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VIA CERTIFIED MAIL

Division of Dockets Management
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, MD 20852

CITIZEN PETITION

The Natural Resources Defense Council (NRDC) submits this petition under section 409 of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 348, and pursuant to 21 C.F.R. §§ 10.30, 171.130, and 189.1. Through this petition, NRDC requests that the Commissioner of the Food and Drug Administration establish a regulation prohibiting the use of BPA (4-4'-isopropylidenediphenol, CAS Reg. No. 80-05-7) in human food and revoke all regulations permitting the use of a food additive that results in BPA becoming a component of food. BPA causes serious adverse health effects, and the FDA's continued approval of BPA for use in food packaging violates federal law.

I. BACKGROUND

BPA is an endocrine disrupting chemical used in many consumer products, including hard, clear plastics called polycarbonate and the resin lining of food and beverage cans. FDA's approval of BPA for use in food packaging results in significant human exposure. In animal

studies, BPA exposure has been associated with a wide range of adverse effects, including reproductive defects, chromosomal damage, nervous system harm, increased rates of breast and prostate cancer, and metabolic changes including obesity and insulin resistance – a condition that commonly precedes the development of diabetes.

These adverse effects in animal studies have been found to occur at levels of exposure occurring in the general public. Biomonitoring done by the U.S. Centers for Disease Control and Prevention (CDC) has revealed that there is widespread human exposure to BPA. The CDC tested over 2,500 urine samples from people over the age of 6 and found nearly 93 percent of samples contained BPA metabolites.¹ Although the CDC does not do biomonitoring in subjects younger than age 6, other researchers have found BPA metabolites in human follicular fluid,² amniotic fluid,³ and breast milk,⁴ indicating that prenatal, fetal, and neonatal BPA exposures are occurring. This evidence of early life exposure to BPA is most troubling because it is occurring during critical periods of organ development when permanent harm can be done.

In addition to the scientific evidence showing harm in laboratory animals, there is a growing body of literature showing BPA causes adverse health effects in humans. Studies in human tissue link BPA exposure with breast cancer and diabetes. A group of thirty-eight internationally-recognized scientific experts recently published a consensus statement saying that

¹ Calafat AM, et al. Exposure of the U.S. population to bisphenol A and 4-tertiary-octylphenol: 2003-2004. *Environ Health Perspect.* 2008 Jan;116(1):39-44.

² Ikezuki Y, et al. Determination of bisphenol A concentrations in human biological fluids reveals significant early prenatal exposure. *Hum Reprod.* 2002 Nov;17(11):2839-41.

³ Ikezuki Y, et al. Determination of bisphenol A concentrations in human biological fluids reveals significant early prenatal exposure. *Hum Reprod.* 2002 Nov;17(11):2839-41. Schönfelder G et al. Parent bisphenol A accumulation in the human maternal-fetal-placental unit. *Environ Health Perspect.* 2002 Nov;110(11):A703-7.

⁴ Kuruto-Niwa R, et al. Measurement of bisphenol A concentrations in human colostrum. *Chemosphere.* 2007 66(6):1160-4. Ye X, et al. Measuring environmental phenols and chlorinated organic chemicals in breast milk using automated on-line column-switching-high performance liquid chromatography-isotope dilution tandem mass spectrometry. *J Chromatogr B Analyt Technol Biomed Life Sci.* 2006 Feb 2;831(1-2):110-5.

the evidence of adverse effects of low doses of BPA from robust laboratory experiments is a “great cause for concern with regard to the potential for similar adverse effects in humans.”⁵ Striking, recently-published research in primates shows associations between BPA exposure and many of the same outcomes seen in animal models including breast cancer,⁶ neurological damage,⁷ insulin resistance⁸ and diabetes,⁹ obesity,¹⁰ cardiovascular disease,¹¹ and abnormalities in liver function.¹²

In light of the data suggesting that BPA is harmful to human health, and in response to the well-founded concerns of experts in the field, FDA must prohibit BPA from use in human food and food packaging, including in can linings and in beverage containers like baby bottles. The FDA must further revoke all regulations permitting the use of any food additive that results in BPA becoming a component of food.

⁵ Vom Saal FS, et al. Chapel Hill bisphenol A expert panel consensus statement: integration of mechanisms, effects in animals and potential to impact human health at current levels of exposure. *Reprod Toxicol.* 2007 Aug-Sep;24(2):131-8.

⁶ Dairkee SH, et al. Bisphenol A induces a profile of tumor aggressiveness in high-risk cells from breast cancer patients. *Cancer Res.* 2008 Apr 1;68(7):2076-80.

