Developmental and Reproductive Toxicants Identification Committee
c/o Ms. Monet Vela
Office of Environmental Health Hazard Assessment
Proposition 65 Implementation Office
P.O. Box 4010, MS-58D
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April 20, 2015

RE: Consideration of bisphenol A (BPA) for possible listing based on female reproductive toxicity

Dear Office of Environmental Health Hazard Assessment,

The following comments are submitted on behalf of the undersigned individuals and organizations, none of whom have any financial interest in the topic of these comments.

Bisphenol A (BPA) is a ubiquitous, high production volume chemical of significant concern to the health of Californians because it is linked to a wide range of health impacts.[1,2] Biomonitoring data indicate that more than 90% of Americans have BPA in their bodies.[3] The Biomonitoring California program detected BPA in the bodies of Californians, including pregnant women.[4] The main source of exposure is through food and beverages; small children may also be exposed by hand to mouth contact with materials containing BPA.[5] Additionally, recent evidence indicates that thermal paper receipts are also a likely source of exposure by direct contact with skin.[6] Medical devices and house dust have also been identified as sources of exposure.[7]

OEHHA staff scientists have reviewed the available publications since 2009, the last time the Developmental and Reproductive Toxicants Identification Committee (DART IC) considered a proposal to list BPA under Proposition 65, and have prepared thorough documentation demonstrating that BPA is a female reproductive toxicant. However, one impact very relevant to female reproductive toxicity, the effect of BPA on the mammary gland is notably missing from this review.

Although it is not a primary reproductive organ, the mammary gland plays an important role in reproductive function, providing nourishment to the offspring after birth, and is firmly encompassed

[1] Vandenberg LN, Ehrlich S, Belcher S, Ben-Jonathan N et al. Low dose effects of bisphenol A: An integrated review of in vitro, laboratory animals and epidemiology studies. 2013. Endocrine Disruptors 1:1
[2] Rochester JR. Bisphenol A and human health: A review of the literature. 2013. Reprod Toxicol 42:132-155
[3] Calafat AM, Ye X, Wong LY, Reidy JA, Needham LL. Exposure of the U.S. population to bisphenol A and 4-tertiary-octylphenol: 2003-2004. 2008. Environ Health Perspect. 116(1):39-44
[4] Biomonitoring California. http://biomonitoring.ca.gov/results/chemical/64
[5] National Biomonitoring Program. Center for Disease Control and Prevention. http://www.cdc.gov/biomonitoring/BisphenolA_FactSheet.html
[6] Hormann AM, vom Saal FS, Nagel SC, et al. Holding thermal paper and eating food after using hand sanitizer results in high serum bioactive and urine total levels of bisphenol A (BPA). 2014. PLOS One Vol 9 Issue 10 DOI: 10.1371/journal.pone.0110509
[7] Vandenberg LN, Chahoud I, Heindel JJ, Padmanabhan V, Paumgartten FJ, Schoenfelder G. Urinary, circulating, and tissue biomonitoring studies indicate widespread exposure to bisphenol A. 2010. Environ Health Perspect. 118(8):1055-70

within the reproductive effects relevant to listing of reproductive toxicants under Proposition 65. The mammary gland's development, maturation, and function depend on many of the same hormones that control the primary reproductive organs, and it is also affected by many endocrine disrupting chemicals.[8,9]

We provide specific comments and references below and in Appendix 1 documenting the evidence that BPA negatively affects the development of the mammary gland for submission into the record.

A) Standards for DART IC to recommend listing a chemical under Proposition 65

Pursuant to the regulations implementing Proposition 65, the DART IC may "[r]ender an opinion . . . as to whether specific chemicals have been clearly shown, through scientifically valid testing according to generally accepted principles, to cause reproductive toxicity." 27 Cal. Code Regs. § 25305(b). The criteria that guide the DART IC's recommendations emphasize a "weight-of-evidence" approach and are "not intended to limit the scope of the Committee's consideration of appropriate scientific information, nor to limit its use of best scientific judgment." [10] However, the criteria provide important indicators of the sufficiency of evidence that would support a recommendation for listing a chemical.

According to the criteria, "developmental toxicity," "female reproductive toxicity," and "male reproductive toxicity" are all included within "reproductive toxicity." A chemical may be recommended for listing if it meets one of the following criteria:

- sufficient evidence of reproductive toxicity in humans, or
- limited evidence or suggestive evidence in humans, supported by sufficient experimental animal (mammal) data, or
- sufficient evidence in experimental animals (mammals), such that extrapolation to humans is appropriate.

