June 30, 2009

Ms. Cynthia Oshita
Office of Environmental Health Hazard Assessment
Proposition 65 Implementation
P.O. Box 4010
1001 I Street, 19th Floor
Sacramento, CA 95812-4010

Dear Ms. Oshita:

The Environmental Working Group (EWG) strongly encourages OEHHA to list the chemical bisphenol A (BPA) as a reproductive and developmental toxicant under California's Proposition 65. There is a growing body of science that supports the listing of BPA as a chemical that may pose risks to human reproduction and development. The strength of this science has prompted recent actions by the Canadian government and state legislatures.

In addition, this growing body of science has been recognized in the past year by an important new assessment and determination by the Center for the Evaluation of Risk to Human Reproduction (CERHR) at the National Toxicology Program (NTP). NTP found that exposure to higher doses of BPA during pregnancy and via lactation can reduce survival, birth weight, inhibit growth, and delay puberty. They concluded, "These high dose effects of bisphenol A are not considered scientifically controversial and provide clear evidence of adverse effects on development in laboratory animals" (NTP 2008).

The Agency also raised concern about the safety of current exposures to the developing fetus, neonate, and small child, which occur at lower doses. NTP determined there is "*some concern* for effects on the brain, behavior, and prostate gland in fetuses, infants, and children at current human exposures to bisphenol A," based on evidence of neuronal and behavioral affects, preneoplastic lesions in the prostate and mammary gland, altered male reproductive tract development, and early onset of puberty in female mice (NTP 2008).

This month the Endocrine Society issued a statement calling for "regulation seeking to decrease human exposure to the many endocrine-disrupting agents" and specifically cited BPA as one of the chemicals of concern (Endocrine Society 2009). Accordingly many such efforts have been initiated at the state level for BPA. The National Caucus of Environmental Legislators (NCEL) reports that over 20 U.S. states have introduced legislation in 2009 (NCEL 2009). All of the state bills share a focus on reducing BPA exposures among vulnerable populations, especially infants and children, due to concerns about developmental toxicity. The first bill to be signed into law was in Minnesota and calls for a ban on BPA in baby bottles and "sippy" cups. This June, Connecticut banned BPA from these products as well as infant formula, baby food containers, and reusable food and beverage containers.

In 2008 the Canadian government classified BPA as a Toxic Substance, and announced measures to reduce infant exposures. These include a ban on polycarbonate baby bottles and steps to limit BPA leaching into liquid infant formula packaged in metal cans. In announcing these actions Canadian Health Minister Tony Clement remarked "We have concluded that early

development is sensitive to the effects of bisphenol A" (Health Canada 2008). As noted in the Proposed Risk Management document,

> "The screening assessment report concluded that bisphenol A be considered as a substance that may be entering the environment in a quantity or concentration or under conditions that constitute or may constitute a danger in Canada to human life or health. The basis of this proposed conclusion is that the neurodevelopmental and behavioural dataset in rodents, though highly uncertain, is suggestive of potential effects at doses at the same order of magnitude to 1–2 orders of magnitude higher than exposures" (Canada 2008).

These actions by NTP, Canada, and state legislators are based on numerous animal studies conducted over the last decade linking *in-utero* and early life BPA exposures to a number of adverse health effects as diverse as obesity, behavioral problems, impaired fertility, early puberty, and cancer. The body of scientific knowledge on BPA toxicity, and concern over its use in consumer products, is advancing at a rapid pace. In addition to actions taken by NTP, Health Canada, and state legislators, there have been some other new developments within the last year that we would like to bring to your attention:

- In a peer reviewed and published commentary, 36 scientists who are experts on BPA research revealed serious flaws in two large industry funded study that found no developmental toxicity with current levels of BPA exposure (Myers et al 2009);
- FDA's draft risk assessment, which concluded that current BPA exposures are well below toxic doses, which was refuted by its own advisory Science Board and resulting in further Agency assessment to determine safety;
- In 2008, the American Academy of Pediatrics, which represents 60,000 pediatricians in the U.S., wrote a letter strongly expressing concerns about adverse effects of BPA exposure on children's health;
- A recent study from Harvard scientists found that drinking from polycarbonate bottles resulted in significant increases in BPA exposure;
- Updated information from Dr. Fred vom Saal discussing divergent findings of studies funded by industry and public funding sources (March 2009); and
- A study published in Environmental Health Perspective in May 2009 finding that neonatal exposure to BPA in female rats resulted in alterations in levels of reproductive hormones and early puberty (Fernandez et al 2009).

Each of these new developments will be discussed in detail below.