⁷ Leranath C, et al. Bisphenol A prevents the synaptogenic response to estradiol in hippocampus and prefrontal cortex of ovariectomized nonhuman primates. *Proc Natl Acad Sci.* 2008 Sep 16;105(37):14187-91.

⁸ Hugo ER, et al. Bisphenol A at Environmentally Relevant Doses Inhibits Adiponectin Release from Human Adipose Tissue Explants and Adipocytes. *Environ Health Perspect.* doi:10.1289/ehp.11537 (available at <http://dx.doi.org/>) Online 14 August 2008.

⁹ Lang IA, et al. Association of urinary bisphenol A concentration with medical disorders and laboratory abnormalities in adults. *JAMA.* 2008 Sep 17;300(11):1303-10.

¹⁰ Hugo ER, et al. Bisphenol A at Environmentally Relevant Doses Inhibits Adiponectin Release from Human Adipose Tissue Explants and Adipocytes. *Environ Health Perspect.* doi:10.1289/ehp.11537 (available at <http://dx.doi.org/>) Online 14 August 2008.

¹¹ Lang IA, et al. Association of urinary bisphenol A concentration with medical disorders and laboratory abnormalities in adults. *JAMA.* 2008 Sep 17;300(11):1303-10.

¹² Lang IA, et al. Association of urinary bisphenol A concentration with medical disorders and laboratory abnormalities in adults. *JAMA.* 2008 Sep 17;300(11):1303-10.

Petitioner NRDC is a national, non-profit environmental and public health membership organization with more than 420,000 members nationwide. NRDC has no financial interest in BPA or any alternative products. NRDC's members are at risk of harm from exposure to BPA in food.

II. ACTION REQUESTED

NRDC petitions the Commissioner to establish the following regulation, pursuant to 21 C.F.R. § 189.1:

21 C.F.R. § 189.2XX Bisphenol A.

(a) Bisphenol A is the chemical 4-4'-isopropylidenediphenol $((\text{CH}_3)_2\text{C}(\text{C}_6\text{H}_4\text{OH})_2$, CAS Reg. No. 80-05-7). It is a synthetic chemical not found in natural products and has been used in the production of epoxy resins, polyester resins, polysulfone resins, polyacrylate resins, and polycarbonate plastics.

(b) Food containing any added Bisphenol A is deemed to be adulterated in violation of the Federal Food, Drug, and Cosmetic Act based upon an order published in the FEDERAL REGISTER of [DATE].

NRDC also petitions the Commissioner to revoke all regulations permitting the use of a food additive that results in BPA becoming a component of food, pursuant to 21 C.F.R. § 171.130.

A. Statement of Grounds.

1. FDA's Approval of BPA for Use in Food Contact Substances Violates the Federal Food, Drug, and Cosmetic Act.

The Federal Food, Drug, and Cosmetic Act (FFDCA) defines "food additive" to mean "any substance the intended use of which results or may reasonably be expected to result, directly or indirectly, in its becoming a component or otherwise affecting the characteristics of any food (including any substance intended for use in producing, manufacturing, packing, processing, preparing, treating, packaging, transporting, or holding food ...)." 21 U.S.C. §

321(s).¹³ The FDA has approved BPA as a food additive through use in food contact applications that result in BPA becoming a component of food. *See* 21 C.F.R. §§ 172.105, 175.300, 177.1440, 177.1580, 177.1585, 177.1655, 177.2600, 177.2280, 177.2420; *see also* FDA, *Draft Assessment of Bisphenol A for Use in Food Contact Applications* at 6 (August 14, 2008). These regulations were promulgated as early as 1961. *See, e.g.*, 26 Fed. Reg. 7088 (Aug. 8, 1961); 28 Fed. Reg. 5083 (May 22, 1963); 28 Fed. Reg. 11,261 (Oct. 22, 1963); 29 Fed. Reg. 12,826 (Sept. 10, 1964).

Congress directed that the FDA may not permit the use of a food additive if a fair evaluation of the data before the FDA “fails to *establish* that the proposed use of the food additive, under the conditions of use to be specified in the regulation, will be safe.” 21 U.S.C. § 348(c)(3) (emphasis added). By regulation, the FDA prohibits substances from use in human food where those substances “have not been *shown* by adequate scientific data *to be safe* for use in human food.” 21 C.F.R. § 189.1 (emphasis added). Both the statute and FDA’s regulations therefore demand an affirmative showing of safety. 21 U.S.C. § 348(c)(3); 21 C.F.R. § 189.1. If BPA is not *proven* to be safe, it may not be approved for continued use as a food additive.

