ENVIRONMENTAL WORKING GROUP

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Martin Philbert, PhD
BPA Subcommittee Chair
c/o Office of Science and Health Coordination
Office of the Commissioner (HF-33)
Food and Drug Administration
Rockville, MD 20857

Re: Comments on the FDA's draft assessment of Bisphenol A (BPA)

Dear Dr. Philbert:

Environmental Working Group is writing to express strong concerns regarding FDA's assessment of the toxic food and infant formula contaminant bisphenol A (BPA) (Draft Assessment of Bisphenol A For Use in Food Contact Applications, August 14, 2008). FDA's conclusion that current standards are adequate to protect public health from BPA's hormone-disrupting effects is at odds with available science on BPA's potential to harm infants and with conclusions drawn by other public health agencies and BPA experts:

- FDA finds no reason to tighten current BPA safety standards even though the National Toxicology Program found concern for permanent changes to brain and reproductive system (NTP 2008a), and Health Canada instituted tight restrictions earlier this year, saying "We have immediately taken action on bisphenol A, because we believe it is our responsibility to ensure families, Canadians and our environment are not exposed to a potentially harmful chemical" (Health Canada 2008a).

- FDA rejects 12 key studies that the National Toxicology Program determined demonstrate that BPA is harmful at low doses. FDA justifies these exclusions with criteria applied inconsistently to favor industry studies and with hand-waving generalizations not backed by fact.

- FDA hinges its conclusions of BPA safety on industry studies that fail to measure so many BPA health endpoints that "what you're left with is not much," according to the National Institute of Environmental Health Services' scientific program administrator (Favole 2008).

- FDA has issued this affirmation of BPA safety even as infant formula manufacturers move to find alternatives, including PBM, the maker of Wal-Mart, Target and other store-brand formulas: "... the possibility that BPA may pose adverse health risks to the infants and children who are fed our formula was more than sufficient to begin the process of eliminating BPA from our infant formula packaging."

With its current flawed assessment, FDA is far from the health-protective positions adopted by other health agencies and independent BPA experts who have taken a serious look at the many studies that demonstrate BPA's potential to harm health at current levels of exposure in the population. We call on FDA to act on the science and to set BPA standards that protect the health of infants and others who are most vulnerable to its effects.

Background

Bisphenol A is (BPA) a high production volume chemical that is found in a number of consumer products including metal food and infant formula cans, polycarbonate baby bottles, and reusable plastic water bottles. The Centers for Disease Control and Prevention (CDC) have detected BPA in the urine of 93% of 2,517 people that they tested, suggesting daily exposure to the chemical (Calafat 2008). BPA has also been found in follicular fluid, umbilical cord blood and breast milk, raising concerns about adverse health effects in children from the earliest stages of pregnancy (Ikezuki 2002, Kuroto-Niwa 2006, Schonfelder 2002). However the most intense exposures are to formula-fed babies. FDA estimates that formula-fed infants ingest 12.5 times more BPA than adults per pound bodyweight. EWG calculates that high-end infant exposures are double FDA's estimate (EWG 2007).

FDA's uses inconsistent and illogical criteria to reject these studies, notably the 12 studies NTP highlights as evidence of 'low dose' toxicity (NTP 2008a). As a result, the safety assessment is pinned on underpowered and insensitive studies funded by BPA producers with a vested interest in proving their chemical is safe (Tyl 2002, Tyl 2008, Ema 2001). FDA estimates that formula-fed infants have the most intense exposure to BPA, with daily ingestion 12.5 times higher than adults, largely through avoidable sources. FDA claims a 2,000-fold margin of safety for formula-fed infants, but uses a "No Adverse Effect Level" that is hundred's of times higher than doses found toxic in the most sensitive academic studies. Even worse, FDA estimates that daily BPA ingestion by formula-fed babies is perilously close to doses found to cause pre-cancerous lesions in breast and prostate issue and permanent adverse effects on brain and behavior.

