AmericanCoatings
ASSOCIATION

April 10, 2013

Monet Vela
Office of Environmental Health Hazard Assessment
P.O. Box 4010, MS-23B
Sacramento, California 95812-4010

Submitted Electronically to: P65Public.Comments@oehha.ca.gov.

Re: Amendment to Section 25805 Specific Regulatory Levels: Chemicals Causing Reproductive Toxicity - BPA

Dear Ms. Vela:

The American Coatings Association (ACA) submits these comments on the proposed amendment to Proposition 65, Section 25805, which seeks a maximum allowable dose level (MADL) for BPA of 290 micrograms per day. ACA is a voluntary, nonprofit trade association representing approximately 350 manufacturers of paints, coatings, adhesives, sealants, and caulks, raw materials suppliers to the industry, and product distributors. The manufacture, sale, and distribution of paints and coatings are a $20 billion dollar industry in the United States. ACA's membership represents over 90% of the total domestic production of paints and coatings in the United States.

For the reasons stated below, ACA believes that the Maximum Allowable Dose Level (MADL) should be raised from 290 micrograms per day to 2,900 micrograms per day.

ACA remains hopeful that with continued collaboration between the California Office of Environmental Health Hazard Assessment (OEHHA) and all interested stakeholders, Proposition 65 will protect human health and the environment while promoting the safe use of chemicals.

For additional information or questions, please contact Stephen Wieroniey at (202) 719-3687.

Respectfully Submitted,

Alexandra Whittaker, Esq.
Counsel, Government Affairs

Stephen Wieroniey
Specialist, Health, Safety and Environmental Affairs

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. The proposed MADL is based on a No Observable Effect Limit (NOEL) of 5 mg/kg/day attributed to multigenerational reproductive toxicity studies of BPA in rats and mice (Tyl et al. 2002, 2008). However, the NOEL value selected by OEHHA does not correspond to any reproductive endpoint; thus, this value represents the *systemic* No Observable Adverse Effect Limit (NOAEL) for the studies. While ACA concurs with selection of the Tyl et al. studies as the basis for the MADL, ACA believes that the *reproductive* NOAEL value of 50 mg/kg/day identified by the study's 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.

For the purposes of regulatory risk assessment and risk management, ACA agrees 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 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.

Taking Tyl et al. 2002 and Tyl et al., 2008 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/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 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 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 17 beta 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 50 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.

References:

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