Safe is defined in the FDA regulations to mean “a reasonable certainty in the minds of competent scientists that the substance is not harmful under the intended conditions of use.” 21 C.F.R. § 170.3(i). Congress clarified that “no additive shall be deemed to be safe if it is found to induce cancer when ingested by man or animal, or if it is found, after tests which are appropriate for the evaluation of the safety of food additives, to induce cancer in man or animal.” 21 U.S.C. § 348(c)(3)(A). With respect to the FDA’s determination of food additive safety, the FFDCRA specifically requires that:

¹³ The statutory definition contains exceptions that are not relevant here, for “prior-sanctioned food ingredients” and substances “generally recognized as safe.” 21 U.S.C. § 321(s).

In determining, for the purposes of this section, whether a proposed use of a food additive is safe, the Secretary shall consider among other relevant factors—

(A) the probable consumption of the additive and of any substance formed in or on food because of the use of the additive;

(B) the cumulative effect of such additive in the diet of man or animals, taking into account any chemically or pharmacologically related substance or substances in such diet; and

(C) safety factors which in the opinion of experts qualified by scientific training and experience to evaluate the safety of food additives are generally recognized as appropriate for the use of animal experimentation data.

21 U.S.C. § 348(c)(5). Unlike drugs, “food additives are likely to be consumed by all segments of the population, including children and the elderly, potentially over the full course of their lifetimes.”¹⁴ This increased likelihood of exposure requires a more conservative approach to assessing safety for food additives.

In light of the evidence of BPA’s adverse health effects, discussed more fully below, BPA must be deemed unsafe for use in human food and food packaging. Since the FDA approved BPA as a food contact substance over four decades ago, new data have become available regarding both the toxicity of BPA at low levels of exposure and the extent of exposure to BPA through food. The totality of available data not only “fails to establish” that BPA is safe, 21 U.S.C. § 348(c)(3), it demonstrates that BPA may cause serious adverse health effects in humans, especially infants and children. Accordingly, FDA should list BPA as a substance prohibited from use in human food, 21 C.F.R. § 189.1, and revoke any regulation permitting the use of a food additive or food contact substance that results in BPA being consumed through food. 21 U.S.C. § 348(i); 21 C.F.R. § 171.130(a).

¹⁴ Lars Noah, *Legal Aspects of the Food Additive Approval Process* at 32, published in National Academy of Sciences, *Enhancing the Regulatory Decisionmaking Approval Process for Direct Food Ingredient Technologies*, Apdx. A (1999).

2. The Scientific Evidence Shows that BPA Is Not Safe.

The FFDCFA prohibits the FDA from approving or maintaining in effect a food additive regulation unless the data prove that the food additive will be safe. In making this determination, the FDA must first consider “the probable consumption of the additive and of any substance formed in or on food because of the use of the additive.” 21 U.S.C. § 348(c)(5)(A). The FDA has approved a number of food contact substances that are produced using BPA and that result in BPA being consumed through food, including food intended for infants. *See, e.g.*, 21 C.F.R. §§ 177.1440, 177.1580. An analysis by the Environmental Working Group found BPA in infant formula at levels as high as 17 parts per billion.¹⁵ FDA sampling found BPA in infant formula at similar levels (up to 13.2 ppb).¹⁶ The Environmental Working Group also found levels of BPA in canned food ranging up to 385 ppb, with the highest levels found in canned pasta and soup.¹⁷ Environment California has reported levels of BPA ranging from 5 to 10 ppb leaching from baby

¹⁵ Jane Houlihan & Sonya Lunder, Environmental Working Group, *Toxic Plastics Chemical in Infant Formula* (August 2007) (“BPA has been detected in 16 of 20 liquid formula samples tested by FDA and EWG. Concentrations range from less than 1 part per billion (ppb) to 17 ppb in these samples, with an average of 5 ppb.”) (online at <http://www.ewg.org/reports/bpaformula>).

¹⁶ Biles JE, McNeal TP, Begley TH. FDA-Determination of bisphenol A migrating from epoxy can coatings to infant formula liquid concentrates. *J Agric Food Chem* (1997) 45: 4697-700. As the FDA’s recent draft bisphenol A assessment notes: “Biles et al. determined BPA levels in 14 samples of infant formula (liquid concentrate) representing 5 brands purchased in metro Washington, DC supermarkets BPA levels in the formula concentrates ranged from 0.1 – 13.2 ppb, with an average of 5 ppb. Label directions specify a 1:1 dilution with water. Thus, BPA levels in prepared formula ranged from 0.05-6.6 ppb with an average of 2.5 ppb.” FDA, *Draft Assessment of Bisphenol A for Use in Food Contact Applications* at 7 (August 14, 2008).