In response to the growing number of studies linking low dose BPA exposure to adverse health effects and evidence of widespread exposure to BPA among the U.S. population, a group of 38 BPA researchers systematically reviewed over 700 scientific papers and published a series of review articles in 2007. These scientists concluded that "much evidence suggests that these adverse effects are occurring in animals within the range of exposure to BPA of the typical human living in a developed country" (vom Saal 2007).

FDA's findings stand in contrast to conclusions of the NIH's National Toxicology Program's (NTP) recently completed monograph assessing the developmental and reproductive effects of BPA. NTP found "some concern for effects on the brain, behavior, and prostate gland in fetuses, infants, and children at current human

exposures to bisphenol A" (NTP 2008a). In a further explanation of these findings, NTP notes on their website "...there is limited evidence of developmental changes occurring in some animal studies at doses that are experienced by humans. It is uncertain if similar changes would occur in humans, but the possibility of adverse health effects cannot be dismissed" (NTP 2008b).

The Canadian government has also listed BPA as a "chemical of concern" prompting actions to reduce BPA exposure among the most vulnerable populations. These include a proposed a ban on polycarbonate baby bottles and more stringent standards to decrease BPA leaching from metal cans into liquid formula (Health Canada 2008b). Several large retailers including Wal-Mart and Babies"R"Us/ Toys"R"Us announced that they were phasing out baby bottles and other baby feeding products that were made with BPA from their stores (Toys"R"Us 2008, Mui 2008). In response to a Congressional inquiry, 4 leading infant formula companies (makers of Nestlé, Enfamil, Isomil and PBM sold under store labels) indicated that they are actively seeking replacements to BPA in the lining of liquid formula cans (House Energy and Commerce Committee 2008).

U.S. legislators have responded to these recent developments by introducing bills in both the House of Representatives and the Senate this year; the House bill (HR 6228) seeks to ban BPA from food packaging and the Senate bill (SB 1713) would ban the use of BPA in children's products. Despite mounting scientific evidence that BPA is toxic at current levels of exposure and increasing concerns among consumers, FDA maintains that BPA is safe as used and offers no guidance to reduce infant exposures or address uncertainties that lead the Agency to ignore indications of low dose toxicity (FDA 2008a).

Formula-fed infants stand to face the greatest harm of all if the conclusions of FDA's draft assessment are not changed. These babies likely face higher exposures than any other segment of the population. FDA estimates that formula-fed infants ingest 12.5 times more BPA than adults per pound of body weight, but EWG's studies of formula contamination show that some infants face exposures twice what FDA has estimated.

In its draft assessment, FDA rejects findings from 12 studies that the National Toxicology Program (NTP) highlights as evidence of "low dose" toxicity (NTP 2008a). As a result the safety assessment is pinned on underpowered and insensitive studies funded by BPA producers with a vested interest in proving their chemical is safe (Tyl 2007, Tyl 2008, Ema 2001). As a result, in this draft assessment FDA calculates a substantial margin of safety for formula-fed infants, but uses a "No Adverse Effect Level" for BPA that is hundreds of times higher than doses found toxic in the most sensitive academic studies. Even as FDA concludes that current BPA exposures pose no risk to health, they present estimates of daily BPA ingestion by formula-fed babies that fall within a margin of only 4 from doses found to cause permanent changes to brain and behavior (Palanza 2002, Laviola 2005, Gioiosa 2007).

Below, we detail key short-comings with FDA's draft assessment, and the magnitude of risk for infants the most highly-exposed group:

I. FDA inappropriately focuses on industry-funded "guideline" studies:
Many researchers and government agencies have noted a clear conflict between the handful of large, industry-funded studies using traditional methods which find no adverse effects of low level BPA exposure, and the dozens of academic studies focusing on more specific impacts on the chemical at key periods of development (vom Saal and Hughes 2005, NTP 2008a). FDA's risk assessment bases safety calculations solely on the large, industry-funded studies. The chief rationale for this decision is FDA's inappropriate weighting of studies adhering to so-called "Good Laboratory Practices" (GLP). GLP is required to ensure the data generated by industry to substantiate the safety of drugs and food additives has been collected in a "valid and accurate manner" (FDA 2000).