<u>36 BPA experts reveal serious flaws in large industry-funded studies that analyzed developmental toxicity of BPA</u>

In its 2008 assessment in which current levels of BPA exposure were found to be safe, the FDA heavily relied on two large industry-funded multigenerational animal studies, primarily because these studies followed good laboratory practices (GLP) (Tyl et al 2002, Tyl et al 2008). In these two studies, the researchers did not find any developmental toxicity with BPA at current levels of exposure among the U.S. population. In the current 2009 OEHHA assessment, the results from these two studies are presented throughout the document in various sections.

Earlier this year, 36 scientists from around the world who have conducted extensive research on BPA published a commentary in Environmental Health Perspectives in which they pointed out major flaws in several industry-funded GLP studies, including the two that were primarily utilized by the FDA (Myers et al 2009). In this commentary, BPA experts reveal that closer analysis of the two Tyl studies shows that they both used animal models that are estrogen insensitive. In addition, the diet used in one of the studies (Tyl et al 2008) has been found to have estrogenic activity, thereby interfering with studies aimed at assessing the effects of BPA exposure.

The BPA experts also comment on two other studies (Ashby et al 1999, Cagen et al 1999) that found no evidence of developmental toxicity except at very high levels of BPA exposure. The results from these two studies are also presented in the OEHHA assessment, despite extensive criticisms from the scientific community because the positive controls in both studies failed (Myers et al 2009). The flaws in all four of these studies (Tyl et al 2002, Tyl et al 2008, Ashby et al 1999, Cagen et al 1999) are so significant that the BPA experts concluded " Each of the four main industry-funded GLP studies of BPA is flawed and not appropriate for use in setting health standards" (Myers et al 2009).

Based on this analysis that reveals serious flaws in the industry-funded GLP studies, EWG strongly recommends that OEHHA place less weight on the results of these studies when evaluating the developmental and reproductive toxicity of BPA. In contrast to these 4 studies, there are scores of BPA studies from independent scientists funded by government agencies who have conducted research that utilizes the most sensitive assays; these studies should receive precedence when evaluating BPA toxicity.

FDA promises speedy reassessment of BPA safety after receiving strong criticism from its own advisory Science Board

In August 2008, FDA published a draft risk assessment for BPA in which it concluded "an adequate margin of safety exists for BPA at current levels of exposure from food contact uses" (FDA 2008a). This assessment was subsequently sent to FDA's advisory Science Board, who established a Subcommittee on BPA. In October, the Science Board voted to adopt the Subcommittee report, which concluded that there were major flaws in this assessment that raised "significant concerns" about the FDA conclusions of safety (FDA 2008b). In response, the Agency has agreed to conduct another risk assessment for BPA, this time agreeing to fully account for risks to infants and a larger body of literature on BPA toxicity.

One of the Science Board's primary criticisms of FDA's draft risk assessment was the agency's decision to disregard data from scores of non-GLP studies. The Subcommittee noted in its executive summary "the Subcommittee does not agree that the large number of non-GLP studies should be excluded from use in the safety assessment" (FDA 2008b). Just this month, FDA, facing increased pressure from Congress, agreed to expedite its BPA reassessment, indicating that it will have findings available by August 2009. In the meantime, American infants continue to be exposed to potentially harmful doses of BPA via food and food packaging.

EWG strongly urges OEHHA to continue to weight the full literature on BPA in its determination. FDA has been strongly reprimanded by its own science advisors for limiting their assessment to a handful of studies finding only high dose effects. However OEHAA's May draft document is inclusive of the breadth of the literature on BPA toxicity.

The American Academy of Pediatrics (AAP) expresses concerns about BPA's effects on children

The AAP, a national organization that represents 60,000 pediatricians, has expressed concern about BPA's adverse effects on vulnerable populations, including infants and children. In a May 2008 letter to the CERHR at the NTP, AAP president Dr. Renee Jenkins wrote "the AAP agrees with the NTP report's statement that the available evidence indicates 'some concern' regarding neural and behavioral effects of BPA on fetuses, infants, and children at current exposures." They also question the Agency's determination of "negligible concern for pregnant women's exposures urging NTP to characterize the evidence as "insufficient to draw this conclusion" (AAP 2008).

The AAP finds that the weight of the evidence supports the strongest findings from the NTP on BPA's developmental toxicity. EWG strongly encourages OEHHA to take into account the AAP's concerns about BPA's developmental toxicity in its determination.