¹⁷ EWG, *Bisphenol A: Toxic Plastics Chemical in Canned Food* (March 2007) (<http://www.ewg.org/node/20933>). The FDA has not tested food for bisphenol A contamination since the early 1990s, when it tested select canned vegetables purchased in Washington D.C. *See* FDA, *Draft Assessment of Bisphenol A for Use in Food Contact Applications* at 9 (August 14, 2008). The FDA tested only six samples (three canned mushrooms, and one sample each of artichokes, tomatoes and mixed vegetables). Bisphenol A levels in those samples ranged from 5 to 39 ppb, with an average of 16 ppb. In its draft assessment, the FDA also considers a study conducted by Brotons et al., published in 1995, that tested 10 samples and found an average level of contamination of 22 ppb. *Id.* The FDA concluded that a “conservative estimate” of exposure from canned food was therefore 22 ppb, but this is not in fact a conservative estimate, and is much lower than the average found by EWG for consuming tomato based products (63.5 ppb).

bottles heated with water.¹⁸ Given the ubiquity of can linings and other packaging produced using BPA, consumption of BPA represents a serious public health risk.

Second, FDA must consider “the cumulative effect of such additive in the diet of man or animals, taking into account any chemically or pharmacologically related substance or substances in such diet.” 21 U.S.C. § 348(c)(5)(B). Analyses of human blood, umbilical cord blood, urine, breast milk, and amniotic fluid indicate that the human population, including fetuses and developing infants, is widely exposed to BPA.¹⁹ Because BPA is rapidly metabolized and excreted by the human body, with a relatively short half-life that is measured in hours, these consistent measures of BPA indicate there is continuous and constant exposure. BPA has been detected in 93% of over 2,500 urine samples collected by the Centers for Disease Control and Prevention (CDC).²⁰ In the CDC studies, the median level of BPA in urine was 2.7 ppb ($\mu\text{g/L}$). According to a recent report of the National Toxicology Program (NTP), formula-fed infants between the ages of 6 and 12 months have an estimated daily intake of between 1.65 and 13 $\mu\text{g/kg bw/day}$ (ppb-day) of BPA.²¹ These levels are well within the range of concern based on animal studies, which have found BPA to cause pre-cancerous changes in mammary

¹⁸ Rachel L. Gibson, Environment California, *Toxic Baby Bottles: Scientific Study Finds Leaching Chemicals in Clear Plastic Baby Bottles* at 19-20 (2007) (<http://www.environmentcalifornia.org/uploads/wm/HH/wmHHMjKT2OLz4Nc4kXzynQ/Toxic-Baby-Bottles.pdf>).

¹⁹ NTP-CERHR Monograph on the Potential Human Reproductive and Developmental Effects of Bisphenol A, NIH Publication No. 08-5994 (September 2008) (available at <http://cerhr.niehs.nih.gov/chemicals/bisphenol/bisphenol.pdf>).

²⁰ Calafat AM, et al. Exposure of the U.S. population to bisphenol A and 4-tertiary-octylphenol: 2003-2004. *Environ Health Perspect.* 2008 Jan;116(1):39-44

²¹ NTP-CERHR Monograph on the Potential Human Reproductive and Developmental Effects of Bisphenol A, NIH Publication No. 08 – 5994 (September 2008) (<http://cerhr.niehs.nih.gov/chemicals/bisphenol/bisphenol.pdf>).

tissue at levels as low as 2.5 µg/kg bw/day (ppb-day), pre-cancerous lesions in the prostate at 10 µg/kg bw/day,²² and neurobehavioral abnormalities at 10 µg/kg bw/day.²³

Based on the findings cited above and the conclusions of the NTP, the FDA should base its safety assessment on a Lowest Observed Adverse Effects Level of 10 µg/kg bw/day and a safety factor of 1000. NTP officials publicly endorsed this LOAEL at the FDA's Science Board Subcommittee meeting regarding the safety of BPA on September 16, 2008. This level of exposure is only four times more than FDA's estimated infant intake of 2.42 µg/kg bw/day and 60 times greater than FDA's estimated adult intake of 0.185 µg/kg bw/day. With 10 µg/kg bw/day as a more appropriate measure of adverse effects, and relying on "safety factors which in the opinion of experts qualified by scientific training and experience to evaluate the safety of food additives are generally recognized as appropriate for the use of animal experimentation data," 21 U.S.C. § 348(c)(5)(C), the FDA must conclude that current levels of human exposure to BPA through food are unsafe.