As such, GLP is a useful but bureaucratic mechanism designed to prevent intentional fraud among laboratories with a vested financial interest. GLP is necessary when there is a financial incentive for scientists to find a drug or chemical additive to be "safe." GLP procedures are unnecessary for research where there is no financial incentive to falsify findings and where replication by other laboratories is the accepted means of validation as is the case for academic research (De Roos 2005). GLP ensures that particular note-taking procedures are followed, for instance, but it prohibit the innovative, sensitive, state-of-the-art study designs now used to investigate low-dose effects of hormone-disrupting chemicals like BPA. For all these reasons, academic studies, even those funded by government agencies, do not typically follow GLP guidance.

FDA test guidelines for reproductive and developmental toxicity are not as specific as academic studies for subtle effects on the reproductive and neurological system, which can lead to studies that underestimate chemical health risks. Therefore studies that meet GLP and toxicity guidelines and still miss toxicity endpoints and adverse health effects. In the case of FDA's assessment of BPA, the reliance on GLP studies excludes information gathered from academic scientists who find sensitive effects to the reproductive system and behavior.

It should come as no surprise that GLP studies can miss critical health effects. A recent case in point is the drug Vioxx: this drug was given approval for use by the FDA after the pharmaceutical company, Merck, provided evidence that more than 5,000 study subjects benefited from it's use. Merck scientists published a study in JAMA in 1999 (Langman 1999) in which they provided data from 8 well-designed studies that supported the safety and efficacy of this medication. Within a few years however, the drug was pulled off the market because these studies did not detect a potentially devastating side effect of the drug, namely an increase in cardiovascular events.

By failing to address the concerns raised by non-GLP studies, FDA essentially asserts that record-keeping and adherence to process is more important than science, a

reckless decision that could put American infants at risk.

FDA's treatment of academic and guideline studies also deviates from accepted practice in the Agency's own pharmaceutical program. In drug approval, GLP studies are required to assure safety, but FDA has the authority and indeed the public health mandate to consider any valid evidence that an exposure is harmful to human health. For example FDA issued immediate guidance to patients and initiated changes to drug labeling when an academic article suggested problems with the drug Procrit in patients with chronic kidney disease (FDA 2008b). This non-guideline study was appropriately utilized to refine treatment recommendations in advance of data from carefully controlled trials. Unlike FDA's health-protective decision on Procrit, however, FDA's food safety division is rejecting findings from numerous studies indicating permanent harm to the nervous and reproductive systems.

BPA enters the body at similar concentrations to pharmaceutical drugs, and dozens of studies suggest potential harm to the developing fetus and young child at these exposure levels. However, while pharmaceuticals are approved for the market by FDA and prescribed by doctors only after a careful consideration of risks and benefits, BPA exposure is involuntary and offers no tangible health benefit to exposed individuals. In fact, the most worrisome exposures to infants--the highest risk group--are easily avoidable. Simply substituting powdered formula for canned liquid formula, and using a non-polycarbonate bottle can dramatically reduce exposures for formula-fed babies.

Considering the weight of the evidence against BPA, FDA's assurances of its safety are misleading and could harm public health. While FDA assures concerned parents that BPA is safe, an ever-growing body of scientific data demonstrate its permanent adverse effects on the brain and reproductive system at low doses, and formula companies and bottle-makers explore alternatives to its use.

II. Faulty industry study designs ensure no low-dose effects are found

FDA bases their safety assessment on 3 industry-funded studies (Tyl 2002, Tyl 2008, Ema 2001) that were chosen because they use traditional test methods, include many animals and dose groups, and follow GLP guidelines. However these studies have critical methodological flaws that make them inappropriate for use in a safety assessment of BPA toxicity. These include lack of validation by a suitable positive control and failure to study the most sensitive targets of the chemical. By relying on these 3 studies in their risk assessment, and failing to include evidence of harm from studies examining different endpoints, FDA came to a decision that is not fully protective of children's health and essentially allows risky exposures to continue among our most vulnerable populations.