BPA exposure increases significantly with use of polycarbonate bottles

A recent study from researchers at Harvard University found that consumption of cold beverages from polycarbonate bottles resulted in significant increases in BPA exposure among the study population of young adults (Carwile et al 2009). In this study, BPA measurements were collected from a group of Harvard students before and after a weeklong period in which all cold beverages were consumed from polycarbonate drink bottles. The researchers found an average increase in urinary BPA levels of 69% among study subjects after the use of the polycarbonate bottles, from 1.2 ug/g creatinine to 2.0 ug/g creatinine.

This study is significant because it establishes a clear link between use of a consumer item that contains BPA and significant increases in BPA exposure. This is especially concerning for infants and children, who could ingest 100% of their daily caloric needs from polycarbonate bottles and who have decreased ability to metabolize BPA. As noted by the authors: "[D]ue to their reduced ability to clear BPA, we predict that children would have higher urinary BPA concentrations due to use of polycarbonate plastic bottles relative to the study population" (Carwile et al 2009). EWG strongly urges OEHHA to consider infant's and children's greater exposures and vulnerabilities to BPA in making its determination.

BPA research findings vary depending upon the funding source

Drs. Fred vom Saal and Claude Hughes (2005) previously published an analysis showing that the results of reproductive and developmental toxicity testing are biased by funding sources, with industry-funded research much more likely to show no adverse effects at low doses. Dr. vom Saal has updated this analysis and now reports 231 studies of "low dose" BPA effects in experimental animals. 202 of these published studies report significant effects, while 29 do not. 14 of the studies finding no effect were funded by the chemical industry. Notably 100% of the industry-funded studies reported no low-dose effects. The use of less sensitive test species

and the lack of positive controls in some studies, in addition to other aspects of study design are noted factors in the negative findings from the 14 studies.

We urge OEHHA to consider funding sources, in addition to factors already discussed in the May 2009 draft (experimental animal and the use of positive controls), when evaluating the weight of the evidence supporting BPA toxicity.

New research confirms BPA's developmental toxicity

A recent study that was published in Environmental Health Perspectives finding that neonatal exposure to BPA among female rats resulted in hormone systems disruption (Fernandez et al 2009). In this study, neonatal rats were injected with BPA at several doses that are below the current LOAEL (lowest adverse effect level) of 50 mg/kg/day for their first 10 days of life. The researchers reported significant changes in levels of reproductive hormones in the BPA-exposed animals compared to controls, concluding BPA dose-dependently accelerated puberty onset and altered estrous cyclicity, with the high dose causing permanent estrus.

In summary, these recent developments and new studies add to a growing body of science that clearly illustrates the potential health risks associated with BPA exposure. In addition to these recent developments, there are two other important points that we would like to bring to your attention:

- **Current body of literature:** To date, more than 100 animal studies have been published in peer reviewed journals that show significant adverse health effects related to BPA exposures that fall below the current 'lowest adverse effect level' (LOAEL) for BPA of 50 mg/kg/day defined by EPA (EPA 1993). These independent studies originated from scientists and labs at academic institutions and government agencies from all over the world. In many of these studies, exposure occurred in-utero or during the neonatal period. As a whole, these studies illustrate that early-life BPA exposure has adverse effects on diverse systems within the body, ranging from the immune system, to the reproductive, neurological, and endocrine systems. Based on these studies, EWG strongly urges OEHHA to recognize BPA as a developmental and reproductive toxicant.

- **Adverse health effects related to BPA exposure mirror US health trends:** In animal studies, BPA exposure at low doses has been linked to structural changes in mammary and prostate tissues that result in cancer later in life, in addition to a number of other adverse health effects including impaired fertility, insulin resistance, and recurrent miscarriage. These findings are especially worrisome in light of current US health trends since all of these adverse health effects are either on the rise or common among our population. While we may never have definitive epidemiological evidence showing cause and effect, the fact that the vast majority of Americans are chronically exposed to BPA, coupled with current health trends provides a compelling reason to exercise the precautionary principle.

In conclusion, EWG strongly urges OEHHA to list BPA as a developmental and reproductive toxin under Proposition 65. There is compelling evidence of its potential developmental and reproductive toxicity from the current science linking BPA exposure at low doses to a number of adverse health effects. The evidence of reproductive and developmental toxicity from higher

doses is incontrovertible. A health-protective decision by OEHHA that clearly recognizes BPA as a developmental and reproductive toxin and resulting efforts to identify products that result in unsafe exposures would have far reaching implications for the public health.

