



May 13, 2010

Ms. Cynthia Oshita
Office of Environmental Health Hazard Assessment
Proposition 65 Implementation
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Dear Ms. Oshita:

The Environmental Working Group (EWG) and the Natural Resources Defense Council (NRDC) strongly encourage OEHHA to list the chemical Bisphenol A (BPA) as a reproductive and developmental toxicant under Proposition 65, via the “authoritative bodies” mechanism (22 CCR § 12306). There is a robust body of science that supports the listing of BPA as a chemical that may pose risks to human reproduction and development.

As NRDC’s petition demonstrated and as OEHHA recognized in proposing listing, BPA meets the requirements for listing under the authoritative bodies listing mechanism¹ as it has been formally identified by an authoritative body recognized by the State of California under Proposition 65 as causing reproductive toxicity (NRDC 2008).

Consistent with the rules guiding the Authoritative Bodies listing mechanism², BPA was the subject of a report published by the National Toxicology Program report in September 2008, which concluded that the chemical causes reproductive toxicity. NTP states there is “clear evidence of adverse developmental effects at ‘high’ doses of Bisphenol A in the form of fetal death, decreased litter size, or decreased number of live pups per litter in rats (≥ 500 mg/kg bw/day) and mice (≥ 875 mg/kg bw/day) reduced growth in rats (≥ 300 mg/kg bw/day) and mice (≥ 600 mg/kg bw/day), and delayed puberty in male mice (600 mg/kg bw/day), male rats (≥ 50 mg/kg bw/day) and female rats (≥ 50 mg/kg bw/day).”

¹ 27 Cal. Code Regs. § 25306(c).

² 27 Cal. Code Regs. § 25306(d)(1).

Moreover NTP also 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 two listing mechanisms are completely independent

Despite the chemical industry's argument to the contrary, the State Development and Reproductive Toxicity Identification Committee's (DART IC) determination not to list BPA in July 2009 has no bearing on listing under the Authoritative Bodies listing mechanism. As OEHHA has consistently asserted, the various listing mechanisms are independent of each other.³ Accordingly, listing must proceed under any mechanism for which the listing requirements are met. BPA satisfies the requirements for listing under the authoritative body mechanism and thus must be listed, irrespective of the DART Committee's findings under a different listing mechanism.

In evaluating chemicals for listing as a reproductive toxin, the DART Committee is required to “[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)(1). The DART Committee thus determines, whether, in its opinion, a chemical has been “clearly shown” to cause reproductive toxicity.

On the other hand, the authoritative bodies mechanism *requires* listing by OEHHA if the chemical has “been formally identified by an authoritative body as causing . . . reproductive toxicity.” *Id.* § 25306(c). A chemical is “formally identified” by an authoritative body when the “*lead agency*,” i.e. OEHHA, determines that the chemical has been included on a list of chemicals causing reproductive toxicity issued by the authoritative body or is the subject of a report concluding that chemical causes reproductive toxicity or has otherwise been identified as causing reproductive toxicity by the authoritative body in a final document. *Id.* § 25306(d)(1). The Proposition 65 regulations define how a chemical is identified “as causing reproductive toxicity” for purposes of the authoritative bodies listing mechanism. A chemical “causes” reproductive toxicity if:

Studies in experimental animals indicate that there are sufficient data, taking into account, the adequacy of the experimental design and other parameters such as, but not limited to, route of administration,

³ Memorandum from Colleen Murphy, OEHHA Chief Counsel, to Members of the Carcinogen Identification Committee and DART Committee (July 20, 1998), at http://oehha.ca.gov/prop65/public_meetings/cicdart2.html; OEHHA, Request for Relevant Information on a Chemical Being Considered for Listing by the Authoritative Bodies Mechanism: Bisphenol-A, February 12, 2010, at http://oehha.ca.gov/prop65/CRNR_notices/admin_listing/requests_info/callinBPA021210.html; see OEHHA, Mechanisms for Listing and Delisting Chemicals Under Proposition 65, May 15, 2007, at http://www.oehha.ca.gov/prop65/policy_procedure/listde051007.html.

