



April 10, 2013

Via e-mail: P65Public.Comments@oehha.ca.gov

Ms. Monet Vela
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Re: Prop 65 BPA MADL - GMA Comments

Dear Ms. Vela:

Based in Washington, D.C., the Grocery Manufacturers Association (GMA)¹ is the voice of more than 300 leading food, beverage and consumer product companies that sustain and enhance the quality of life for hundreds of millions of people in the United States and around the globe. Founded in 1908, GMA is an active, vocal advocate for its member companies and a trusted source of information about the industry and the products consumers rely on and enjoy every day. The association and its member companies are committed to meeting the needs of consumers through product innovation, responsible business practices and effective public policy solutions developed through a genuine partnership with policymakers and other stakeholders. In keeping with its founding principles, GMA helps its members produce safe products through a strong and ongoing commitment to scientific research, testing and evaluation and to providing consumers with the products, tools and information they need to achieve a healthy diet and an active lifestyle.

GMA is pleased to provide the following comments in response to the Office of Environmental Health Hazard Assessment's (OEHHA) January 25, 2013 proposal to adopt a Proposition 65 Maximum Allowable Dose Level (MADL) of 290 micrograms per day for exposures to bisphenol A (BPA) by amending Section 25805(b) of Title 27 of the California Code of Regulations.² GMA hereby references and endorses the detailed comments provided by Dr. Rochelle Tyi³ on May 12, 2010 and the Polycarbonate/BPA Global Group of the American Chemistry Council (ACC) submitted to OEHHA on May 13, 2010, August 10, 2011, and September 1, 2011.⁴

¹ GMA represents the world's leading food, beverage and consumer products companies. The association promotes sound public policy, champion's initiatives that increase productivity and growth and helps to protect the safety and security of the food supply through scientific excellence. The GMA board of directors is comprised of 48 chief executive officers from the Association's member companies. The \$2.1 trillion food, beverage and consumer packaged goods industry employs 14 million workers, and contributes over \$1 trillion in added value to the nation's economy.

² Amendment to Section 25805 Specific Regulatory Levels: Chemicals Causing Reproductive Toxicity – BPA [01/25/13] (http://oehha.ca.gov/Prop65/law/012513BPA_MADL.html)

³ RTI International May 12, 2010 Response to Request for Relevant Information on Bisphenol A (http://oehha.ca.gov/Prop65/CRNR_notices/admin_listing/requests_info/pdf/C7RTYBPA.pdf)

⁴ American Chemistry Council (ACC) May 13, 2010 comments in response to Request for Relevant Information on Bisphenol A. (see pp. 17-18, http://oehha.ca.gov/Prop65/CRNR_notices/admin_listing/requests_info/pdf/C17accBPA.pdf); ACC comments submitted August 10, 2011 (http://oehha.ca.gov/Prop65/CRNR_notices/admin_listing/requests_info/pdf/C17aACCSupplementalDCI.pdf); ACC comments submitted September 1, 2011 (http://oehha.ca.gov/Prop65/CRNR_notices/admin_listing/requests_info/pdf/C17bACCsupBPA.pdf).

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OEHHA has proposed a Maximum Allowable Dose Level (MADL) for BPA of 290 micrograms/day in its Initial Statement of Reasons⁵, Title 27, California Code of Regulations Proposed Amendment to Section 25805(b) dated January 25, 2013. Although GMA contends that Prop 65 listing of BPA is unwarranted per comments submitted on March 27, 2013 regarding the Notice-Of-Intent-to-List BPA (and incorporated here by reference), GMA agrees that according to 22 CCR § 25803(a)(1) the proposed MADL should be derived from the No Observed Effect Levels (NOEL) identified in "... studies producing the reproductive effect which provides the basis for the determination that a chemical is known to the state to cause reproductive toxicity" 22 CCR § 25803(a)(1).⁶

The rationale for this proposed MADL is detailed in the ISOR Proposed Amendment under the "Study Selection" section. Seven of the eight animal studies demonstrating developmental toxicity at "high doses" included a prenatal exposure component. The most sensitive of these seven studies were by Tinwall et al. (2002), Tyl et al. (2002b) and Tyl et al. (2008).⁷ Setting aside the fact that BPA is not a reproductive toxicant, these studies are of sufficient quality to serve as the basis for the MADL and are the most sensitive and credible studies for this endpoint. (22 CCR § 25803(a)(5))⁸ However, GMA disagrees with OEHHA in its selection of a NOEL of 5 mg/kg bw/d in the adult female to derive the MADL.