The weight of the scientific evidence now shows that human exposure to BPA can not be confirmed safe. A consensus statement of 38 scientists with expertise in researching the effects of BPA exposure stated the following:

The published scientific literature on human and animal exposure to low doses of BPA in relation to in vitro mechanistic studies reveals that human exposure to BPA is within the range that is predicted to be biologically active in over 95% of people sampled. The wide range of adverse effects of low doses of BPA in laboratory animals exposed both during development and in adulthood is a great cause for concern with regard to the potential for similar adverse effects in humans. Recent trends in human diseases relate to adverse effects observed in experimental animals exposed to low doses of BPA. Specific

²² Ho, S-M, et al. 2006. Developmental Exposure to Estradiol and Bisphenol A Increases Susceptibility to Prostate Carcinogenesis and Epigenetically Regulates Phosphodiesterase Type 4 Variant 4. *Cancer Research* 66: 5624-5632.

²³ NTP-CERHR Monograph on the Potential Human Reproductive and Developmental Effects of Bisphenol A, NIH Publication No. 08 – 5994 (September 2008) (available online at <http://cerhr.niehs.nih.gov/chemicals/bisphenol/bisphenol.pdf>).

examples include: the increase in prostate and breast cancer, uro-genital abnormalities in male babies, a decline in semen quality in men, early onset of puberty in girls, metabolic disorders including insulin resistant (type 2) diabetes and obesity, and neurobehavioral problems such as attention deficit hyperactivity disorder (ADHD).²⁴

In the past year since this statement was published, there have been additional studies published demonstrating harm from BPA at environmentally relevant levels of exposure. A February 2008 supplement of the journal *Fertility and Sterility* has several articles that review the science of low dose effects of BPA on reproductive toxicity that include the endpoints of disrupted meiosis in mouse oocytes, and prostate cancer.²⁵

Female reproduction has been shown in laboratory studies to be disrupted in a number of different ways after exposure to BPA. Specifically, BPA exposure is associated with early onset puberty,²⁶ hormonal alterations,²⁷ and altered cyclicity.²⁸ Neonatal exposure to BPA at levels as low as 10 µg/kg bw/day is associated with the development of uterine fibroids and cystic ovaries

²⁴ Vom Saal FS, Akingbemi BT, Belcher SM, Birnbaum LS, Crain DA, Eriksen M, Farabollini F, Guillette LJ Jr, Hauser R, Heindel JJ, Ho SM, Hunt PA, Iguchi T, Jobling S, Kanno J, Keri RA, Knudsen KE, Laufer H, LeBlanc GA, Marcus M, McLachlan JA, Myers JP, Nadal A, Newbold RR, Olea N, Prins GS, Richter CA, Rubin BS, Sonnenschein C, Soto AM, Talsness CE, Vandenberg JG, Vandenberg LN, Walser-Kuntz DR, Watson CS, Welshons WV, Wetherill Y, Zoeller RT. Chapel Hill bisphenol A expert panel consensus statement: integration of mechanisms, effects in animals and potential to impact human health at current levels of exposure. *Reprod Toxicol*. 2007 Aug-Sep;24(2):131-8.

²⁵ Susiarjo M, Hunt P. Bisphenol A exposure disrupts egg development in the mouse. *Fertil Steril*. 2008 Feb;89(2 Suppl):e97. Prins GS, et al. Developmental exposure to bisphenol A increases prostate cancer susceptibility in adult rats: epigenetic mode of action is implicated. *Fertil Steril*. 2008 Feb;89(2 Suppl) e 41.

²⁶ Honma S, et al. Low dose effect of in utero exposure to bisphenol A and diethylstilbestrol on female mouse reproduction. *Reprod Toxicol* 2002;16:117–22. and Howdeshell KL, et al. Exposure to bisphenol A advances puberty. *Nature* 1999;401:763–4.

²⁷ Rubin BS, et al. Perinatal exposure to low doses of bisphenol A affects body weight, patterns of estrous cyclicity, and plasma LH levels. *Environ Health Perspect* 2001;109: 675–80.