frequency and duration of exposure, number of test animals, choice of species, choice of dosage levels, and consideration of maternal toxicity, *indicating that an association between adverse reproductive effects in humans and the toxic agent in question is biological plausible.*

27 Cal. Code Regs. § 25306(g)(2) (emphasis added).

Whether or not a chemical has or has not been previously considered by the DART Committee is irrelevant to whether the chemical meets the independent listing requirement of having been formally identified by an authoritative body as causing reproductive and developmental harm pursuant to Section 25306. The only time that DART becomes involved in the authoritative bodies listing process is if OEHHA determines that a chemical *does not* meet the requirements of Section 25306, in which case OEHHA procedure requires that the chemical be referred to the DART committee for evaluation. 27 Cal. Code Regs. § 25306(i). If the chemical *does* meet the Section 25306 requirements, DART has no role.

BPA easily meets the listing requirements via the authoritative bodies mechanism

This chemical easily meets the Proposition 65 standard for listing under the authoritative bodies mechanism based on the *NTP-CERHR Monograph on the Potential Human Reproductive and Developmental Effects of Bisphenol A* (“NTP Monograph”) published by an authoritative body, the Center for the Evaluation of Risks to Human Reproduction of the National Toxicology Program of the U.S. Department of Health and Human Services. 27 Cal. Code Regs. § 25306(l)(3). First, contrary to American Chemistry Council’s (“ACC”) implication, *see* ACC Comments at 19-20, 22, the fact that the NTP Monograph did not directly state in the “Conclusions” section that BPA is a reproductive toxicant in humans or the precise categorization of the form of the monograph is immaterial. *See Exxon Mobil v. OEHHA*, 169 Cal. App. 4th 1264, 1281-82 (2009) (“We do not agree . . . that the authoritative body’s report is the only permissible evidence that the authoritative body made the regulatory findings. . . . So long as OEHHA can conclude, on the basis of the entire record before it, that the authoritative body made the regulation 25306(g) findings, it may list a chemical pursuant to the authoritative body provision of the statute.”).

Second, there is more than sufficient basis in the NTP Monograph for OEHHA to conclude that NTP-CERHR formally identified BPA as “causing reproductive toxicity.” OEHHA’s regulations make clear that animal studies showing that it is “biologically plausible” for BPA to cause harmful effects in humans are sufficient to establish that BPA “causes” reproductive toxicity. *See also Exxon Mobil*, 169 Cal. App. 4th at 1288 (“Nothing in the regulation thus precludes OEHHA from concluding that there is substantial evidence of biological plausibility based solely on animal studies—to the contrary, the regulation appears to contemplate extrapolation from animal studies to humans.”).

That criterion is easily met for BPA. The finding that animal studies show “clear evidence of development effects at high doses” indicates that it is “biologically plausible” for BPA to have adverse effects in humans, in light of the generally accepted toxicological assumption that a chemical that causes developmental harm in experimental animals will cause similar harm in humans. *See id.* at 1288-89 (citing EPA guidance and referring to the record in the case). The NTP monograph relies on the high-dose studies as evidence supporting the conclusion that BPA can “possibly” affect “human development and reproduction,” thus explicitly recognizing the biological plausibility of adverse effects in humans from BPA. NTP Monograph, NTP Brief on Bisphenol A at 6-7, NIH Publication No. 08-5994 (September 2008). The NTP monograph also relies on animal studies, including both high- and low-dose studies, to reach an explicit “conclusion” regarding the “possibility that human development or reproduction might be effected by exposure to bisphenol A”—stating that there is “some concern for adverse effects” vis a vis “development toxicity for fetuses, infants & children (effects on the brain, behavior and prostate gland).” *Id.* at 7-8, 38. The NTP Monograph relies on a variety of evidence, including evidence of adverse developmental effects in animal studies involving levels of exposure comparable to human exposures:

In addition to effects on survival and growth seen at high dose levels of bisphenol A, a variety of effects related to neural and behavior alterations, potentially precancerous lesions in the prostate and mammary glands, altered prostate gland and urinary tract development, and early onset of puberty in females have been reported in laboratory rodents exposed during development to much lower doses of bisphenol A (≥ 0.0024 mg/kg bw/day) that are more similar to human exposures.