Industry studies lack validation from positive controls

A study that is aimed at detecting low dose effects of endocrine disruptors needs to be designed in a way that minimizes the impacts of external factors such as phytoestrogens in animal feed, BPA in cage materials, and other sources of hormone disruption that may impact the study. In addition, some animal strains are less

sensitive to endocrine disruptors. To assure that studies have the power to detect low dose effects, well-designed experiments often include a group of animals known as positive controls, which are given a known hormone disruptor and monitored for effects to guarantee that the study design is working.

The 3 industry studies that FDA uses in their risk assessment do not find any low dose effects, but these findings are undermined by inadequate validation by positive controls. Two of the 3 industry studies do not use any positive control (Tyl 2002 and Ema 2001). The 3rd study (Tyl 2008) used an unreasonably large dose of 17ß Estradiol, calling into question the study's ability to detect low dose effects. In fact, NTP scientists commented on this shortcoming, noting "[The] experimental model used in this study did not appear to be sensitive in detecting estrogenic effects at low doses" (NTP 2008a). Yet when facing conflicting findings between low dose academic studies and high-dose industry studies, FDA hinges their findings of BPA safety on industry's faulty studies.

This same study using high doses of estradiol in the positive control (Tyl 2008) also relied on feed known to have a high phytoestrogen content (Purina 5002) (Heindel 2008, NTP 2008a). FDA's own internal reviewer noted the following about the feed in this study, "The diet, PM1 5002, used in this study has been characterized as a high phytoestrogen diet. This might reduce the sensitivity of the study for low-dose effects of BPA" (FDA 2007). These issues raise serious concerns about whether any of the 3 studies FDA chose for drawing its conclusions on BPA safety are able to detect low dose effects of BPA.

GLP studies fail to explore most sensitive impacts of BPA

NTP expresses concern about the safety of current infant exposures based on evidence of precancerous changes to the breast and prostate when exposure occurs in-utero or during early life (NTP 2008a). NTP bases their conclusion on 12 low dose studies which include endpoint that are not fully explored in the 3 guideline studies FDA relies upon (Palanza 2002, Laviola 2005, Gioiosa 2007, Ceccarelli 2007, Ryan 2006, Della Seta 2006, Negishi 2004, Ho 2006, Durando 2007, Murray 2007, Timms 2005, Ryan 2006, Howdeshell 1999).

FDA itself notes that precancerous prostate effects "would not be detected in standard assays" (FDA 2008a). These include high-grade prostate lesions (Ho 2006) and cytokeratin 10 production which is an early indicator of changes leading to estrogen-induced squamous metaplasia (Ogura 2007). Both are precancerous effects in the prostate. NTP's 1982 cancer study did not find prostate cancer, but failed to include pre-natal dosing and used rodents that are not susceptible to prostate cancer (NTP 2008, NTP 1982).

Low-dose BPA studies also find precancerous changes to breast cells. NTP notes key studies finding precancerous breast lesions (Durando 2007, Murray 2007) and changes to cell structure (Moral 2008) which are risk factors for invasive breast cancer in women (NTP 2008c). These changes would not have been detected in the 3 industry studies used in the safety assessment. One industry study (Tyl 2002) did not examine

mammary tissue, and the other 2 (Tyl 2008, Ema 2001) didn't collect mammary tissue in a way to detect precancerous changes by not preparing whole mounts of breast tissue (NTP 2008a). Finally, although the study animals did not have elevated rates of cancer, but they were sacrificed post-weaning (at 1 year) which is not sufficiently old to expect tumor formation (NTP 2008a) Finally the large, guideline cancer study by NTP (1982) did not administer BPA *in-utero* and is therefore useless for evaluating breast and prostate cancer concerns (NTP 1982).

