CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
OFFICE OF ENVIRONMENTAL HEALTH HAZARD ASSESSMENT

SAFE DRINKING WATER AND TOXIC ENFORCEMENT ACT OF 1986 (PROPOSITION 65)

Notice of Intent to List: Bisphenol A

January 25, 2013

The California Environmental Protection Agency's Office of Environmental Health Hazard Assessment (OEHHA) intends to list the chemical Bisphenol A as known to the State to cause reproductive toxicity (developmental endpoint) under the Safe Drinking Water and Toxic Enforcement Act of 1986.[1] This action is being proposed under the authoritative bodies listing mechanism.[2]

Chemical	CAS No.	Endpoint	Reference	Chemical Use
Bisphenol A	80-05-7	Developmental	NTP-CERHR (2008)	Component in polycarbonate plastic used in water bottles, present in epoxy resins used to line food cans.

OEHHA requested information relevant to the possible listing of Bisphenol A in a notice published in the California Regulatory Notice Register on February 12, 2010 (Register 2010, Vol. No. 7-Z). OEHHA received several comments. Responses to those comments are being provided separately.

Background on listing via the authoritative bodies mechanism: Under the Proposition 65 regulations, a chemical must be listed via the authoritative bodies mechanism when two conditions are met:

1) An authoritative body formally identifies the chemical as causing reproductive toxicity (Section 25306(d)[3]).

[1] Commonly known as Proposition 65, the Safe Drinking Water and Toxic Enforcement Act of 1986 is codified in Health and Safety Code section 25249.5 *et seq*.
[2] See Health and Safety Code section 25249.8(b) and Title 27, Cal. Code of Regs., section 25306.
[3] All referenced sections are from Title 27 of the Cal. Code of Regulations.

2) The evidence considered by the authoritative body meets the sufficiency criteria contained in the regulations (Section 25306(g)).

However, the chemical is not listed if scientifically valid data which were not considered by the authoritative body clearly establish that the sufficiency of evidence criteria were not met (Section 25306(h)).

The National Toxicology Program (solely as to final reports of its Center for the Evaluation of Risks to Human Reproduction [NTP-CERHR]) is one of several institutions designated as authoritative for the identification of chemicals as causing reproductive toxicity (Section 25306(l)).

OEHHA is the lead agency for Proposition 65 implementation. After an authoritative body has made a determination about a chemical, OEHHA evaluates whether listing under Proposition 65 is required using the criteria contained in the regulations.

OEHHA's determination: Bisphenol A meets the criteria for listing as known to the State to cause reproductive toxicity (developmental endpoint) under Proposition 65, based on findings of NTP (NTP-CERHR, 2008).

Formal identification and sufficiency of evidence for BPA: In 2008, the NTP-CERHR published a report on Bisphenol A titled "NTP-CERHR Monograph on the Potential Human Reproductive and Developmental Effects of Bisphenol A" (NTP-CERHR, 2008). The report concluded that the chemical causes developmental toxicity in laboratory animals at high levels of exposure. This report satisfies the formal identification and sufficiency of evidence criteria in the Proposition 65 regulations.

OEHHA is relying on the NTP's conclusion in the report that there is clear evidence of adverse developmental effects in laboratory animals at "high" levels of exposure. NTP found that Bisphenol A caused decreases in litter size or number of live pups/litter in rats (Kim et al. 2001, Tyl et al. 2002b) and in mice (Morrissey et al. 1987, Tyl et al. 2002a, NTP, 1985); effects on prenatal or early postnatal growth in rats (Kim et al. 2001, Tyl et al. 2002b) and in mice (Morrissey et al. 1987, Tyl et al. 2002a, Tyl et al. 2008); and delayed puberty in male mice (Tyl et al. 2008), male rats (Tyl et al. 2002b, Tan et al. 2003) and female rats (Tyl et al. 2002b, Tinwell et al. 2002). These studies are briefly summarized in Table 1. These studies were reviewed by OEHHA with regard to the criteria in the regulation (Section 25306(g)(2)). Information reviewed in these studies included experimental design, route of administration, numbers of test animals, choice of species, choice of dosage levels and maternal toxicity. The table emphasizes

data relevant to the criteria in the regulation and does not provide a comprehensive description of all findings in the studies tabulated.

Table 1. Information from studies cited by NTP in concluding that Bisphenol A had clear evidence for developmental toxicity at high levels of exposure.

Study	**Design**	**Observations at the LOAEL**	
		Maternal Toxicity	**Developmental Toxicity**
Morrissey et al., 1987	CD-1 mice N=21–26 Exposures - Period: GD 6–15 Route: gavage Doses: 0, 500, 750, 1000, or 1250 mg/kg-day	LOAEL: 1250 mg/kg-day ↑ mortality ↓ body weight gain ↑ liver weight ↑ clinical observations Not reported: Food intake Kidney weight Histopathology	LOAEL: 1250 mg/kg-day ↑ % resorptions/litter ↓ fetal body weight
Kim et al., 2001	SD rats N=14–20 Exposures - Period: GD 1–20 Route: gavage Doses: 0, 100, 300, 1000 mg/kg-day,	LOAEL: 300 mg/kg-day No mortality ↑ clinical observations ↓ body weight gain ↓ food intake GD4 Not reported: Organ weights Histopathology	LOAEL: 300 mg/kg-day ↓ fetal body weight/litter ↓live fetuses/litter
NTP, 1985	CD-1 mice N=19 Female exposure only, beginning one week prior to mating, for 14 weeks Route: Diet Dose: 1920 mg/kg-day	LOAEL: 1920 mg/kg-day No ↑mortality ↑ liver and kidney weights ↑ liver/kidney histopathology Not reported: Clinical observations Food intake (reported for mating pairs)	LOAEL: 1920 mg/kg-day ↓ live pups/litter ↓ live male pups/litter ↓ live female pups/litter
Tyl et al., 2002b	SD rats 3-Generation Study F_0 N=30 Male and female exposures Period: premating through lactation Route: Diet Doses: 0, 0.001, 0.02, 0.3, 5, 50, 500 mg/kg-day	LOAEL: 500 mg/kg-day No mortality Clinical observations not statistically analyzed ↑ food intake during gestation ↓ postpartum body weight ↑ kidney, liver, brain weight ↓ ovary weight ↑ liver/kidney histopathology	LOAEL: 500 mg/kg-day ↓ live pups/litter ↓ pups/litter ↓ implantation sites ↓ pup body weight pnd 4, 7, 14, 21 LOAEL (FI generation): 50 mg/kg-day ↑ age at vaginal opening ↑ age at preputial separation