As per comments submitted March 27, 2013, GMA contends that Prop 65 listing is unwarranted. If OEHHA were to maintain the flawed conclusion that BPA is a reproductive toxicant, a MADL of 2400 microg/day would be more accurate, taking the lowest NOAEL of 50 mg/kg bw/day in females in accordance with 22 CCR § 25803 (a)(2)⁹, and the relevant human body weight of 58 kg for the adult female.¹⁰ The salient data are as follows:

- In the 2008 two-generational Tyl study, the systemic no observable effect level (NOEL) was 30 ppm BPA (~5mg/kg/day) while the reproductive/developmental NOEL was 300 ppm (~50 mg/kg/day).
- In the 2002 three-generational Tyl study, adult systemic no observed adverse effect level (NOAEL) was 75 ppm (5 mg/kg/day) while reproductive and postnatal NOAELs was 750 ppm (50

⁵ OEHHA Initial Statement of Reasons regarding BPA MADL (http://oehha.ca.gov/Prop65/law/pdf_zip/012513ISORBisphenolA_MADL.pdf)

⁶ 22 CCR § 25803 (a) A quantitative assessment which conforms to this section shall be deemed to determine the level of exposure to a listed chemical which will have no observable effect, assuming the exposure at one thousand times the level in question. The assessment shall be based on evidence and standards of comparable scientific validity to the evidence and standards which form the scientific basis for listing the chemical as known to the state to cause reproductive toxicity. In the absence of principles or assumptions scientifically more appropriate, based upon the available data, the following default principles and assumptions shall apply in any such assessment:

(1) Only studies producing the reproductive effect which provides the basis for the determination that a chemical is known to the state to cause reproductive toxicity shall be utilized for the determination of the NOEL.

⁷ Tinwall H, Haseman J, Lefevre PA, Wallis N, Ashby J (2002) Normal sexual development of two strains of rat exposed in utero to low doses of bisphenol A. *Toxicol Sci.* 68:339 – 348.

Tyl RW, Myers CB, Marr MC, Thomas BF, Keimowitz AR, Brine DR, Veselica MM, Fail PA, Chang TY, Seely JC, Joiner RL, Butala JH, Dimond SS, Cagen SZ, Shiotsuka RN, Stropp GD, Waechter JM (2002b) Three-generation reproductive toxicity study of dietary bisphenol A in CD Sprague-Dawley rats. *Toxicol Sci.* 68:121 – 146.

Tyl RW, Myers CB, Marr MC, Sloan CS, Castillo NP, Veselica MM, Seely JC, Dimond SS, Van Miller JP, Shiotsuka RN, Beyer D, Hentges SG, Waechter JM, Jr. (2008) Two-generation reproductive toxicity study of dietary bisphenol A (Bisphenol A) in CD-1(R) (Swiss) mice. *Toxicol Sci.* 104:362 – 384.

⁸ Title 22, California Code of Regulations ARTICLE 8. No Observable Effect Levels (http://oehha.ca.gov/prop65/law/pdf_zip/RegTextArt8_041511.pdf)

⁹ 22 CCR § 25803. (a)(2) Where multiple reproductive effects provide the basis for the determination that a chemical is known to the state to cause reproductive toxicity, the reproductive effect for which studies produce the lowest NOEL shall be utilized for the determination of the NOEL. The NOEL shall be the highest exposure level which results in no observable reproductive effect expressed in milligrams of chemical per kilogram of bodyweight per day. This may be the no observed effect level in a scientific study or, alternatively, may be calculated by means of a generally accepted scientific methodology such as the benchmark dose methodology. Where a study (e.g., epidemiological publication) reports a range of exposure levels associated with no observed effect, the NOEL may be selected from within the range or calculated by benchmark dose or other accepted scientific methodology.