The guideline studies also fail to conclusively disprove concerns of early puberty in females. There are conflicting findings of timing of puberty with several positive findings in female mice and negative findings in rats (NTP 2008a). FDA notes that the guideline Tyl study (2008), which FDA considers to be of the highest utility, observed an acceleration of puberty in the only dose group studied. "[T]he day of acquisition was statistically significant accelerated when adjusted by body weight in the highest dose administered (3500 ppm) on PND 21 for F1 (only animals measured). " (FDA 2008a)

The final key concern raised by NTP and their CERHR Expert Panel was the effect of BPA on brain and behavior. Two of the guideline studies do not assess brain and behavior (Tyl 2002, Tyl 2008). The third (Ema 2001) partially assessed these effects, but not the specific impacts highlighted by NTP (NTP 2008c). In particular Ema does not thoroughly evaluate the loss of sexually dimorphic behaviors, a critical concern for NTP (NTP 2008a).

FDA discounts the utility of brain and behavior effects by calling for "validated" studies but then noting that protocols for validated studies do not exist. FDA states that the data collectively "appear to suggest that developmental BPA treatment can cause alterations in brain development and behavior." FDA calls for more replication of these findings "...more research, using validated studies with feeding protocols modeling human exposure are necessary prior to establishing a NOAEL for this endpoint for use in regulatory safety assessments." (FDA 2008a) However then admit that the endpoints evaluated are "an emerging area in developmental neurotoxicity for which validated protocols are currently unavailable" (FDA 2008a). This wait–indefinitely-and-see approach is completely out of step with the urgency posed by current infant exposures that are uncomfortably similar to toxic doses in a variety of well-performed neurological studies.

III. FDA uses illogical and inconsistent criteria for dismissing findings from low dose academic studies

FDA dismisses all of the evidence from academic publications showing harm at low doses, relying on a wide variety of justifications. Many of FDA's study critiques concern the small sample size and limited dose groups used in academic studies. But these studies find statistically significant effects, and FDA overlooks the fact that a small sample size would make the studies *less* likely to detect statistically significant effects, not the reverse. Other bogus criteria lead the Agency to downplay findings from studies using subcutaneous exposure and dismiss findings from brain and

behavior studies even though contradictory findings do not exist by stating, in essence, that contradictory findings may at some point be published.

Route of administration: FDA notes in their assessment that subcutaneous dosing of lab animals with BPA is an "inappropriate route of exposure" and discounts data from studies that use this route of administration (FDA 2008a). In doing so, FDA disregards data from several well-conducted studies linking low dose BPA exposure to precancerous lesions in prostate and mammary gland tissue based on subcutaneous route of administration (Ho 2006, Ogura 2007, Durando 2007, Murray 2007). In these studies, researchers were looking at the effects of either early life BPA exposure on adult animals or prenatal exposure on offspring. In both of these situations, internal doses are more important than actual route of administration, but seldom measured in any studies of BPA toxicity.

This is confirmed by 2 studies finding that non-oral routes of BPA administration are completely valid in assessing potential health effects (Taylor 2008, Domoradzki 2004). Domoranzki observed peak BPA concentrations in 4-day old rat pups to be 160 and 2000 times higher than adults treated with the same doses (Domoradzki 2004). Taylor (2008) administered BPA to neonatal mice by both oral and subcutaneous routes and found no significant difference in plasma levels of unconjugated BPA, leading study authors to conclude "the large numbers of BPA studies that used non-oral administration at very low doses during the neonatal period should not be dismissed by scientists or the regulatory community based on route of administration".

NTP's assessment of BPA metabolism concurred with the above findings, concluding: "Taken together these data indicate that, compared to adults at a give dose, neonatal rats (and presumably mice) metabolize bisphenol A more slowly and suggest that differences in circulating levels of free bisphenol A arising from oral and subcutaneous routes of administration as a result of "first-pass metabolism" are reduced in fetal or infant animals compared to adults" (NTP 2008a). They found studies using a subcutaneous route of administration to be acceptable in their assessment (NTP 2008a). FDA's decision to disregard important studies that used a subcutaneous route of administration is not justified by the science nor is it supported by NTP.