Sincerely,

Renee Sharp
Director, California Office
Environmental Working Group
2201 Broadway Ave, Suite 308
Oakland, CA 94612

Bill Allayaud
CA Government Affairs Director
Environmental Working Group
1107 9th Street, Suite 340
Sacramento, CA 95814

References:

AAP. 2008. Letter from Renee Jenkins, President, American Academy of Pediatrics to Center for the Risk to Human Reproduction. May 23, 2008. Available online at: http://cerhr.niehs.nih.gov/chemicals/bisphenol/pubcomm/BPA(34)AmerAcadPeds052308.pdf

Ashby J, Tinwell H, Haseman J. 1999. Lack of effects for low dose levels of bisphenol A (BPA) and diethylstilbestrol (DES) on the prostate gland of CF1 mice exposed in utero. Regulatory Toxicolology and Pharmacology 30:156–166.

Cagen SZ, Waechter JM, Dimond SS, Breslin WJ, Butala JH, Jekat FW, et al. 1999. Normal reproductive organ development in CF-1 mice following prenatal exposure to bisphenol A. Toxicological Sciences 11:15–29.

Canada. 2008. Proposed Risk Management Approach for Phenol, 4,4'-(1-methylethylidene) bis (Bisphenol A). Environment Canada-Health Canada. October, 2008. Available at: http://www.ec.gc.ca/substances/ese/eng/challenge/batch2/batch2_80-05-7_rm.cfm

Carwile JL, Luu HT, Bassett LS, Driscoll DA, Yuan C, Chang JY, Ye X, Calafat AM, Michels KB. 2009. Use of Polycarbonate bottles and urinary bisphenol A concentrations. Environmental Health Perspectives, epub May 12th, 2009,

Endocrine Society. 2009. Endocrine-Disrupting Chemicals: An Endocrine Society Scientific Statement. Endocrine Reviews, June 2009, 30(4):293–342 Available at: http://www.endo-society.org/journals/ScientificStatements/upload/EDC_Scientific_Statement.pdf

EPA (U.S. Environmental Protection Agency). 1993. Bisphenol A, CASRN 80-05-7, IRIS, Integrated Risk Information System. Available online at: http://www.epa.gov/iriswebp/iris/sust/0356.htm

Fernandez M, Bianchi M, Lux-Lantos V, Libertun C. 2009. Exposure to bisphenol A alters reproductive parameters and gonadotropin releasing hormone signaling in female rats. Environmental Health Perspectives 117(5): 757-62.

Food and Drug Administration. 2008a. Draft assessment of bisphenol A for use in food contact applications. Available online at: http://www.fda.gov/ohrms/dockets/ac/08/briefing/2008-0038b1_01_00_index.htm

Food and Drug Administration. 2008b. Scientific peer-review of the draft assessment of bisphenol A for use in food contact applications. FDA Science Board Subcommittee on Bisphenol A. October 31, 2008. Available online at: http://www.fda.gov/ohrms/dockets/ac/08/briefing/2008-4386b1-05.pdf

Health Canada. 2008. Minister's remarks on Bisphenol A. Available online at: http://www.hc-sc.gc.ca/ahc-asc/minist/speeches-discours/2008_04_18-eng.php

National Caucus of Environmental Legislators. 2009. Minnesota, Vermont chemical policy bills pass legislature. Available online at: http://www.ncel.net/newsmanager/news_article.cgi?news_id=199.

National Toxicology Program. (2008). Draft NTP report on bisphenol A. Available at: http://cerhr.niehs.nih.gov/chemicals/bisphenol/bisphenol.html.

Tyl R. 2002. Three-generation reproductive toxicity evaluation of Bisphenol A in the feed of CD (Sprague-Dawley) rats. Toxicological Sciences 68, 121-146.

Tyl RW, Myers C, Marr M, Sloan CS, Castillo N, Veselica MM, et al. 2008. Two-generation reproductive toxicity study of dietary bisphenol A (BPA) in CD-1 (Swiss) mice. Toxicological Sciences 104:362–384.

vom Saal FS, Hughes C. 2005. An extensive new literature concerning low-dose effects of bisphenol A shows the need for a new risk assessment. Environ Health Perspect. 113(8):926-33.

vom Saal FS, Belcher SM, Guillette LJ, Hauser R, Myers JP, Prins GS, et al. 2007. Chapel Hill Bisphenol A Expert Panel Consensus Statement: Integration of mechanisms, effects in animals and potential impact to human health at current exposure levels. Reproductive Toxicology 24(2).

vom Saal FS. 2009. Assessment of the outcomes of low-dose Bisphenol A studies. Prepared March 2009. Available at: http://endocrinedisruptors.missouri.edu/vomsaal/vomsaal.html