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ITI and TechAmerica Comments on the Proposed Rulemaking to adopt a Maximum Allowable Dose Level for bisphenol A

The Information Technology Industry Council (ITI) and TechAmerica thank you for the opportunity to provide comments on the proposed maximum allowable dose level (MADL) for bisphenol A (BPA).
Our member companies have long been leaders in innovation and sustainability, often taking measures to exceed regulatory requirements on environmental design, energy efficiency and product stewardship. ITI and TechAmerica 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 at as a critical endpoint
- Need for a dermal MADL for BPA

A detailed discussion of each topic is provided below.

Selection of the Point of Departure

The Office of Environmental Health Hazard Assessment (OEHHA) has proposed a 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. The proposed MADL is based on a no observed adverse effect level (NOAEL) of 5 mg/kg/day attributed to multigenerational reproductive toxicity studies of BPA in rats and mice (Tyl et al. 2002, 2008). A specific endpoint is not listed for the 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 as 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 National Toxicology Program (NTP) Monograph on BPA (NTP-CERHR, 2008) 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 (Tyl et al., 2002) and Tyl (Tyl et al., 2008) 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 extracted below:

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

Study	Design	Maternal Toxicity	Developmental Toxicity
Tyl et al., 2002b	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	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	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 et al. 2002 and Tyl et al., 2008 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 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.

Taking Tyl et al. 2002 and Tyl et al., 2008 into consideration, the NOAEL for reproductive or post-natal development (not the 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/kg/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 safe harbor value of 2,900 micrograms/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 the 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 et al. 2002, Tyl et al., 2008 or Tinwell et al, 2002. 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 (Tyl et al. 2002, Tyl et al., 2008 and Tinwell et al, 2002). The effect cited in these studies is increased age at vaginal opening (Tyl et al., 2008 and Tinwell et al.,) and increased age at preputial (Tyl et al. 2002 and Tyl et al., 2008) 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 (Gaido et al., 1997), 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 (Laudenbach et al., 2001). 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 et al., 2008 demonstrated that these effects (delayed preputial separation and vaginal opening) were secondary to decreased body weight. The clear association (Tyl et al. 2002 and Tyl et al., 2008) and correlation (Tinwell et al, 2002) between delayed vaginal opening and decreased body weight strongly supports biological plausibility that this observed effect is secondary to body weight changes and not a direct toxic effect on reproduction. This is consistent with the remarks from the US EPA (1996, p. 56295) 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 5 mg/kg/d for a reproductive endpoint from the Tyl study. Rather, the point of departure for the calculation of the MADL should be 50 mg/kg/d, 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 (OEHHA, 2004):

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 et al., 2011 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 (Chapin et al., 2008) cites an unpublished in vitro study that estimates dermal absorption of BPA to be ~ 10%. Using the revised proposed MADL, based on a reproductive NOEL of 50 mg/kg/day, of 2900 micrograms / day, the derived dermal MADL for BPA would be 29, 000 micrograms / day. It is requested that OEHHA establish this safe harbor value for dermal exposures to BPA as these will also be of critical importance to the business community when complying with the requirements of Proposition 65.

Conclusion

ITI and TechAmerica thank OEHHA for the opportunity to provide these comments on the MADL listing for BPA. We hope to continue working with the department to ensure the MADL is set at the optimal level to ensure both maximum necessary public health protection, while maintaining critical commercial uses of BPA. Please do do not hesitate to contact Chris Cleet at (202) 626-5759 or ccleet@itic.org, Robert Callahan at (916) 443-9088 or robert.callahan@techamerica.org, if you have any questions.

Sincerely,

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