ENVIRONMENTAL WORKING GROUP

1436 U Street NW, Suite
100 Washington, DC 20009
T: 202.667.6982
F: 202.232.2592

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Dr. Barbara Shane
Executive Secretary for the NTP BSC
NTP Office of Liaison, Policy and REVIEW
NIEHS
P.O. Box 12233
Research Triangle Park, NC 27709

Re: Comments on the Draft National Toxicology Program Brief on Bisphenol A

Dear Dr. Shane:

We are writing to provide comments on the National Toxicology Program (NTP) draft brief on the developmental and reproductive risks posed by Bisphenol A (BPA) exposure (NTP 2008). This toxic plastics chemical contaminates canned food, infant formula and the blood of 93% of Americans (NTP 2008, EWG 2007, Biles 1997, Calafat 2008), and is shown in more than 100 peer-reviewed studies to be linked to a diverse range of potential health risks at low doses of exposure, including brain and behavioral changes, preneoplastic lesions in the prostate and breast, early onset of puberty, altered reproductive tract development and insulin resistance. (Della Seta 2006, Durando 2007, Howdeshell 1999, Timms 2005, Alonso-Magdalena 2006). The NTP assessment could not be more timely in light of Canada's recent declaration of BPA as a hazardous chemical and actions to reduce exposure sources for infants, and resulting announcements by companies including Wal-Mart and Playtex that they will phase-out polycarbonate bottles in response to the public's concern and government inaction.

EWG applauds NTP's rigorous assessment and concurs with the conclusion that BPA poses concerns for human reproduction and development. We particularly commend NTP for repairing many of the major scientific flaws in the earlier findings from the Center for the Evaluation of Risks to Human Reproduction (CERHR) expert panel (CERHR 2007). This panel was plagued by concerns over conflicts of interest, raised by members of Congress, when it was discovered that the panel was run by a consulting firm, subsequently fired, that worked with BPA manufacturers.

Although we commend the NTP's rigorous assessment, we believe that NTP would be justified in raising the weight of evidence assessment for developmental toxicity at low doses, and the level of concern for effects in fetuses, infants and children. NTP's draft document bases the weight of evidence for developmental toxicity on the findings of high-dose toxicity tests ($\geq$50 mg/kg-d), designating evidence from "low" dose studies as "limited" for developmental toxicity. NTP cites 12 "low" dose studies showing developmental toxicity, and categorizes these as indicating "limited evidence of developmental toxicity." The rationale provided is that low-dose studies examine non-traditional endpoints, which complicates interpretation of results, and that they often do not include higher dosing ranges to clarify the dose-response relationship (NTP 2008).

We urge NTP to increase their weight of the evidence assessment by acknowledging that the 12 studies cited join a much larger body of literature that reports consistent indications of

developmental impacts at low doses. These include studies supporting impacts to breast and prostate, timing of puberty, and brain and behavioral changes, as well as those reporting insulin resistance, decreased sperm count, and chromosomal abnormalities (CERHR 2007, Alonso-Magdalena 2006, vom Saal 1998, Hunt 2003, Susiarjo 2007).

vom Saal and Hughes (2005) reviewed BPA studies through December 2004, and noted 31 studies reporting reproductive and developmental effects at doses < 50 ug/kg-day. Many more such studies have been published over the past 3.5 years. Notably, vom Saal and Hughes report that 90% of government-supported low-dose studies find adverse effects, a major difference when compared with industry-funded studies, where none have found low-dose adverse effects (vom Saal 2005).

Furthermore, CERHR guidance allows NTP to designate exposures to be of "serious concern" when, "human exposures are similar to doses that clearly cause adverse developmental or reproductive effects in laboratory animals" (CERHR 2008). The 12 studies finding low-dose toxicity that NTP cites in their draft document clearly fall within the range of daily intake estimates for children, particularly within their first year of life. Most of these studies administer BPA via oral exposure, making intake levels easily comparable to oral intake by children.

NTP intake estimates:	Daily exposures (µg/kg bodyweight per day)	Citation
Daily intake for: formula-fed infants, breastfed infants, infants 6 to 12 months, and children up to 6 years	 1 to 11 0.2 to 1 1.65 to 13 0.043 to 14.7	NTP 2008
Toxicity studies:	**Daily exposures (µg/kg bodyweight per day)**	**Citation**
neural and behavioral alterations in rats and mice	≥10	Palanza 2002*, Laviola 2005*, Gioiosa 2007*, Ceccarelli 2007*, Ryan 2006*, Della Seta 2006*, Negishi 2004*
preneoplastic lesions in the prostate and mammary gland in rats	2.5 to 10	Ho 2006, Durando 2007, Murray 2007
altered prostate and urinary tract development in mice	10	Timms 2005*
early onset of puberty in female mice	2.4 to 200	Ryan 2006*, Howdeshell 1999*

* oral administration.