Tyl, 2008	CD-1 mice 2-Generation Study N=55 (control) 19–25 (BPA) Exposures: Period: premating through lactation Route: Diet Doses: 0, 0.003, 0.03, 0.3,5, 50, 600 mg/kg-day	LOAEL: 600 mg/kg-day No mortality Clinical observations not analyzed statistically No reduced food intake No body weight effects ↑ liver and kidney weight; ↑ liver/kidney histopathology	LOAEL: 600 mg/kg-day ↓ pup body weight pnd 7,14,21 ↑ age at preputial separation
Tyl et al., 2002a	CD-1 mice, 1-Generation Study N=20 Exposure: Period: premating through birth Route: Diet Doses: 0, 875, 1750 mg/kg-day during gestation	LOAEL: 1750 mg/kg-day No mortality Clinical observations not analyzed statistically No reduced food intake (g/kg) ↓ postpartum body weight ↑ postpartum liver kidney weights ↑ gestation length ↑ liver, kidney histopathology	LOAEL: 1750 mg/kg-day ↓ live pups/litter ↓ total pups/litter Significant trend test; no pairwise effects ↓female pup weight
Tinwell et al., 2002	SD and Wistar rats, male and female N=7 Exposure: Period: GD 6–21 Route: gavage Doses: 20, 100 µg/kg, 50 mg/kg,	LOAEL: 50 mg/kg-day No mortality Not reported: Body weight Liver /kidney weight Food intake Clinical observations Histopathology	LOAEL: 50 mg/kg-day No effects litter size, sex ratio, birth weight ↑ age at vaginal opening (Wistar)
Tan et al., 2003	SD rats, Male N=12 Exposure: Period days 23-53 postnatal Route: gavage Dose: 100 mg/kg	Not applicable	LOAEL: 100 mg/kg ↓ number with preputial separation by day 53

↑ = increase; ↓ = decrease; GD= gestation day; pnd= postnatal day; N=number of animals per exposure group; LOAEL = Lowest Observed Adverse Effect Level for maternal or developmental toxicity

In the table, statistically significant results are presented with the exception of clinical observations and histopathology incidence, which were not statistically analyzed. Organ weights are relative to body weight. Maternal weight effects are reported as corrected gestational weight/weight gain or postpartum weight (weights that do not

include fetuses). For multigeneration studies, data are from the F_0 generation parents and offspring.

The above-described scientific evidence meets the criteria for listing specified in Section 25306(g)(2). In identifying clear evidence for "high" dose developmental toxicity of Bisphenol A, NTP identified the specific studies of individual endpoints of developmental toxicity that led to its overall conclusion. For all of the studies cited by NTP for decreases in litter size or number of live pups/litter in rats and mice, the exposures resulting in this manifestation of developmental toxicity were entirely prenatal (Kim et al. 2001, Tyl et al. 2002b, Morrissey et al. 1987, Tyl et al. 2002a, NTP, 1985). This endpoint provides a clear basis for listing of Bisphenol A under Proposition 65.

Effects on growth were also identified at birth in some studies (Kim et al. 2001, Morrissey et al. 1987), and early during the postnatal period in others (Tyl et al. 2002b, Tyl et al. 2008). In addition, effects on age at onset of puberty were reported after prenatal exposure only in one study (Tinwell et al. 2002), as well as after perinatal (Tyl et al. 2002b, Tyl et al. 2008) or postnatal exposure (Tan et al. 2003) in others. The formal identification of Bisphenol A as causing developmental toxicity is therefore supported by sufficient evidence of adverse developmental effects resulting from exposure during the prenatal period, and is consistent with findings from studies involving exposure during the postnatal period.

Request for comments: OEHHA is requesting comments as to whether Bisphenol A meets the criteria set forth in the Proposition 65 regulations for authoritative bodies listings. In order to be considered, **OEHHA must receive comments by 5:00 p.m. on Monday, February 25, 2013.** We encourage you to submit comments via e-mail, rather than in paper form. Comments transmitted by e-mail should be addressed to P65Public.Comments@oehha.ca.gov with "NOIL-Bisphenol A" in the subject line. Hard copy comments may be mailed, faxed, or delivered in person to the addresses below:

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Comments received during the public comment period will be posted on the OEHHA web site after the close of the comment period.

If you have any questions, please contact Ms. Oshita at cynthia.oshita@oehha.ca.gov or at (916) 445-6900.

References

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