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Developmental and Reproductive Toxicants Identification Committee
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Office of Environmental Health Hazard Assessment
Proposition 65 Implementation
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Submitted via email: coshita@oehha.ca.gov

Re: Proposed Listing of Bisphenol A as a Developmental and Reproductive Toxicant on California's Prop 65 list.

Dear Office of Environmental Health Hazard Assessment,

The following comments are on behalf of the Natural Resources Defense Council (NRDC), a non-profit organization with over 1.2 million members and activists, 250,000 of whom are Californians. NRDC has no financial interest in bisphenol A.

Bisphenol A (BPA) is of significant concern to the health of Californians due to the wide range of health impacts linked to current levels of exposure. Based on biomonitoring done in the general U.S. population, California residents are presumed to be widely exposed to this chemical through the use of consumer products containing BPA. Although many people recognize the label "BPA-free", most members of the general public do not know how to recognize products that do contain BPA. Labeling would help the consumer to make informed choices.

OEHHA staff scientists have prepared a very thorough document which reviews the developmental, male and female reproductive toxicity, including the early onset of puberty. However, notably missing from this document is a discussion of the widespread exposure in the general population, including potential sources of exposure which include many products that a developing child is exposed to. Furthermore, there is lacking a discussion of findings in non-human primate models which support the rodent data linking neurodevelopmental harm to BPA exposure. Nor was there a discussion of alterations in adipogenesis or hormone disruption in adipose tissue potentially contributing to metabolic syndrome, insulin resistance and chronic diseases such as diabetes and cardiovascular disease. In addition, a number of peer-reviewed studies were published after the OEHHA

draft document was completed. These studies are described in brief and attached here for submission into the record.

Exposure monitoring.

- **There is widespread exposure in the general population, including fetuses and infants**.

CDC NHANES data has demonstrated that >90% of population ages 6-60^{+} years old have metabolic breakdown products of BPA in their urine.[1] In addition, BPA has been measured in follicular fluid[2], amniotic fluid[3] colostrum[4], breast milk[5], cord blood[6] and placenta[7] indicating that exposures are occurring during vulnerable periods of development.

Sources of Exposure.

- **Food packaging –** BPA used in the lining of canned food containers is a source of exposure to BPA.[8] Also food packaging made from recycled paper content contains BPA and could result in migration of BPA into food.[9]

- **Polycarbonate beverage containers** – In addition to data which has already been summarized by FDA and the NTP demonstrating that beverages heated in polycarbonate plastic contain BPA that leaches from the container, drinking COLD beverages from reusable polycarbonate containers increased urinary BPA concentrations by 69%, irrespective of exposure to BPA from other sources.[10]

- **Medical Devices** – Premature infants in the ICU were found to have BPA levels eleven times higher than general population. High exposure to medical devices correlated with higher levels of BPA.[11]

- **Dental devices –** Dental sealants and composite resins contain BPA, most often in the form of bis-GMA. Application results in short bursts of exposure over back ground levels.

Pharmacokinetics

- Comparisons of BPA levels with fasting time measured in the NHANES population, found BPA levels did not decline as rapidly with fasting as would be predicted by the assumed half-life in humans of several hours. This study's preliminary results challenge previously held assumptions about metabolism and sources of exposure of BPA, indicating either that the half-life of BPA is longer and/or food is not the major source of exposure.[12]

- The free or unconjugated form of BPA (the more toxic form of the chemical) is the most prevalent form found in many biological samples including the placenta[13] and breast milk[14]. Also deconjugation in prenatal and neonatal tissues may result in higher levels of exposure to free BPA.[15] Therefore, it should not be assumed that in vulnerable populations such as the fetus or neonate, BPA will be rapidly metabolized and conjugated into less toxic metabolites.

Early Onset of Puberty

- **In vivo – animal studies**

Previous research cited in the OEHHA document has demonstrated that BPA accelerates the onset of puberty in female mice.[16] Early onset of puberty is a risk factor for breast cancer and pyschosocial impacts of early development including an earlier age at first intercourse and substance abuse.

There are two studies documenting early onset of puberty in rodent models that were not cited in the OEHHA draft.

1. Neonatal BPA exposure is linked to permanent hormonal changes resulting in early puberty.[17] This study examined how BPA affects reproductive development and hormones in female adolescent and adult rats that were exposed during their first couple of weeks of life. The exposure time frame corresponds to infancy through pre-puberty in humans. Female rats were injected subcutaneously, daily, from postnatal day 1 (PND1) to PND10 with BPA [500 microg/50 microL (high) or 50 microg/50 microL (low)] in castor oil or with castor oil vehicle alone. BPA dose-dependently accelerated puberty onset and altered estrous cyclicity, with the high dose causing permanent estrus. These results demonstrate that neonatal BPA exposure permanently affects reproductive parameters. Past studies have found a similar early onset of puberty when exposures occur during prenatal development.