Id. The DART IC also takes account of biological plausibility and statistical considerations. *Id.* Considerations for sufficiency of evidence in humans include scientifically valid epidemiological studies conducted according to generally accepted principles, clinical cases, and weight of evidence considerations. *Id.* In animals, sufficiency of evidence considerations include: experimental design, relevance of exposure to expected human exposures and timing of exposure, number of dose levels sufficient to evaluate the presence of a dose-response relationship, maternal and systemic toxicity, number of tests or experimental animal species (including weight of evidence), and other considerations. *Id.* The evidence for female reproductive toxicity presented by OEHHA, as well as additional evidence of effects on the mammary gland, meets these criteria, and therefore the DART IC should recommend BPA for listing.

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[8] Fenton SE, Hamm JT, Birnbaum LS, Youngblood GL. Persistent abnormalities in the rat mammary gland following gestational and lactational exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). 2002. Toxicol Sci 67:63-74

[9] Tucker DK, Macon MB, Strynar MJ, Dagnino S, Andersen E, Fenton SE. The mammary gland is a sensitive pubertal target in CD-1 and C57Bl/6 mice following perinatal perfluorooctanoic acid (PFOA) exposure. 2014. Reprod Toxicol doi: 10.1016/j.reprotox.2014.12.002. [Epub ahead of print]

[10] Criteria For Recommending Chemicals For Listing As "Known To The State To Cause Reproductive Toxicity" (November 1993). See http://www.oehha.org/prop65/policy_procedure/pdf_zip/dartCriteriaNov1993.pdf

B) BPA is a female reproductive toxicant and should be listed under Proposition 65

The main source of scientific evidence presented by OEHHA is a literature review[11] performed by Peretz and colleagues and published in the peer-reviewed journal Environmental Health Perspectives. This extensive work is the first comprehensive evaluation of the reproductive health literature on BPA published since the 2007 reports by the Chapel Hill bisphenol A expert panels.[12]

The Peretz review is thorough and methodologically strong. It includes hundreds of peer-reviewed journal articles published and catalogued in PubMed between 2007 and 2013. Due to the paucity of research in some categories, all journal articles were included and the strength of the evidence was based on similarity of effects on tissues or endpoints across species. Peer review of both the Peretz review and the underlying references helps ensure that the studies are scientifically valid according to generally accepted principles, have good experimental design, and are analytically robust so that they support the conclusions reached (i.e. meet the criteria above for sufficient evidence).

This scientifically-sound analysis discusses in detail evidence for 13 female health-related outcomes, from early development of oocytes during gestation to puberty, birth weight, and placental health. Human, *in vivo* animal, and *in vitro* studies are included in the analysis. The evidence is presented by study type, timing of exposure (i.e. pre-natal, neonatal, and post-natal) and doses (low dose was defined as a BPA dose equal to or below 50 mg/kg body weight per day, the currently accepted lowest adverse effect level (LOAEL) used by the U.S. Environmental Protection Agency).

We agree with the conclusions of Peretz and colleagues that the combination of mechanistic, animal and human studies shows that BPA:

- Adversely affects the male and female reproductive system at low doses in animal models
- Is an ovarian toxicant in women and animal models
- Is a uterine toxicant in animal models

The authors also found limited evidence from human studies that BPA causes other adverse female reproductive effects including: 1) association with hyperandrogenism such as in polycystic ovarian syndrome in women, and 2) association with impaired implantation in women undergoing *in vitro* fertilization. As described below in section E, another paper which used systematic criteria to review human epidemiological studies also concluded there is some evidence that BPA contributes to infertility in women.

A large and strong body of *in vivo* and epidemiological studies in both humans and animals, including non-human primates, provide more than sufficient evidence of reproductive toxicity. These studies are bolstered by the mechanistic studies, which demonstrate biological plausibility. This significant body of literature shows that BPA meets the criteria to be listed as a reproductive toxicant under Proposition 65.

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[11] Peretz JP, Vrooman L, Ricke WA, Hunt PA, Ehrlich S, Hauser R, Padmanabhan V, Taylor HS, Swan SH, VandeVoort CA, Flaws JA. Bisphenol A and Reproductive Health: Update of Experimental and Human Evidence, 2007–2013. 2014. Environ Health Perspect 122:775–786

[12] vom Saal FS, Akingbemi BT, Belcher SM, Birnbaum LS, Crain DA, Eriksen M, et al. 2007. 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 24:131–138.