Id. at 7. Thus, the NTP Monograph states that “the possibility that bisphenol A may alter human development cannot be dismissed.” *Id.*

These statements meet the requirements for listing BPA under Section 25306. The record amply supports OEHHA’s proposed conclusion that the NTP-CERHR has formally identified BPA as causing reproductive toxicity for the purposes of Section 25306 and the authoritative bodies mechanism.

OEHHA has listed chemicals with similar toxicity profiles using this mechanism.

As of 2001, OEHHA has used the Authoritative Bodies mechanism to identify roughly half of all listed Prop 65 chemicals (Denton 2001). The National Toxicology Program (NTP), specifically its Center for the Evaluation of Risks to Human Reproduction (CERHR), is recognized as an authoritative body for the listing of reproductive toxins under Proposition 65. 27 Cal. Code Regs. § 25306(1)(3). CERHR determinations have been used as triggers to seven list chemicals, including five phthalates (diisodecyl phthalate - DIDP in 2007, Di(2-ethylhexyl)phthalate (DEHP) in 2003, Butyl benzyl phthalate (BBP) in 2005, Di-*n*-hexyl phthalate (DnHP) in 2005, and dibutyl phthalate - DBP in 2005) and 1-bromopropane in 2003 and 2-Bromopropane (2-BP) in 2005.

Appendix 1 compares the determinations reached by the NTP CERHR for each of these

chemicals in terms of exposure, effects on reproduction, level of concern, weight of evidence and overall conclusions. BPA is also listed in this table for comparison to demonstrate that the determinations reached on BPA are clearly consistent with those reached on other chemicals listed on Prop 65 by the authoritative bodies mechanism recognizing the NTP CERHR analyses.

Other entities designate BPA as a reproductive and developmental toxicant

The NTP determination is in line with other governments and regulatory agencies. The European Chemicals Bureau (ECB) has classified Bisphenol A as a Category 3 reproductive toxicant; that is a substance which causes concern for human fertility based on sufficient evidence of reproductive toxicity in experimental animals (ECB 2003). The Canadian government has listed BPA as a “Toxic Substance” adding it to its “Schedule 1” list, which allows agencies to develop risk management tools under the Canadian Environmental Protection Act (Canada 2009).

More recently the U.S. Environmental Protection Agency determined that BPA is a chemical of concern, publishing an Action Plan to assess and avert exposure to the chemical. In its justification EPA stated: “Because BPA is a reproductive, developmental, and systemic toxicant in animal studies and is weakly estrogenic, there are questions about its potential impact particularly on children’s health and the environment” (EPA 2010). Like other Agencies EPA found strong evidence of high-dose toxicity. “There is general agreement that BPA is a reproductive and developmental toxicant at doses in animal studies of > 50 mg/kg-bw/day [delayed puberty] > 235 mg/kg-bw/day [reduced growth or bodyweight and testicular damage]; and > 500 mg/kg-bw/day [fertility, estrous cycling and survival]. Systemic effects were observed at doses above 5 mg/kg-bw/day” (EPA 2010).

Recent findings from an American Chemistry Council-sponsored BPA study confirmed body weight reductions at 50 and 130 mg/kg-d (for gestation and lactation) (Stump 2010).

BPA exhibits “low dose” toxicity

In addition to the clear evidence of reproductive and developmental damage at higher doses, there is also extensive evidence suggesting toxicity at much lower exposure levels. NTP acknowledged the strength of this evidence and 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” (NTP 2008).

In the United States, both OEHHA and the NTP identify studies showing loss of sexually dimorphic behavior as the strongest and most consistent findings of developmental toxicity. NTP highlighted 7 high quality studies administering low doses of BPA orally. OEHHA adds that the effects noted in sex-differentiated behavioral studies are

particularly well designed and performed, consistent with known impacts of estrogenic chemicals, and focused on gestational exposures, which are relevant to the State's focus on post-natal exposures (OEHHA 2009).

In recent comments to the FDA, John Bucher, the Associate Director for the National Toxicology Program, stated that the "collected results" of low-dose studies demonstrate adverse findings to human health and urged FDA to drop its claim of No Adverse Effects at levels 5 mg/kg-day. He predicted that studies using oral dose levels of 10 ug/kg-d will be considered as the lowest doses that cause harm (Bucher 2009).