2. Low doses of BPA administered during neonatal development have also been shown to accelerate the onset of puberty in rats and alter ovarian development resulting in cysts and premature loss of their estrus cycle.[18] These effects are consistent with an estrogenic mode of action. Altered ovarian development and premature loss of estrus cyclicity will result in infertility.

Neurobehavioral Abnormalities.

Studies of non-human primates have found alterations in brain development that support the rodent data linking neurodevelopmental harm to BPA exposure.

- **In vivo - - Non-human Primate studies**

BPA alters estradiol-induced synaptogenesis in pre-frontal cortex and hippocampus of non-human primates.[19] This study examined the impacts of daily exposure to the current reference dose, on estradiol-induced synapse formation in the hippocampus and prefrontal cortex of a nonhuman primate model. BPA was found to completely abolish the synaptogenic response to estradiol. Because remodeling of synapses may play a critical role in cognition and mood, the ability of BPA to interfere with synapse formation has profound implications. This study is the first to demonstrate an adverse effect of BPA on the brain in a nonhuman primate model.

BPA alters sexually dimorphic behavior in non-human primates. Infant male monkeys exposed to BPA at low doses behaved more like infant females.[20] This study is in agreement with rodent models which have demonstrated alterations in sexually dimorphic behavior after BPA exposure.

Animal models and now non-human primate models have demonstrated exposure to BPA during vulnerable periods of development interferes with development of the brain and dopaminergic signaling which could impact behavior and learning.

Alterations in metabolism

Insulin Resistance/glucose metabolism.

Numerous peer-reviewed published studies have been published which have demonstrated the BPA interferes with glucose homeostasis by altering glucose transport and promoting insulin resistance. Much of this research has been conducted during vulnerable periods of development. Some of these studies are highlighted below.

- **In vitro**

BPA increases glucose uptake into adipocytes.[21]

- **In vivo**

BPA disrupts pancreatic beta-cell function producing insulin resistance in male mice.[22] BPA exerts rapid non-genomic effects on insulin releasing beta-cells and glucagon releasing alpha-cells within freshly isolated islets of Langerhans. When mice were treated with BPA 100mug/kg/day for 4 days, BPA caused an increase in beta-cell insulin content along with a post-prandial hyperinsulinaemia and insulin resistance. Altered glucose metabolism and insulin resistance are precursors to the development of diabetes and metabolic syndrome.

Fat metabolism

- **In vitro**

BPA decreases secretion of adiponectin from human adipose tissue.[23] Adiponectin is an adipocyte-specific hormone that increases insulin sensitivity and reduces tissue inflammation. Thus, any factor that suppresses adiponectin release could lead to insulin resistance and increased susceptibility to obesity-associated diseases.

BPA stimulates the release of inflammatory factors such as interleukin-6 (IL-6) and tumor necrosis factor alpha (TNFalpha) from human adipose tissue.[24] Elevated serum IL-6 levels are associated with increased cardiovascular risk in obese and diabetic patients and contribute to the low grade inflammation that accompanies the metabolic syndrome. There is a strong correlation between increased TNF alpha production, adiposity and insulin resistance.

Finally, a study published just a few days ago adds further evidence to the impact of BPA on adipose tissue and function. **Perinatal exposure to low doses of BPA resulted in a 3-fold increase in the fat pads of female mice.**[25] There was no difference in chow intake leading authors suggest that adult body weight may be programmed during early life.

Cardiovascular disease

- **Human epidemiology**

This study was a cross-sectional analysis of BPA concentrations and health status of general U.S. adult population using the CDC NHANES data from 2003-2004. The researchers found

increase risk of cardiovascular disease and diabetes with evidence of higher levels of BPA exposure.[26]

We now have *in vitro, in vivo* and human data which indicates BPA is associated with alterations in metabolism that could result in the development of insulin resistance, diabetes and conditions associated with the development of metabolic syndrome and cardiovascular disease. Some of these impacts have been shown to result from exposures that occur during development and should be considered as part of the developmental toxicity associated with exposure to BPA.

In summary, the *in vitro, in vivo* and non-human primate data provide compelling evidence of harm for multiple endpoints of developmental and reproductive toxicity. The weight of evidence supports a listing of BPA on the Prop 65 list. The additional studies submitted herein should be added to the record and considered along with other data already compiled by OEHHA staff.

Please contact me with any questions or concerns about these comments.

Sincerely,

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