Following similar findings in 2014, the European Chemicals Agency (ECHA) proposed to upgrade the classification of BPA from a "suspected" (category 2) to a "presumed" (category 1B) reproductive toxicant based on studies showing adverse impacts on female fertility and sexual function in animal and human studies.[13]

C) Impacts on the mammary gland are included in the definition of "female reproductive toxicity"

The 1993 Criteria for Recommending Chemicals define female reproductive toxicity "to include effects on the adult or, where appropriate, developing female organism, including, but not limited to . . . [i]mpaired reproductive performance." The Criteria list adverse effects on lactation as an example of impaired reproductive performance and the mammary gland is, of course, essential to lactation.

According to OEHHA's criteria, an adverse effect on milk production with a subsequent reduction in the offspring's body weight qualifies as impaired reproductive performance. In fact, in its 2009 document submitted to DART IC, supporting the listing of BPA, OEHHA summarized peer-reviewed studies showing the impact of BPA on the mammary gland. One of them was a 2004 study showing that BPA alters milk production in mice. OEHHA summarized as follows:

> Studies report that BPA treatment during pregnancy may also alter milk production in mice. A few studies have shown prolactin levels can be altered by exposure to BPA. Prolactin is a hormone known to positively regulate the secretion of breast milk in maternal mice. From GD 14 until delivery, ddY mice were fed 1% BPA (w/w) in feed. Subsequent results showed maternal serum prolactin levels were significantly less compared with controls, and offspring weighed significantly less compared with controls (Matsumoto et al., 2004).[14]

D) BPA consistently affects the mammary gland across species and experimental models

A more recent peer-reviewed study also showed the adverse and long lasting impact of BPA on mammary gland function. Kass et al. showed that female rats exposed to BPA pre-and post-natally subsequently produced less milk and milk of an altered composition when they became pregnant[15]. These findings show that BPA exposure affects lactation and thus causes female reproductive toxicity.

Between 2009 and January 2015, 19 additional animal studies have been published showing other effects of BPA exposure on the mammary gland in three species: mouse, rat and non-human primates. The effects included altered development, impaired tissue differentiation (such as cell death and proliferation in terminal end buds and hormone receptor expression), altered response to hormones, and increased risk of mammary tumors. Additionally, animal studies showed that the development of

[13] http://echa.europa.eu/view-article/-/journal_content/title/rac-proposes-to-strengthen-the-classification-of-bisphenol-a

[14] Evidence of the developmental and reproductive toxicity of Bisphenol A. October 2009. Reproductive and Cancer Hazard Assessment Branch. Office of Environmental Health Hazard Assessment. California Environmental Protection Agency.

[15] Kass L, Altamirano GA, Bosquiazzo VL, Luque EH, Munoz de Toro M. Perinatal exposure to xenoestrogens impairs mammary gland differentiation and modifies milk composition in Wistar rats. 2012. Reproductive Toxicology 3:390-400

the male mammary gland is also adversely affected by perinatal exposure to BPA. See Appendix 1 for a complete list of references.

There were also six in vitro studies using breast cells showing BPA effects on the epigenome, cell differentiation, proliferation and cell death pathways, and DNA damage. (References in Appendix 1). These studies relate to the mechanism of action and show the biological plausibility of the effects observed in animal studies.

Moreover, a study of 264 postmenopausal women in Wisconsin showed that circulating BPA was positively associated with mammographic breast density.[16] Mammographic breast density is a strong risk factor for breast cancer.[17]

In its 2015 Scientific Opinion,[18] the European Food Safety Authority (EFSA) concluded it was "likely" that exposures to BPA before birth or up to 90 days after birth "induced proliferative changes in the mammary gland." The panel of experts evaluated studies addressing effects on ductal hyperplasia, intraductal hyperplasia and cell proliferation. Regarding the relevance and adversity to humans, the experts concluded that "[i]ntraductal hyperplasia is observed in humans and is considered a precursor of ductal carcinoma both in rodents and humans. Therefore this lesion is of high relevance to predict cancer in human and animal mammary gland and is considered as adverse."[19] This conclusion is well supported by dozens of peer-reviewed scientific studies (Appendix 1).

The consistency of peer-reviewed findings across experimental models and species along with the mechanistic data from *in vitro* studies provides strong evidence that BPA exposure can adversely affect the mammary gland, an organ that is part of the female reproductive system.

The additional studies submitted herein should be added to the record and considered along with the other data already compiled by OEHHA staff.