Since the NTP CERHR report was published, there have been additional studies published which support the conclusions of the report that there is "some concern" for the impacts of low dose exposure to BPA on brain and behavior. Studies of non-human primates and now humans have found alterations in brain development and behavior that support the previously described rodent data linking neurodevelopmental harm to BPA exposure.

In non-human primate studies BPA was found to alter estradiol-induced synaptogenesis in pre-frontal cortex and hippocampus of non-human primates (Leranth 2008). 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.

In a second study of non-human primates, BPA was found to alter sexually dimorphic behavior. Infant male monkeys exposed to BPA at low doses behaved more like infant females (Nakagami 2009). This study is in agreement with rodent models which have demonstrated alterations in sexually dimorphic behavior after BPA exposure.

Now, a study in toddlers has found that girls whose mothers were exposed to higher levels of BPA during pregnancy were more aggressive and hyperactive at age 2 than other girls who were exposed to lower levels of BPA (Braun 2009).

Animal models and now primate studies 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.

Human exposure to BPA is widespread

Finally, it is important to note that the listing of BPA under Proposition 65 via the authoritative bodies mechanism has some urgency due to the mounting evidence of nearly universal exposure to BPA within the general population. A recent review summarized BPA detections in more than 80 published biomonitoring studies. These

include the detection of toxicologically-active, unconjugated BPA in most studies analyzing human blood samples (Vandenberg 2010). In December 2009, EWG released the first U.S. results detecting BPA in umbilical cord blood samples. EWG found BPA in 9 or 10 samples analyzed, with a geometric mean of 2.8 ng/g in serum, and a maximum value of 8.6 ng/g (EWG 2009). BPA is widely detected in urine samples for more than 95% of the general population. In addition the chemical is found in amniotic fluid, follicular fluid, breast milk, and urine samples from newborn babies in Neonatal Intensive Care units (Vandenberg 2010, Calafat 2009).

Conclusion

In conclusion, the high-dose evidence of BPA toxicity, and formal identification by NTP-CERHR as a reproductive toxicant offers sufficient evidence for listing BPA under Proposition 65. Actions by the European Chemicals Bureau and Canadian government support these determinations. In addition to the high-dose evidence, OEHHA should carefully consider the results of low-dose toxicity studies, as experts suggests that BPA may be toxicologically active as levels that overlap current exposures for newborns, children and adults.

Thank you for considering these comments.

Sincerely,

The image shows two handwritten signatures. On the left is the signature of Sarah Janssen, and on the right is the signature of Renée Sharp. A long horizontal line connects the two signatures, indicating they are co-signatories.

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References:

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Appendix 1. Chemicals listed on Prop 65 through the authoritative body mechanism as evaluated by NTP CERHR

Chemical	On Prop 65 List?	Are People Exposed?	Can it Affect Human Development or Reproduction?	Are Current Exposures Cause for Concern?	Weight of Evidence in Humans	Weight of Evidence in Laboratory Animals	NTP Conclusions about possible adverse effects to human development or reproduction might be adversely affected
Di-(2-ethylhexyl) Phthalate (DEHP)	Yes	Yes	Probably	Yes	Developmental and Reproductive Toxicity → Insufficient evidence for a conclusion	Developmental and Reproductive Toxicity → Clear evidence of adverse effects	Critically ill male infant → Serious concern for adverse effects
							Male infants younger than one year → Concern for adverse effect
							Male offspring of women undergoing certain medical treatments during pregnancy → Concern for adverse effects
							Male offspring exposed during pregnancy → Some concern for adverse effects
							Male children older than one year → Some concern for adverse effects
							Reproduction in adults → Minimal concern for adverse effects