***Short-term exposure studies*:** FDA disregards studies showing deleterious effects of short-term BPA exposure stating, "In the presence of continuous exposure, changes or adaptations may occur that impact the potential toxicity of the substance" (FDA 2008a). There is no evidence for such an adaptation. FDA's exclusion of these studies demonstrating BPA toxicity is based on their reliance on a hand-waving theory not supported by any published science.

Few dose groups in academic studies: Similarly FDA places inappropriate weight on discounting results from studies of few dose groups compared to larger guideline or GLP studies. In this regard FDA's focus on data enabling dose-response assessments blinds them to concerns raised by many high quality studies especially those that capture sensitive impacts that would not be noted in GLP studies. For example

prostatic intraepithelial neoplasia (PIN) lesions detected in 100% of animals exposed during 3 days of development is a powerful, statistically significant finding not easily dismissed solely by the use of a single dose group in Ho and Prins' 2006 study. The Timms study (2005) administering low doses of BPA (10 ug/kg-d) via oral exposures to neonatal mice for 6 days, found significant changes in prostate value, ducts, and changes to the urethra. FDA was called, "extremely interesting and unique," but discounts the study utility as "very limited due to the use of only one dose" (FDA 2008a). But this single dose represents an amount of BPA that is toxic to test animals, and therefore should be considered in assessments of BPA's potential risks to humans.

***Weight of evidence assessment for brain and behavior*:** In addition to the above criteria used to dismiss findings of reproductive toxicity, FDA's assessment of brain and behavior effects dismisses evidence based on FDA's interpretation that the investigators had 'anthropomorphized" animal behaviors, by using terms of "impulsivity, stress and anxiety" to describe behavioral changes (FDA 2008d). This is a baseless criticism not raised by any independent scientist or any of the other government agencies in the U.S. or abroad who have evaluated the same literature. Permanent changes in behavior that lead to measurable changes in activity levels in novel environments such as those reported by Adriani (2003) were considered reliable measures of harm for regulatory use by Denmark, Sweden, and Norway in their risk assessment (EU 2008), and Health Canada's risk assessment (Health Canada 2008b).

IV. New findings of low dose toxicity are being published at a rapid pace

Two important studies on BPA have been published in the last several weeks; these two studies are especially significant because one uses adult human fat cells to monitor BPA effects and the other uses a primate model. In the first of these studies, researcher exposed human fat cells to BPA and measured the amount of adinopectin that is released from fat cells; adinopectin is a hormone that augments insulin sensitivity and is thought to help prevent the development of metabolic syndrome (Hugo 2008). The researchers found that when human fat cells were exposed to BPA concentrations as low as 0.1 nM, they released significantly less adinopectin; this effect peaked at a BPA concentration of 1 nm, when exposure resulted in a 40% reduction in adinopectin release. This study also showed that the fat cells had a non-monotonic response to BPA, where higher concentrations of BPA (10nM and 100nM) didn't result in a reduction of adinopectin release.

Metabolic syndrome is characterized by a number of different conditions, including glucose intolerance, high lipid levels, and obesity. It is a major risk factor for diabetes and heart disease and currently affects millions of Americans. This study confirms findings from an earlier rodent study that found that BPA exposure at environmentally relevant doses is associated with insulin resistance and obesity (Alonso-Magdalena 2006). The findings from this study suggest that BPA exposure may have a more significant role than previously thought in a host of common medical conditions like obesity, diabetes, and cardiovascular disease.

In the second study, researchers exposed adult female ovariectomized monkeys to 28 days of BPA at a dose of 50 ug/kg/day, the current EPA reference dose (Leranth 2008a). They studied the effects of BPA exposure on estrogen induced synapse formation in the brains of these animals and found that the animals that were exposed to BPA had a significant decrease in synapse formation, in some cases by more than 50%. Proper synaptic formation is thought to be critical in preventing conditions such as mental retardation, schizophrenia, and dementia. This study confirms earlier finding from rodent studies that reported inhibition of synaptic formation in animals with early life exposure to BPA (MacLusky 2005, Leranth 2008b).