²⁸ Rubin BS, et al. Perinatal exposure to low doses of bisphenol A affects body weight, patterns of estrous cyclicity, and plasma LH levels. *Environ Health Perspect* 2001;109: 675–80. Markey CM, et al. Mammalian development in a changing environment: exposure to endocrine disruptors reveals the developmental plasticity of steroid-hormone target organs. *Evol Dev* 2003;5:67–75.

in adult mice later in life.²⁹ Finally, BPA exposure has been shown by at least two laboratories to disrupt meiosis.³⁰ Disrupted meiosis can lead to an abnormal number of chromosomes or aneuploidy in gametes,³¹ and is associated with increased rates of pregnancy loss and birth defects. A preliminary study in Japan has found that women with repeated miscarriages had higher levels of BPA.³²

In addition to female reproductive toxicity, BPA also has been shown to cause male reproductive toxicity. In mice, exposure to BPA during development is associated with a decrease in serum testosterone and sperm counts, and adult exposure to BPA is associated with testicular toxicity.³³

Some of the reproductive toxicity caused by BPA occurs across generations as the effects are seen in the exposed offspring but not the pregnant dam. These transgenerational effects occur through epigenetic mechanisms, including changes in DNA methylation patterns.³⁴ A recent study in mice has demonstrated that early life exposure to BPA at environmentally relevant low doses caused changes in methylation patterns of prostate tissue genes. As these

²⁹ Newbold, RR, WR Jefferson, and EP Banks. 2007. Long-term Adverse Effects of Neonatal Exposure to Bisphenol A on the Murine Female Reproductive Tract. *Reproductive Toxicology* 24:253-258.

³⁰ Susiarjo M, Hunt P. Bisphenol A exposure disrupts egg development in the mouse. *Fertil Steril*. 2008 Feb;89(2 Suppl):e97. Lenie S, et al. Continuous exposure to bisphenol A during in vitro follicular development induces meiotic abnormalities. *Mutat Res*. 2008 Mar 12;651(1-2):71-81.

³¹ Richter CA, et al. In vivo effects of bisphenol A in laboratory rodent studies. *Reprod Toxicol*. 2007 Aug-Sep;24(2):199-224

³² Sugiura-Ogasawara M, et al. Exposure to bisphenol A is associated with recurrent miscarriage. *Hum Reprod*. 2005 Aug;20(8):2325-9.

³³ Richter CA, et al. In vivo effects of bisphenol A in laboratory rodent studies. *Reprod Toxicol*. 2007 Aug-Sep;24(2):199-224

³⁴ Dolinoy DC, Huang D, Jirtle RL. Maternal nutrient supplementation counteracts bisphenol A-induced DNA hypomethylation in early development. *Proc Natl Acad Sci U S A*. 2007. 104(32):13056-61. Prins GS, et al. Perinatal exposure to oestradiol and bisphenol A alters the prostate epigenome and increases susceptibility to carcinogenesis. *Basic Clin Pharmacol Toxicol*. 2008.102(2):134-8.

rodents aged, these methylation patterns changed prostate gene expression, predisposing them to developing pre-cancerous lesions, including high grade prostate intraepithelial neoplasia (PIN) lesions.³⁵ In humans, high grade PIN lesions are highly predictive for the development of cancer, with one-third to one-half of men with high grade PIN on biopsy found to develop cancer on follow-up biopsy.^{36, 37} Although no research yet has been done with BPA, changes in methylation patterns are also known to occur in human prostate cancer.³⁸

In addition to prostate cancer, BPA exposure is associated with mammary or breast cancer. An important new study in human tissues has demonstrated that when breast tissue is exposed to low, environmentally relevant levels of BPA, there are changes in gene expression indicative of a highly aggressive type of breast cancer associated with poor survival. This study supports previous animal data showing that BPA can promote development of mammary cancer.³⁹

BPA is well recognized for its ability to act as an estrogen mimic.⁴⁰ New research has shown that BPA also can interfere with thyroid hormone. Thyroid hormone is important for neurodevelopment in fetuses, infants, and children, and thyroid hormone disruption could

³⁵ Prins GS, et al. Perinatal exposure to oestradiol and bisphenol A alters the prostate epigenome and increases susceptibility to carcinogenesis. *Basic Clin Pharmacol Toxicol.* 2008 102(2):134-8.

³⁶ Kronz JD, Allan CH, Shaikh AA, Epstein JI. Predicting cancer following a diagnosis of high-grade prostatic intraepithelial neoplasia on needle biopsy: data on men with more than one follow-up biopsy. *Am J Surg Pathol.* 2001 Aug;25(8):1079-85.

³⁷ Park S, Shinohara K, Grossfeld GD, Carroll PR. Prostate cancer detection in men with prior high grade prostatic intraepithelial neoplasia or atypical prostate biopsy. *J Urol.* 2001 May;165(5):1409-14.

