bottles[3] as well as legislation already introduced in California, Connecticut, and Minnesota.[4]

As we have observed previously, history shows that critical public health measures have been delayed – often for many years if not decades – because of misplaced trust in animal tests. Arsenic, for example, was not classified as carcinogenic following animal studies

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[1] Kinney, J. Senators Introduce Legislation to Ban Bisphenol-A From Children's Products. *Chemical Regulation Reporter*. 2008; 32(18): 425
[2] Rizzuto, P. Dingell, Stupack Call for Review of Safety Of Bisphenol A Following Federal Report. *Chemical Regulation Reporter*. 2008; 32(16): 366
[3] Menyasz, P. Canadian Health Minister Proposes to Ban Bisphenol A in Polycarbonate Baby Bottles. *Chemical Regulation Reporter*. 2008; 32(16): 365
[4] Rizzuto, P. Canadian Action on Bisphenol A Predicted To Spur U.S. States to Restrict Chemical. *Chemical Regulation Reporter*. 2008; 32(17): 393

but was later found to cause lung cancer in smelter workers exposed to arsenic in the air.[5] Similarly, the link between benzene and human leukemia was established in 1928, but more than a dozen subsequent animal studies failed to replicate this effect.[6] More recently, NIEHS scientists were unable to cause reproductive effects in rats by exposing them to mercury even though reproductive effects have long been documented in dental hygienists.[7] Likewise, the weak estrogenicity of bisphenol A has been known for more than 60 years.[8]

Sadly, both the NTP in its draft brief and the NTP-CERHR expert panel in its report on bisphenol A continue to promote seemingly unending, irrelevant animal tests by calling for new studies on mammary and prostate gland and urinary tract development as well as altered puberty. These multi-generation reproductive and developmental studies along with chronic toxicity tests would result in the deaths of thousands of animals but can only delay regulation that is needed now to protect public health. Further, this comes in spite of the NTP-CERHR expert panel's own admission that conducting animal studies is especially problematic for bisphenol A, because "the endpoints of concern are endocrine-mediated and potentially impacted by factors that include phytoestrogen content of the animal feed, extent of bisphenol A exposure from caging or water bottles, and the alleged sensitivity of the animal model to estrogens."[9]

In its draft brief, the NTP acknowledges the resulting controversy over the interpretation of data from existing low dose animal studies. Indeed, the NTP-CERHR expert panel expresses its own frustration:

> While the panel did not necessarily expect a specific effect to display a monotonic dose response…, many members of the panel expected the high dose studies with bisphenol A to detect some manifestation of toxicity… in tissues reported to be affected at low doses even if the study could not replicate the reported low dose effect. *There are several large, robust, well designed studies with multiple dose groups using several strains of rats and mice and none of these detected any adverse reproductive effects at low to moderate dosage levels of BPA administered via the relevant route of human exposures.* [Emphasis added.][10]

In 2002, the European Commission's Scientific Committee on Toxicity, Ecotoxicity and the Environment (CSTEE) questioned whether the uncertainties in the database on the

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[5] Pershagen G, Lung cancer mortality among men living near an arsenic-emitting smelter. *Am J Epidemiol* 1985; 122(4):684-94.
[6] DeMarini, DM, et al. *In: Benchmarks: Alternative Methods in Toxicology*, Mehlman, MA, ed. Princeton Scientific Publishing, Princeton, NJ 1989; 205–216.
[7] May M. Breathtaking research. *Environ Health Perspect* 2000; 108: A168–9.
[8] Scientific Committee on Toxicity, Ecotoxicity and the Environment (CSTEE), European Commission Directorate-General Health and Consumer Protection. *Opinion on the results of the Risk Assessment of: Bisphenol A Human Health Part.* 31th CSTEE plenary meeting. Brussels, May 22, 2002.
[9] Center for the Evaluation of Risks to Human Reproduction (CERHR), National Toxicology Program (NTP), U.S. Department of Health and Human Services. NTP-CERHR Expert Panel Report on the Reproductive and Developmental Toxicity of Bisphenol A. November 26, 2007.
[10] CERHR. 2007.

developmental toxicity of bisphenol A could be resolved by further studies limited to effects of bisphenol A also noting that a number of high quality studies on the reproductive and developmental effects of bisphenol A are already available and do not support low dose effects. Instead, the CSTEE identified a need to first improve our understanding of how factors such as housing, diet, species, strain, study design and issues of species extrapolation influence the outcome of developmental toxicity studies.[11] Most recently, a two-generation study published May 6th in *Toxicological Sciences* in which estrogen-sensitive CD-1 mice were exposed orally to a wide range of doses found that bisphenol A did not cause reproductive or developmental harm.[12] This study, conducted in response to questions raised in a 2003 European Union risk assessment and with oversight by the EU Bisphenol A Steering Group, included the controversial mammary and prostate gland as well as altered puberty endpoints. Additionally, a study using human volunteers showed that bisphenol A is metabolized to a non-toxic form three times faster than it is in rats.[13] Such species differences suggest that regardless of the results in animals, they are unlikely to be relevant to humans.