These two studies add to the growing body of science that demonstrates BPA's biological activity at extremely low concentrations and it ability to exert adverse effects on a variety of organ systems. The BPA literature shows that exposure at very low levels results in adverse health effects in rodent models, human cellular systems, and primate models.

V. FDA's exposure assessment underestimates exposures among formula-fed infants

FDA's so called "conservative" exposure assessment for infants significantly underestimates exposures from BPA contamination of infant formula. FDA claims to have "considered the maximum exposure for the full exposure period," (FDA 2008a) yet an analysis of formula concentrations shows that many infants are exposed to BPA above the levels calculated by FDA.

FDA bases their assessment on data from their 1997 study of 14 samples of liquid formula; the researchers found BPA at concentrations ranging from 0.1 to 13.2 ppb in these samples, with an average of 5 ppb (Biles 2007). But in FDA's draft assessment of BPA safety, the Agency assumes BPA concentrations in formula to be just 2.5 ppb, dividing the average concentration by 2 under the assumption that all liquid formula is diluted 1:1 with water.

Although FDA tested concentrated canned liquid infant formula, there is no reason to believe that leaching would be different with ready-to-eat formula, which is not diluted prior to serving. It would be critical 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 11% of formula-fed infants received ready-to-eat formula (USDA 2004).

Given that FDA tested only 14 formula samples, and both EWG (2007) and Health Canada (2008) have detected maximum concentrations of 17 ppb in similarly small studies, FDA should assess exposures the full range of measured BPA levels and upper-bound levels identified through statistical models. Substituting the value of 17 ppb for 2.5 ppb in FDA's exposure calculation roughly doubles intake estimates for 0 to 2 month old babies.

FDA focuses on BPA exposures for 1 to 2 month old infants, but some infants are exposed to high doses for the entire first 6 months of life, when formula typically makes up 100% of an infant's diet. EWG recommends that FDA consider high-end exposures to BPA in ready-to-eat formula. FDA should adopt probabilistic (e.g., Monte Carlo style) exposure assessment methods so that the full range of infant exposures can be estimated, to allow for assessment of BPA exposures at high-end exposures, such as the 99.9th percentile of exposure, as is typical for other toxic chemicals, like pesticides in food.

Conclusion: Immediate action is warranted to reduce infant exposures

Available science and recent public health assessments do not support FDA's conclusions on the strength of the low dose literature for BPA and effects on the nervous and reproductive system. FDA has failed to utilize this rich body of research which collectively suggests to us and to the NTP, concern for a variety of permanent effects resulting from short-term exposures in the microgram/kilogram bodyweight range. FDA fails to use this evidence to reexamine short-comings in the guideline (GLP) studies and rethink their hasty conclusion about the safety of current exposures.

FDA's draft assessment defines safe as "reasonable certainty in the minds of competent scientists that the substance is not harmful under the intended conditions of use" (FDA 2008a). However, their assessment of the evidence stands in clear conflict with NTP's conclusions, and clearly fails to support a reasonable certainty of no harm. In contrast to the pharmaceutical program, in which all evidence of harm is considered relevant to approval of a new drug, FDA ignores numerous studies indicating overlap between infant intake and toxic doses to juvenile animals.

The data on neurological and reproductive impacts collectively suggest that immediate action is needed to reduce BPA exposures for formula-fed babies. Given that FDA's weak exposure estimates predict formula-fed babies will have exposures nearing those found toxic in a variety of studies, FDA should strengthen safety standards for BPA and immediately offer parents clear guidance about ways to reduce their infants' exposures. This guidance should include recommendations to switch from liquid to powdered formula, and to avoid bottles made of polycarbonate. These are immediate and affordable options that will dramatically lower infant exposures this toxic hormone-disrupting chemical.

Sincerely,

[signed]
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and

[signed]
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