¹⁰ 22 CCR § 25803(b) In the absence of principles or assumptions scientifically more appropriate based upon the available data, the following default principles or assumptions shall apply in any such assessment. The NOEL shall be converted to a milligram per day dose level by multiplying it by the assumed human body weight. When the applicable reproductive effect is upon the adult male, human body weight of 70 kilograms shall be assumed. When the applicable reproductive effect is upon the adult female or conceptus, human body weight of 58 kilograms shall be assumed...

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mg/kg/day). Regarding the preputial separation, as this was only statistically significant for the F1 generation rodents, not F2 nor F3, this effect was not replicated and could not be treatment-related. Additionally, this study does not report an increase in age of vaginal opening in the F1 generation (LOAEL 50 mg/kg) as noted in the NOIL. Thus, an appropriate NOAEL for reproductive toxicity is in fact 50 mg/kg bw/day.

- Delayed puberty in male rats treated during development has also been reported at oral doses of ≥ 50 mg/kg bw/day.¹¹
- Additionally, Prop 65 requires that a MADL be derived from pre-natal exposures. However, in the pivotal studies, there were also post-natal exposures. Thus, a MADL derived from a NOEL wherein post-natal exposures also occurred would result in an overly conservative estimate.

Furthermore, recently completed FDA studies¹² on BPA pharmacokinetics demonstrate:

- (i) efficient metabolism of oral exposure to BPA to biologically inactive metabolites (i.e., bisphenol A-glucuronide and bisphenol A-sulfate) primarily in mothers but also in developing fetus and then quickly eliminated from the body, and
- (ii) the inherent physiological differences between rodents and primates.

These studies underscore the lack of biological plausibility of potential adverse effect on reproduction and development from BPA exposure,¹³

GMA believes that OEHHA should adopt minor revisions to the proposed MADL to 2400 microg/day in order to produce a safe harbor MADL that is (1) compliant with the Proposition 65 regulations should BPA be listed, (2) scientifically more defensible, and (3) appropriately conservative.

Please do not hesitate to contact Dr. Emilia Lonardo, GMA VP of Consumer Product Safety and Science Policy (ELonardo@gmaonline.org, 202-639-5983) should you have any questions.

Thank you for taking these comments into consideration.

Sincerely,



Emilia Lonardo, Ph.D.

VP Consumer Product Safety and Science Policy

¹¹ NTP-CERHR Monograph on the Potential Human Reproductive and Developmental Effects of Bisphenol A (see p.17, <http://ntp.niehs.nih.gov/ntp/ohat/bisphenol/bisphenol.pdf>)

¹² Doerge, D. R., Twaddle, N. C., Vanlandingham, M., and Fisher, J. W. 2010. Pharmacokinetics of bisphenol A in neonatal and adult Sprague-Dawley rats. *Toxicology and Applied Pharmacology*. 247(2):158-165. Available at <http://dx.doi.org/10.1016/j.taap.2010.06.008>.

Doerge, D. R., Vanlandingham, M., Twaddle, N. C., and Delclos, K. B. 2010. Lactational transfer of bisphenol A in Sprague-Dawley rats. *Toxicology Letters*. 199(3):372-376. Available at <http://dx.doi.org/10.1016/j.toxlet.2010.09.022>.

Doerge, D. R., Twaddle, N. C., Vanlandingham, M., Brown, R. P., and Fisher, J. W. 2011. Distribution of bisphenol A into tissues of adult, neonatal, and fetal Sprague-Dawley rats. *Toxicology and Applied Pharmacology*. Available at <http://dx.doi.org/10.1016/j.taap.2011.07.009>.

Doerge, D. R., Twaddle, N. C., Woodling, K. A., and Fisher, J. W. 2010. Pharmacokinetics of bisphenol A in neonatal and adult rhesus monkeys. *Toxicology and Applied Pharmacology*. 248(1):1-11. Available at <http://dx.doi.org/10.1016/j.taap.2010.07.009>.

¹³ 22 CCR § 25803. (a)(7) When available data are of such quality that anatomic, physiologic, pharmacokinetic and metabolic considerations can be taken into account with confidence, they may be used in the assessment.

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