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April 10, 2013

Via email: P65Public.Comments@oehha.ca.gov

Monet Vela
Office of Environmental Health Hazard Assessment
P. O. Box 4010
1001 I Street
Sacramento, California 95812-4010

Re: CSPA Comments on Notice of Proposed Rulemaking to adopt a Maximum Allowable Dose Level for bisphenol A

Dear Ms. Vela:

On behalf of the Consumer Specialty Products Association (CSPA)[1], we appreciate the opportunity to submit comments on the proposed Maximum Allowable Dose Level (MADL) for bisphenol A (BPA). Please note that the scope of these comments is limited to the MADL issue; CSPA has no position on the underlying science issue and did not comment on the proposed listing of BPA as a reproductive toxicant.

We are providing comments on three topics related to the proposed MADL:

- Selection of the point of departure for calculation of the MADL;
- Relevance of delayed puberty as a critical endpoint; and
- Need for a dermal MADL for BPA.

A detailed discussion of each topic is provided below.

[1] The Consumer Specialty Products Association (CSPA) is the premier trade association representing the interests of companies engaged in the manufacture, formulation, distribution and sale of more than $80 billion annually in the U.S. of familiar consumer products that help household and institutional customers create cleaner and healthier environments. CSPA member companies employ hundreds of thousands of people globally. Products CSPA represents include disinfectants that kill germs in homes, hospitals and restaurants; candles, and fragrances and air fresheners that eliminate odors; pest management products for home, garden and pets; cleaning products and polishes for use throughout the home and institutions; products used to protect and improve the performance and appearance of automobiles; aerosol products and a host of other products used every day. Through its product stewardship program, Product Care®, and scientific and business-to-business endeavors, CSPA provides its members a platform to effectively address issues regarding the health, safety and sustainability of their products.

Selection of the Point of Departure

The Office of Environmental Health Hazard Assessment (OEHHA) has proposed a Maximum Allowable Dose Level (MADL) for BPA under Proposition 65 in Title 27, California Code of Regulations, section 25805(b) of 290 micrograms per day, according to the methods outlined in Section 25803[2]. The proposed MADL is based on a No Observed Effect Level (NOEL) of 5 mg/kg/day attributed to multigenerational reproductive toxicity studies of BPA in rats and mice[3,4]. A specific endpoint is not listed for the No Observed Adverse Effect Level (NOAEL) in the Proposed Amendment to Section 25805(b) and this value does not appear to correspond to any reproductive endpoint; thus, it appears that this value represents the *systemic* NOAEL for the studies. While we concur with selection of the Tyl et al. studies as the basis for the MADL, we believe that the *reproductive* NOAEL value of 50 mg/kg/day identified by the study authors is the appropriate effect level for derivation of the MADL for the reasons discussed below.

The scientific method outlined in Section 25803 indicates that the NOAEL selected for the basis of the MADL shall be the "highest exposure level which results in no observable reproductive effect." This distinction is very clear within the text of the regulation; in no part of Section 25803 is there mention of using a systemic NOAEL as the basis for the derivation of a safe harbor level for a chemical which has been listed as known to the state to cause reproductive toxicity. In the Notice of Intent to List published by OEHHA in support of listing BPA, OEHHA relied upon studies outlined in the NTP Monograph on BPA[5] and these data were further referenced by OEHHA for the selection of the point of departure for the generation of the proposed safe harbor level. The NOAEL selected from Tyl[3] and Tyl[4] was 5 mg/kg/day, which was the no effect level for *systemic toxicity* and not for *reproductive toxicity*. A summary of the effects cited by OEHHA in the Proposed Amendment to Section 25805(b) is noted in Table 1.

[2] http://www.oehha.org/prop65/law/012513BPA_MADL.html

[3] Tyl, R. W., Myers, C. B., Marr, M. C., Thomas, B. F., Keimowitz, A. R., et al. (2002) Three-generation reproductive toxicity study of dietary bisphenol A in CD Sprague-Dawley rats. Toxicological Sciences 68:121-146.

[4] Tyl., RW., Myers, CB., Marr, MC., Sloan, CS., Castillo, NP et al. (2008) Two-generation reproductive toxicity study of dietary bisphenol A in CD-1 (Swiss) mice. Toxicological Sciences 104(2):362-384.