E) Evidence that BPA exposures cause other kinds of developmental and reproductive toxicity in addition to female reproductive toxicity

The scientific evidence documenting other adverse reproductive health outcomes caused by or linked to BPA exposures continues to grow in quantity and strength.

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[16] Sprague BL, Trentham-Dietz A, Hedman CJ, Wang J, Hemming JD, Hampton JM, Buist DS, Aiello Bowles EJ, Sisney GS, Burnside ES. Circulating serum xenoestrogens and mammographic breast density. 2013. Breast Cancer Res. 15(3):R45

[17] Razzaghi H, Troester MA, Gierach GL, Olshan AF, Yankaskas BC, Millikan RC. Association between mammographic density and basal-like and luminal A breast cancer subtypes. 2013. Breast Cancer Res. 15:R76

[18] Scientific Opinion on the risks to public health related to the presence of bisphenol A (BPA) in foodstuffs: PART II - Toxicological assessment and risk characterization. 2015. EFSA Journal 2015; 13(1):3978

[19] Although EFSA concluded that BPA was of low health concern in spite of mammary gland and other toxicity, it based that conclusion partly on an exposure assessment that utilized a number of methodologies and assumptions that have been disputed in the peer-reviewed scientific literature. These include: assuming that all free unconjugated BPA measured in human serum was due to laboratory contamination; excluding exposures from medical devices; assuming that animal meat only contains conjugated BPA; assuming very low dermal absorption (from thermal paper and cosmetics); and using only average exposure levels (for BPA from products, dust or indoor air) rather than a range of values to represent low, average, and high end exposures.

Peretz and colleagues also reviewed the effects of BPA on developmental outcomes and the male reproductive system.[20] Using the same methods mentioned earlier, the authors concluded that there is limited evidence that BPA exposures impact birth weight in animal studies. They also found strong evidence that BPA is a prostate toxicant in animal studies, and limited evidence for testicular toxicity in animals and sexual dysfunction in men.

ECHA's evaluation also concluded that BPA is associated with adverse impacts on male fertility and sexual function based on evidence from animal and human studies.[21]

Other evidence described below highlights that sensitive populations including children and workers are more vulnerable to the toxic impacts of BPA. Specifically, more and more evidence points to critical prenatal periods during which BPA exposures can disrupt normal development.

Particularly compelling are a series of studies on non-human primates from the California National Primate Research Center at UC Davis showing a variety of effects of prenatal exposure to BPA, including alterations in the development of the brain, mammary gland, fetal ovary, and airways.[22,23,24,25,26]

A 2013 peer-reviewed paper focused on BPA's effects on human health by conducting a comprehensive review of 86 epidemiological studies to evaluate the evidence linking BPA exposures to adverse perinatal, childhood and adult health outcomes[27]. The strength of the evidence for each health effect was analyzed according to parameters based on the National Toxicology Program Office of Health Assessment and Translation (OHAT) approach, including study design features, possible biases (selection, performance, attrition/exclusion, detection, and selective reporting), statistical methods, sample size, unexplained variation or outcomes, magnitude of effect, dose–response, bias towards the

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[20] Peretz JP, Vrooman L, Ricke WA, Hunt PA, Ehrlich S, Hauser R, Padmanabhan V, Taylor HS, Swan SH, VandeVoort CA, Flaws JA. Bisphenol A and Reproductive Health: Update of Experimental and Human Evidence, 2007 -2013. 2014. Environ Health Perspect 122:775–786

[21] http://echa.europa.eu/view-article/-/journal_content/title/rac-proposes-to-strengthen-the-classification-of-bisphenol-a

[22] Elsworth, John D., J. David Jentsch, Catherine A. VandeVoort, Robert H. Roth, D. Eugene Redmond, and Csaba Leranth. "Prenatal Exposure to Bisphenol A Impacts Midbrain Dopamine Neurons and Hippocampal Spine Synapses in Non-Human Primates." Neurotoxicology 35 (March 2013): 113–20. doi:10.1016/j.neuro.2013.01.001.

[23] Chapalamadugu, Kalyan C., Catherine A. VandeVoort, Matthew L. Settles, Barrie D. Robison, and Gordon K. Murdoch. "Maternal Bisphenol A Exposure Impacts the Fetal Heart Transcriptome." PLoS ONE 9, no. 2 (February 25, 2014): e89096. doi:10.1371/journal.pone.0089096.