Nevertheless, both the NTP and the NTP-CERHR expert panel respond by calling for still more animal studies! Surely, this meets Alcoholics Anonymous' definition of insanity as doing the same thing over and over and expecting different results.

The NTP and the NTP-CERHR expert panel find a sufficiently consistent body of literature to suggest that exposure to low doses of bisphenol A during development may cause neural and behavioral alterations related to sexual dimorphisms. This appears to be the only relatively uncontroversial finding, and in this case the NTP-CERHR expert panel recommends further investigation by *in vitro* and human studies. We support this human-relevant approach which is consistent with the BPA-Free Kids Act as well as Tony Clement's announcement that Canada will dedicate funding from its Chemicals Management Plan to conduct "aggressive" research on mothers and newborn children.[14]

Further, banning bisphenol A as a precaution on the basis of this concern will also eliminate any exposures that could result in the more controversial effects noted above for which new animal studies are recommended. Notably, Canadian retailers responded proactively to the bisphenol A controversy by pulling products containing it from their shelves even before the ban was announced indicating that compliance is unlikely to be problematic.

In summary, there is already an extensive body of literature on the toxicity of bisphenol A in animals. While some of the reported low-dose effects are controversial, recently published studies have been unable to reproduce these effects. Neural and behavioral effects in developing animals are less controversial and have led to calls for human

[11] CSTEE. 2002.

[12] Rochelle W. Tyl, et al. Two-Generation Reproductive Toxicity Study of Dietary Bisphenol A (BPA) in CD-1 (Swiss) Mice. *Toxicol Sci.* May 6, 2008. [Epub ahead of print].

[13] Volkel, W et al. Metabolism and kinetics of bisphenol A in humans at low doses following oral administration. *Chem. Res. Toxicol*. 2002. 15: 1281-1287.

[14] Menyasz, P. 2008.

relevant research as well as to legislative efforts to prohibit the use of bisphenol A in childrens's products. Further animal testing is extremely unlikely to provide more actionable information.

Finally, we must note again that it is unclear why the NTP and the NTP-CERHR evaluate substances such as bisphenol A, and previously Prozac and hydroxyurea, which would appear to be the responsibility of the FDA. There have been other instances in which the work of the NTP-CERHR appears to duplicate that of other agencies. In 2001 and 2002, both the NTP and the EPA requested additional animal data on methanol. Even the director of the NIEHS at the time, Dr. Ken Olden, expressed surprise at this overlap in a 2002 Toxicology Forum in Aspen, Colorado and stated that the NTP could have saved taxpayer funds had it known that EPA was conducting similar studies. Such overlap between the NTP-CERHR and other government programs must be avoided, since as it currently stands, the NTP-CERHR is responsible for the continued use of large numbers of animals in clearly duplicative testing.

Also, while the NTP-CERHR claims to value public input into the chemical evaluation process, there is, in fact, no opportunity for meaningful public comment on the most significant findings produced by this process: the critical data needs identified by the expert panel and the new studies recommended as a result. Although comment is accepted on what is called the "draft" expert panel report, this document is only a partial draft that does not include the critical data needs section. Interested parties, such as PETA, can only guess at which new studies might be called for at this step, and when we have commented on draft reports in the past, our comments have not been mentioned in the final document and apparently not considered in its preparation. Critical data needs are not identified until the final expert panel report is released. While comment is again accepted at this time, the report is finished at this point and it is too late for public comment to affect its content. If the NTP-CERHR truly valued public input, it would give interested parties the opportunity to comment on the identified data needs and recommended studies at a point in the process at which such comment could still affect the content of the final report. Instead, the agency provides several "opportunities" for public comment at steps in the process at which such comment can have only minimal effect.

Thank you for your attention to these comments. I may be reached at (757) 622-7382, ext. 8001, or via e-mail at josephm@peta.org.

Sincerely,

Joseph Manuppello
Research Associate
Division of Regulatory Testing