³⁸ Enokida H, Shiina H, Urakami S, Igawa M, Ogishima T, Li LC, Kawahara M, Nakagawa M, Kane CJ, Carroll PR, Dahiya R. Multigene methylation analysis for detection and staging of prostate cancer. *Clin Cancer Res.* 2005 Sep 15;11(18):6582-8.

³⁹ Dairkee SH, et al. Bisphenol A induces a profile of tumor aggressiveness in high-risk cells from breast cancer patients. *Cancer Res.* 2008. 68(7):2076-80.

⁴⁰ NTP-CERHR Monograph on the Potential Human Reproductive and Developmental Effects of Bisphenol A, NIH Publication No. 08 – 5994 (September 2008) (<http://cerhr.niehs.nih.gov/chemicals/bisphenol/bisphenol.pdf>).

represent another important mode of action for BPA in causing neurodevelopmental toxicity.⁴¹ Early life exposure to BPA has been shown to alter neurobehavioral development in mice.⁴² In addition, new research in primates supports the animal data that already has been recognized by NTP for BPA to cause changes in neurobehavioral outcomes. A study of non-human primates has found that exposure to BPA at 50 µg/kg/day causes alterations in the formation of synapses in the prefrontal cortex and hippocampus, areas of the brain associated with memory, learning and behavior.⁴³ Another new analysis has hypothesized an association between BPA and schizophrenia.⁴⁴

Finally, research has shown an association between BPA and the development of diseases found in metabolic syndrome, including diabetes, cardiovascular disease, and obesity. Animal models have demonstrated perinatal and postnatal exposures to BPA result in the development of obesity and hyperlipidemia in mice.⁴⁵ New research using human adipose tissue has found that exposure to low, environmentally relevant levels of BPA decreases the secretion of the hormone adiponectin. A decrease in adiponectin could result in insulin resistance and an increased susceptibility to obesity-associated diseases.⁴⁶ Another recent analysis of data collected by the

⁴¹ Kaneko M, et al. Bisphenol A acts differently from and independently of thyroid hormone in suppressing thyrotropin release from the bullfrog pituitary. *Gen Comp Endocrinol.* 2008 155(3):574-80. Zoeller RT. Environmental chemicals impacting the thyroid: targets and consequences. *Thyroid.* 2007. 17(9):811-7.

⁴² Palanaza P, et al. Effects of developmental exposure to bisphenol A on brain and behavior in mice. *Env Res* 2008. 108:150-157.

⁴³ Leranth C, et al. Bisphenol A prevents the synaptogenic response to estradiol in hippocampus and prefrontal cortex of ovariectomized nonhuman primates. *Proc Natl Acad Sci U S A.* 2008 Sep 16;105(37):14187-91.

⁴⁴ Brown JS Jr. Effects of Bisphenol-A and Other Endocrine Disruptors Compared With Abnormalities of Schizophrenia: An Endocrine-Disruption Theory of Schizophrenia. *Schizophr Bull.* 2008 Jan 31.

⁴⁵ Miyawaki J, et al. Perinatal and postnatal exposure to bisphenol a increases adipose tissue mass and serum cholesterol level in mice. *J Atheroscler Thromb.* 2007. 14(5):245-52.

CDC found that exposure to BPA was associated with the common diseases of diabetes, cardiovascular disease, and abnormalities in liver function.⁴⁷

3. Summary of Information that May Be Unfavorable.

FDA's regulations require inclusion in this petition of representative information known to NRDC that may not support the actions requested herein. 21 C.F.R. § 10.30(b). To the extent that there is any information unfavorable to this petition, it is summarized by the FDA in its *Draft Assessment of Bisphenol A for use in Food Contact Applications*, published on August 14, 2008. This draft assessment relies on two studies, published by Tyl et al., to conclude that "an adequate margin of safety exists for BPA at current levels of exposure from food contact uses." FDA, *Draft Assessment of Bisphenol A for Use in Food Contact Applications* at 2 (August 14, 2008).

NRDC strongly disagrees with the draft FDA conclusion that current levels of exposure to BPA are safe for human consumption. In laboratory animal studies, exposure to BPA within the range of human exposure levels has been associated with the wide array of adverse outcomes discussed above. These effects include neurobehavioral changes, pre-cancerous lesions in the prostate and mammary glands, obesity and metabolic disturbances, early puberty and other reproductive abnormalities. These studies have been done by a number of investigators in different laboratories who have no financial interest in or affiliations with the manufacturers or users of BPA.