Chemical	On Prop 65 List?	Are People Exposed?	Can it Affect Human Development or Reproduction?	Are Current Exposures Cause for Concern?	Weight of Evidence in Humans	Weight of Evidence in Laboratory Animals	NTP Conclusions about possible adverse effects to human development or reproduction might be adversely affected
Butyl Benzyl Phthalate	Yes	Yes	Probably	Probably not	NA	Developmental Toxicity → Clear evidence of adverse effects	Developmental effects → Minimal concern for adverse effects
					NA	Reproductive Toxicity (Males) → Some evidence of adverse effects	Reproductive effects (adult males) → Negligible concern for adverse effects
					NA	Reproductive Toxicity (Females) → Limited evidence of adverse effects	Reproductive effects (adult females) → Insufficient hazard and/or exposure data
Di-n-Butyl Phthalate (DBP)	Yes	Yes	Probably	Possibly	NA	Developmental and Reproductive Toxicity → Clear evidence of adverse effects	Developmental effects at high exposures → Some concern for adverse effects
							Developmental effects → Minimal concern for adverse effects
							Reproductive effects in adults → Negligible concern for adverse effects

Chemical	On Prop 65 List?	Are People Exposed?	Can it Affect Human Development or Reproduction?	Are Current Exposures Cause for Concern?	Weight of Evidence in Humans	Weight of Evidence in Laboratory Animals	NTP Conclusions about possible adverse effects to human development or reproduction might be adversely affected
Di-isodecyl phthalate (DIDP)	Yes	Yes	Possibly	Probably not	NA	Developmental Toxicity → Clear evidence of adverse effects	Developmental effects → Minimal concern for adverse effects
						Reproductive Toxicity → Some evidence of no adverse effects	Reproductive effects → Negligible concern for adverse effects
						Reproductive Toxicity → Limited evidence of no adverse effects	
Di-n-Hexyl Phthalate (DnHP)	Yes	Yes	Possibly	Unknown	NA	Developmental Toxicity → Limited evidence of adverse effects	Development and Reproduction → Insufficient hazard and/or exposure data
						Reproductive Toxicity → Clear evidence of adverse effects	
						Reproductive toxicity → Some evidence of no adverse effects	

Chemical	On Prop 65 List?	Are People Exposed?	Can it Affect Human Development or Reproduction?	Are Current Exposures Cause for Concern?	Weight of Evidence in Humans	Weight of Evidence in Laboratory Animals	NTP Conclusions about possible adverse effects to human development or reproduction might be adversely affected
1- Bromoprop ane	Yes	Yes	Possibly	Possibly	NA	Developmental and reproductive toxicity → Clear evidence of adverse effects	Developmental and reproductive effects (Exposure at 18 to 381 ppm) → Serious concern for adverse effects
							Developmental and reproductive effects (Exposure at 0.04 to 0.63 ppm) → Minimal concern for adverse effects
2- Bromoprop ane	Yes	Yes	Probably	Possibly	NA	Reproductive Toxicity → Clear evidence of adverse effects	Reproductive Toxicity (Upper end of Occ. Exp) → Some concern for adverse effects
							Reproductive Toxicity (Lower end of Occ. Exp) → Minimal concern for adverse effects
						Developmental toxicity → Limited evidence of adverse effects	Developmental Toxicity → Insufficient hazard and/or exposure data

Chemical	On Prop 65 List?	Are People Exposed?	Can it Affect Human Development or Reproduction?	Are Current Exposures Cause for Concern?	Weight of Evidence in Humans	Weight of Evidence in Laboratory Animals	NTP Conclusions about possible adverse effects to human development or reproduction might be adversely affected
Bisphenol A (BPA)	No – but meets the criteria for listing	Yes	Possibly	Possibly	Developmental and reproductive toxicity → Insufficient evidence for a conclusion	<p>“High” dose developmental toxicity → Clear evidence of adverse effects</p> <p>Reproductive toxicity → Some evidence of adverse effects</p> <p>“Low” dose developmental toxicity → Limited evidence of adverse effects</p>	<p>Developmental toxicity for fetuses, infants & children (effects on the brain, behavior and prostate gland) → Some concern for adverse effects</p> <p>Developmental toxicity for fetuses, infants & children (effects on mammary gland & early puberty in females) → Minimal concern for adverse effects</p> <p>Reproductive toxicity in workers → Minimal concern for adverse effects</p> <p>Reproductive toxicity in adult men and women → Negligible concern for adverse effects</p> <p>Fetal or neonatal mortality, birth defects, or reduced birth weight and growth → Negligible concern for adverse effects</p>