[24] Tharp, Andrew P., Maricel V. Maffini, Patricia A. Hunt, Catherine A. VandeVoort, Carlos Sonnenschein, and Ana M. Soto. "Bisphenol A Alters the Development of the Rhesus Monkey Mammary Gland." Proceedings of the National Academy of Sciences 109, no. 21 (May 22, 2012): 8190–95. doi:10.1073/pnas.1120488109.

[25] Hunt, Patricia A., Crystal Lawson, Mary Gieske, Brenda Murdoch, Helen Smith, Alyssa Marre, Terry Hassold, and Catherine A. VandeVoort. "Bisphenol A Alters Early Oogenesis and Follicle Formation in the Fetal Ovary of the Rhesus Monkey." Proceedings of the National Academy of Sciences 109, no. 43 (October 23, 2012): 17525–30. doi:10.1073/pnas.1207854109.

[26] Van Winkle, Laura S., Shannon R. Murphy, Miriam V. Boetticher, and Catherine A. VandeVoort. "Fetal Exposure of Rhesus Macaques to Bisphenol A Alters Cellular Development of the Conducting Airway by Changing Epithelial Secretory Product Expression." Environmental Health Perspectives 121, no. 8 (June 11, 2013): 912–18. doi:10.1289/ehp.1206064.

[27] Rochester JR. Bisphenol A and human health: A review of the literature. 2013. Reproductive Toxicology 42:132-155

null, biological plausibility, and cross-species/population consistency. Overall, the author concluded that "…the growing human literature correlating environmental BPA exposure to adverse effects in humans, along with laboratory studies in many species including primates, provides increasing support that environmental BPA exposure can be harmful to humans, especially in regards to behavioral and other effects in children." The review also found that:

- There is strong epidemiological evidence that early life BPA exposures are associated with disrupted neurodevelopment and altered behaviors in children.
- There is strong epidemiological evidence that early life BPA exposures are associated with increased probability of childhood asthma and wheeze (developmental toxicity).
- There is some evidence from epidemiological studies that BPA may contribute to infertility in humans.
- Many epidemiological studies find significant adverse impacts, including reproductive impacts, in populations exposed to BPA at levels 70-5000 times lower than the current Tolerable Daily Intake of 50 µg/kg/day.

Another peer-reviewed journal article specifically assessed the low dose effects of BPA through an integrated review of epidemiology, *in vivo* animal, and *in vitro* studies.[28] This extensive review also focused on developmental exposures and presented integrated evidence that BPA has similar effects *in vitro*, in laboratory animals, and in human studies. The authors concluded that low dose effects are consistent and reproducible across different experimental systems and that BPA often poses a greater health threat when exposures occur during vulnerable developmental stages (i.e. organ development) and critical post-natal periods (i.e. organ and tissue differentiation). Based on the available evidence, Vandenberg and colleagues are confident that "low dose effects have been demonstrated in rodents following developmental exposures to BPA, including effects on male and female reproductive tracts, [and] brain development and behavior…"

The above-mentioned studies provide sufficient evidence of developmental toxicity and male reproductive toxicity from BPA in humans and experimental animals, supporting listing under Proposition 65. The additional studies submitted herein should be added to the record and considered along with the other data already compiled by OEHHA staff.

In conclusion, endocrine disruptors in general have been linked to many adverse health outcomes including adverse reproductive impacts in females and males, as well as negative developmental and neurobehavioral effects. [29,30] Bisphenol A in particular has been associated with many of those adverse effects. In the last 15 years, multiple lines of scientific evidence from many hundreds of *in vitro*, animal, and epidemiological studies have contributed to the body of literature showing the role of BPA in female

[28] Vandenberg LN, Ehrlich S, Belcher SM, et al. Low dose effects of bisphenol A. An integrated review of in vitro, laboratory animal, and epidemiology studies. 2013. Endocrine Disruptors 1:1 e1-20.

[29] Exposure to Toxic Environmental Agents. Committee Opinion. 2013. The American College of Obstetricians and Gynecologists Committee on Health Care for Underserved Women. American Society for Reproductive Medicine Practice Committee. The University of California, San Francisco Program on Reproductive Health and the Environment.

[30] Trasande L, Zoeller RT, Hass U, Kortenkamp A et al. Estimating Burden and Disease Costs of Exposure to Endocrine-Disrupting Chemicals in the European Union. 2015. J Clin Endocrinol Metab. doi: 10.1210/jc.2014-4324

reproductive toxicity, including the mammary gland, as well as on other developmental and reproductive end points. For all these reasons, we strongly support the listing of BPA under Proposition 65.

Respectfully submitted,

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Appendix 1

Additional References

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