These effects are of critical importance due to unacceptably high rates of breast and prostate cancer, and behavioral disorders in the American population. These disorders burden the affected individuals, their families, and contribute to increased social costs of education and medical care. NTP notes that the breast cell changes noted in experimental studies correlate with a dramatic increase in breast cancer risk for women—a 1.5 to 10-fold increase in the risk of invasive breast cancer (NTP 2008, citing Fitzgibbons 1998).

Furthermore, the falling age of puberty in children has been noted for decades, and is associated with a variety of serious physical and social consequences for youth, both as they develop and later in life (Steingraber 2007).

NTP's draft document dramatically strengthens the conclusion of CERHR's expert panel in three key ways. EWG wholly concurs with NTP's determinations, which are firmly supported by available science:

- NTP finds studies in which BPA was administered by non-oral routes of administration to be useful in its evaluation of BPA toxicity to the fetus and neonate.

- NTP notes that results from studies in which DMSO was used as the vehicle for BPA should be included in its evaluation.

- NTP lays out a clear rationale for the discrepancies between low-dose studies and the major industry-funded studies that did not detect effects of BPA exposure. These include the fact that several studies of age of puberty did not use the most sensitive indicator of puberty (the number of days from vaginal opening to first estrus), and studies finding no breast tissue effects failed to raise females through adulthood, and did not examine breast tissue for subtle indicators of effect.

Four key areas in which the NTP assessment could be improved include the following:

- NTP should increase their weight of evidence from low-dose studies from "limited evidence" to "some evidence" or "clear evidence."

- NTP should increase the level of concern for the fetus, infant and child to "concern" or "serious concern".

- NTP should consider the use of positive controls when judging the utility of a study's results. Particularly the conclusions drawn from the Tyl et al. study (2006) should be qualified in light of this shortcoming. A study that uses an estrogen insensitive animal model and doesn't include positive controls is fundamentally flawed, and the results from this study must hold less weight than more carefully controlled studies.

- NTP should improve its exposure assessment for formula fed infants, which currently underestimates exposure for some babies.

With respect to the last point raised, available data show that infants' exposures to BPA are often higher than what NTP has assumed. NTP recognizes formula-fed infants as the most highly exposed group among the general population, yet still may understate their exposures.

The vast majority of American infants are fed formula during their first six months of life, and for a substantial number of these infants, formula often makes up 100% of their diet for the first 6 months of life. This is especially worrisome given the number of animal studies that show that infancy is a particularly vulnerable time for BPA toxicity. However, NTP's exposure assessment underestimates the potential exposure of BPA canned infant formula for some infants.

NTP bases their exposure assessment on FDA's tests of concentrated liquid canned infant formula performed in 1997 (Biles 1997). These tests found levels of BPA ranging from 0.1 to 13.2 µg/L. Because FDA tested concentrated formula, NTP divided the highest concentration found in FDA samples (13.2 µg/L) by 2 to account for suggested dilution with water to come up with a maximum concentration detected of 6.6 µg/L.

Although FDA tested concentrated canned liquid formula, there is no reason to believe that leaching would be any different with ready-to-eat formula, which is not diluted prior to serving. It would be more accurate to base an exposure assessment for formula-fed infants on the subpopulation within this group with the highest exposure, namely those babies that are fed ready-to-eat formula. Ready-to-eat formula is the type administered in hospitals and recommended for medically vulnerable infants. USDA estimated that in 2000, 11 percent of formula-fed infants receive ready-to-feed formula (USDA 2004).

Babies fed ready-to-eat formula could potentially be exposed to BPA levels as high as 13.2 µg/L in formula, thereby doubling NTP's estimated daily intake from liquid formula. It should also be noted that EWG's independent tests of liquid infant formula found a maximum concentration of 17 µg/L (EWG 2007). In addition, NTP's intake estimate of 1 µg/kg-day does not include any potential for leaching from polycarbonate baby bottles, which contributes a large fraction of the intake estimates for babies fed powdered formula drawn from the European Union safety assessment (which estimates 2.3 µg/kg-day from powdered formula and 8.7 µg/kg-day from the bottles). Thus NTP should estimate that a baby fed ready-to-feed formula in a polycarbonate bottle would receive a similar intake to a baby fed powdered formula. It is worth noting that all intake estimates for babies are near levels found toxic in low-dose developmental toxicity studies.

BPA is a ubiquitous human pollutant, is widely used in a range of consumer products, and is toxic at very low doses. NTP's draft document is a major improvement from previous conclusions of the CERHR expert panel. We urge NTP to carefully consider the breadth of evidence from low-dose developmental toxicity tests in light of intake estimates for children, the most vulnerable population. NTP's quick work to finalize this document will allow other government agencies to move forward in strengthening public health standards for this chemical.

Sincerely,

[Signed]

Sonya Lunder MPH
Senior Analyst
Environmental Working Group
1436 U Street, Suite 100, NW
Washington DC 20009

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