[5] NTP-CERHR (2008). NTP-CERHR Monograph on the Potential Human Reproductive and Developmental Effects of Bisphenol A. Research Triangle Park, NC, National Toxicology Program: NIH Publication No. 08 – 5994.

Table 1: Summary of effects observed in the three key studies identified by OEHHA

Study	Design	Maternal Toxicity	Developmental Toxicity
Tyl et al., 2002b[3]	SD rats 3-Generation Study F0 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[4]	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
Tinwell et al., 2002[6]	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)

For the purposes of regulatory risk assessment and risk management, we agree with the State of California that the guideline compliant studies of Tyl[3] and Tyl[4] are the preferable studies, as described in the Proposed Amendment to Section 25805 (b). In these guideline compliant studies, the reproducibility of the findings can be assessed across multiple generations of offspring and the larger number of litters allows for greater statistical power to detect effects as well as reduce the likelihood of false positives that are possible when studies of inadequate sample size are evaluated. The Tinwell study was small (n=7) which could result in litter effects influencing the statistical analysis (as was observed for vaginal opening, the only reproductive effect observed in this small study). While the Tinwell study was ideal for exploratory analysis of low dose effects, it was not adequately sized to be of sufficient quality for risk assessment purposes.

[6] Tinwell, H., Haseman, P. A., Lefevre, P. A., Wallis, N., and Ashby, J. (2002) Normal sexual development of two strains of rat exposed in utero to low doses of bisphenol A. Toxicological Sciences (68): 339-348.

Taking Tyl and Tyl into consideration, the NOAEL for reproductive or post-natal development (not the Lowest Observed Adverse Effect Level [LOAEL] as cited by OEHHA) was 50 mg/kg/day in both rats and mice. It is this value, and not 5 mg/kg/day, that should be used to establish the safe harbor value for BPA as specified in Section 25803, as this was the highest exposure level which resulted in no observable reproductive effect in a study of sufficient quality. The selection of 5 mg/kg/day by OEHHA as the NOAEL for the derivation of the MADL for BPA does not comply with the scientific methods outlined in section 25803, and therefore a safe harbor value of 290 mg per day is overly conservative. Carrying forward the appropriate NOAEL for reproductive effect of 50 mg/kg/day in the calculation of the MADL for BPA would result in a safe harbor value of 2,900 micrograms per day and not the 290 micrograms per day proposed by OEHHA.

Relevance of Delayed Puberty as a Critical Endpoint

The NTP monograph, an OEHHA reference document for the proposed listing of BPA under the Authoritative Bodies listing mechanism, has indicated that early onset of puberty of laboratory animals can be considered an adverse effect in reproductive toxicology; however, the NTP monograph is very careful to point out that vaginal opening is a marker of sexual maturation, but is not a surrogate measure of puberty (first estrus). Accelerated puberty was not observed in Tyl (2002), Tyl (2008) or Tinwell. The NTP monograph does not indicate that the NTP considered delayed puberty to be an adverse effect, nor was a delay in puberty (age at first estrus) observed in any of the key studies cited by OEHHA when setting the proposed MADL[3,4,6]. The effect cited in these studies is increased age at vaginal opening[4,6] and increased age at preputial[3,4] separation. The biological mechanism by which BPA might result in a delay in vaginal opening is not clear. As an estrogen receptor agonist, even one reported to be 15,000 fold less potent that 17beta estradiol[7], the predicted effect on puberty would be accelerated puberty - not delayed. Additionally, BPA has not been shown to have anti-androgenic properties which could provide an endocrine mediated mechanism for delayed preputial separation in the male[8]. As stated in Tyl (2008), the common mechanism for the "acquisition of developmental landmarks (preputial separation and vaginal patency), is dependent on age and body weight" in both sexes. Through statistical analysis, Tyl (2008) demonstrated that these effects (delayed preputial separation and vaginal opening) were secondary to decreased body weight. The clear association[3,4] and correlation[6] between delayed vaginal opening and decreased body weight strongly supports biological plausibility that this observed effect is secondary to body weight

[7] Gaido, K.W., Leonard, L.S., Lovell, S., Gould, J.C., Babai, D. et al. (1997) Evaluation of chemicals with endocrine modulating activity in a yeast-based steroid hormone receptor gene transcription assay. Toxicol. Appl. Pharmacol. 143: 205-212.