⁴⁶ Hugo ER, et al. Bisphenol A at Environmentally Relevant Doses Inhibits Adiponectin Release from Human Adipose Tissue Explants and Adipocytes. *Environ Health Perspect.* doi:10.1289/ehp.11537 (available at <http://dx.doi.org/>) Online 14 August 2008.

⁴⁷ Lang IA, et al. Association of urinary bisphenol A concentration with medical disorders and laboratory abnormalities in adults. *JAMA.* 2008 Sep 17;300(11):1303-10.

For its draft assessment, the FDA relied on two industry-funded studies with analyses limited to traditional reproductive toxicological endpoints.⁴⁸ These studies did not examine the endpoints most noted to be of highest concern for BPA: neurobehavioral changes and histopathological changes in the prostate or mammary gland or other reproductive organs. Therefore, FDA, in its current draft assessment, has not used the most appropriate endpoint in determining a NOAEL as a point of departure for margins of safety. Specifically, the National Toxicology Program expressed “some concern” for early life exposures to BPA causing neurobehavioral changes and prostate cancer, which were identified at doses of 10 µg/kg-bw/day. This dose is 500 times lower than the NOAEL chosen by FDA. Furthermore, as mentioned above, a dose of 10 µg/kg-bw/day is only four times greater than FDA’s estimated infant intake and around 60 times greater than FDA’s estimated adult intake. With safety factors taken into consideration, as required by 21 U.S.C. § 348(c)(5)(C), and using a more proper point of departure of 10 micrograms per kilogram body weight per day, the FDA’s margin of safety is clearly not protective of the majority of humans, including the most vulnerable populations of fetuses and infants. This conclusion alone requires the FDA to revoke its approval of BPA for use in food contact substances.

B. Environmental Impact.

This petition requests action to prohibit the use of a substance in food packaging and is therefore categorically excluded from the requirement to prepare an environmental assessment or environmental impact statement under 21 C.F.R. § 25.32.

⁴⁸ Tyl RW, et al. Two-generation reproductive toxicity study of dietary bisphenol A in CD-1 (Swiss) mice. *Toxicol Sci.* 2008 Aug;104(2):362-84. Tyl RW, et al. Three-generation reproductive toxicity study of dietary bisphenol A in CD Sprague-Dawley rats. *Toxicol Sci.* 2002 Jul;68(1):121-46.

C. Certification.

This petition includes all information and views on which the petition relies, and it includes representative data and information known to NRDC which may be unfavorable to the petition. NRDC attaches and incorporates by reference the public comments and reports listed below, as well as copies of all studies cited in this petition. As required by 21 C.F.R. § 10.20(a), NRDC is submitting the original and four copies of this petition to the FDA Division of Dockets Management. NRDC reserves the right to supplement this petition pursuant to 21 C.F.R. § 10.30(g).

III. CONCLUSION

For the reasons presented above, as supported by the attached studies and reports, NRDC requests that the FDA: (a) establish a regulation prohibiting the use of BPA in human food and food packaging, and (b) revoke all regulations permitting the use of any food additive that results in BPA being consumed through food.

Respectfully submitted,

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LIST OF ATTACHMENTS

1. NRDC, Comments on the Draft NTP Brief on Bisphenol A (May 23, 2008).
2. NRDC, Comments on the NTP CERHR Bisphenol A Expert Panel Report (Jan. 28, 2008).
3. NRDC, Comments on the Draft FDA Assessment of Bisphenol A, Docket No. FDA-2008-N-0038 (Sept. 15, 2008).
4. NRDC, *Chemicals in Plastic Bottles: How to Know What's Safe for Your Family* (May 2008).
5. Rachel L. Gibson, Environment California, *Toxic Baby Bottles: Scientific Study Finds Leaching Chemicals in Clear Plastic Baby Bottles* (2007).
6. Public comment, Gail S. Prins, Ph.D., to Michael Shelby, NIEHS (Jan. 23, 2008).
7. Sonya Lunder, Environmental Working Group, Comments on the Draft National Toxicology Program Brief on Bisphenol A (May 23, 2008).
8. Public comment, Drs. Ana M. Soto, et al., to Dr. Gail McCarver, NTP Board of Scientific Counselors (May 22, 2008).
9. Frederick S. vom Saal, Ph.D., Comments on NTP April 2008 Draft Report on Bisphenol A.
10. Public comment, R. Thomas Zoeller, Ph.D., to Michael D. Shelby, NIEHS (May 19, 2007).
11. Environment California, *Bisphenol-A Overview*.