[8] Laudenbach, U., Diel, P., Smolnikar, K., Schult, T and Michna, H. (2001) Bishenol A does not mimic (anti-) androgen-like activities in orchiectomized Wistar rats. Toxicologist 60(1): 297 (Abstract).

changes and not a direct toxic effect on reproduction. This is consistent with the remarks from the US EPA[9] that indicate "body weight at puberty may provide a means to separate specific delays in puberty from those that are related to general delays in development." Given these data, there does not seem to be justification for the setting of a LOAEL of 50 mg/kg/day for a reproductive endpoint from the Tyl study. Rather, the point of departure for the calculation of the MADL should be 50 mg/kg/day, the NOAEL identified by the study's authors on the basis of delayed puberty as a secondary effect on body weight and not as a direct effect on reproductive performance.

Need for a Dermal MADL for BPA

A safe harbor value for oral exposures to BPA is important, given that oral exposures through mouthing behavior is a possible source of exposure to BPA in infants and children. However dermal exposures to adults, in consumer products primarily marketed to adults, are also of critical importance to the business community when determining compliance with Proposition 65. It is requested that OEHHA establish a dermal-specific safe harbor value at the same time as the oral safe harbor value is adopted. In the past, the approach used by OEHHA for route to route extrapolate has been used[10].

Dermal MADL = (Oral MADL) X (oral systemic absorption)/(dermal systemic absorption)

Bisphenol A is well absorbed by the oral route. A review of the human pharmacokinetics of BPA in Hengstler[11] indicates that urinary recovery or BPA in human volunteers was 97% in males and 84% in females. Given this extensive absorption of BPA by the oral route, it is conservatively estimated that oral absorption is 100%. The NTP Expert Panel on BPA[12] cites an unpublished human dermal study[13] that estimates dermal absorption of BPA to be ~ 10%. Using

[9] U.S. EPA (1996). Part II, Environmental Protection Agency: Reproductive Toxicity Risk Assessment Guidelines: Notice. U.S. Environmental Protection Agency. Federal Register 61(212): 56295.

[10] OEHHA (2004). Proposition 65 MADL for reproductive toxicity for ethyl dipropylthiocarbamate (EPTC), http://oehha.ca.gov/prop65/law/pdf_zip/ISRSet5.pdf.

[11] J. G. Hengstler, H. Foth, T. Gebel, P.-J. Kramer, W. Lilienblum, H. Schweinfurth, W. Völkel, K.-M. Wollin, and U. Gundert-Remy, "Critical evaluation of key evidence on the human health hazards of exposure to bisphenol A", Critical Reviews in Toxicology 2011 41:4, 263-291.

[12] Chapin R. E, Adams J., Boekelheide K., Gray L. E., Jr., Hayward S.W., et al. (2008) Birth Defects Res B Dev Reprod Toxicol. NTP-CERHR Expert Panel Report on the Reproductive and Developmental Toxicity of Bisphenol A. 83:157 – 395.

[13] NTP-CERHR (2008). NTP-CERHR Monograph on the Potential Human Reproductive and Developmental Effects of Bisphenol A. Research Triangle Park, NC, National Toxicology Program: NIH Publication No. 08 – 5994, page 183.

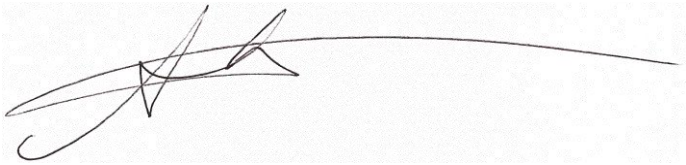
the revised proposed MADL, based on a reproductive NOEL of 50 mg/kg/day, of 2900 µg/day, the derived dermal MADL for BPA would be 29,000 µg/day.

Summary

It is requested that if BPA is listed, OEHHA establish a safe harbor value consistent with the concerns raised here for both oral and dermal exposures to BPA as these will also be of critical importance to the business community when complying with the requirements of Proposition 65.

Respectfully submitted,

Beth L. Law
Assistant General Counsel and Vice President for International Affairs



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