Can Manufacturers Institute
CANS: INFINITELY RECYCLABLE℠

April 17, 2015

Via email: P65Public.Comments@oehha.ca.gov; monet.vela@oehha.ca.gov

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

Re: CMI Comments in Opposition to Listing Bisphenol A as a Female Reproductive Toxicant

Dear Ms. Vela:

The Can Manufacturers Institute (CMI) appreciates the opportunity to submit these comments on the California Environmental Protection Agency Office of Environmental Health Hazard Assessment (OEHHA) proposal to determine whether or not Bisphenol A (BPA) "has been clearly shown through scientifically valid testing according to generally accepted principles to cause female reproductive toxicity" and to list it under Proposition 65 as a female reproductive toxicant. CMI is the national trade association of the metal can manufacturing industry and its suppliers in the United States. The can industry accounts for the annual domestic production of approximately 120 billion food, beverage, and other metal cans. Together, CMI member companies employ some 20,000 people in 34 states. In addition, CMI member companies have more plants (17) and more employees (1798) in the state of California than in any other state in the nation.

As recently as February 2015, international and government organizations concluded that the weight of scientific evidence indicates that BPA does not pose reproductive or developmental health risks. Although Peretz *et al.* (2014),[1] which appears to be a primary reference in the Hazard Identification materials, concluded otherwise, this is not a weight-of-evidence assessment of all the relevant literature and therefore does not accurately represent the state of the science. In addition, there are several original articles and reviews (more than 60) that should be included in the BPA Hazard Identification Materials. High-quality, robust multigenerational animal studies indicate a lack of female reproductive effects associated with BPA exposure, and epidemiology studies are not sufficiently robust to properly evaluate the potential health effects of BPA. CMI opposes the listing proposal for BPA because it is inappropriate and scientifically unsound. In addition, CMI endorses the comprehensive comments submitted by the Polycarbonate/BPA Global Group of the American Chemistry Council on this matter.

The Peretz *et al.* (2014) Study Has Limitations That Impact the Reliability of Its Conclusions

Peretz *et al.* (2014) was selected as a primary study (if not *the* primary study) for consideration by the Developmental and Reproductive Toxicant Identification Committee (DART-IC) members. There are more robust earlier evaluations that, unlike Peretz *et al.* (2014), have systematically evaluated the weight of evidence regarding the possible association between female reproductive effects and BPA exposure that considered both

1 Peretz, J; Vrooman, L; Ricke, WA; Hunt, PA; Ehrlich, S; Hauser, R; Padmanabhan, V; Taylor, HS; Swan, SH; VandeVoort, CA; Flaws, JA. 2014. "Bisphenol A and reproductive health: Update of experimental and animal evidence, 2007-2013." *EHP* 122(8):775-786.

study quality and relevance.[2] In addition, other regulatory bodies have prepared extensive balanced reviews.[3] These evaluations should be more heavily relied on because they evaluate both study quality and relevance in a consistent manner. This is particularly important because the Peretz *et al.* (2014) review did not do so.

- Peretz *et al.* (2014) only includes studies published after 2007, but there were many high-quality, relevant studies published before that date. In addition, Peretz *et al*. (2014) omits several relevant studies published after 2007. By not considering the entire relevant literature database, Peretz *et al.* (2014) present an incomplete evaluation.
- Peretz *et al*. (2014) did not systematically evaluate study quality. For example, Peretz *et al*. (2014) present an "article strength" determination, but do not address aspects of the robustness of individual study designs, the power to detect effects, and other statistical considerations. A single-dose subcutaneous study with five animals appears to be considered as strong as multigenerational regulatory studies conducted under good laboratory practice (GLP) guidelines with six dietary dose levels. These two study designs are not equal in their ability to identify hazards (or a lack thereof), yet the Peretz *et al.* (2014) review does not appear to distinguish between them.
- In Peretz *et al*. (2014), effects found in subcutaneous and *in vitro* dosing studies are evaluated alongside oral dosing studies, even though the "true" dose (and possibly effects thereof) from these routes are much different. Although Peretz *et al.* (2014) indicate that they have considered differences in dose routes in their review, it is not evident that this is, in fact, the case. By combining different dose routes into the same tables in the Supplemental Materials and not discussing oral and non-oral studies separately, the authors imply that these studies are of equal relevance regarding human health hazards.
- The summary tables in the Supplemental Materials of the Peretz *et al.* (2014) article provide an unbalanced and imprecise representation of the studies evaluated. We give only a few examples below of the way in which these studies are presented, but can provide you with a study-by-study evaluation, if it is of interest. For the animal studies, null effects are rarely described (*e.g.*, there were multiple null effects in Adewale *et al.*, 2009[4] that do not appear in the tables). Effects are also sometimes implied to be statistically significant, even if they are not. For example, the "disrupted ovarian development" effect cited in Table S1 for Adewale *et al.* (2009) implies that effects occurred at both the 50 µg/kg and 50 mg/kg dose levels. However, this study reported that the findings were significant only at the high dose level. This was also the case for the Tyl *et al.* (2008)[5] study in Table S5, which is a multigeneration reproductive toxicity study that used six dose levels as well as appropriate controls. Peretz *et al.* (2014) indicate that the study reported

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2 Gray, GM; Cohen, JT; Cunha, G; Hughes, C; McConnell, EE; Rhomberg, L; Sipes, IG; Mattison, D. 2004. "Weight of the evidence evaluation of low-dose reproductive and developmental effects of bisphenol A." *Hum. Ecol. Risk Assess.* 10:875-921.
Goodman, JE; McConnell, EE; Sipes, IG; Witorsch, RJ; Slayton, TM; Yu, CJ; Lewis, AS; Rhomberg, LR. 2006. "An updated weight of the evidence evaluation of reproductive and developmental effects of low doses of bisphenol A." *Crit. Rev. Toxicol.* 36(5):387-457.
Goodman, JE; Witorsch, RJ; McConnell, EE; Sipes, IG; Slayton, TM; Yu, CJ; Franz, AM; Rhomberg, LR. 2009. "Weight-of-evidence evaluation of reproductive and developmental effects of low doses of bisphenol A." *Crit. Rev. Toxicol.* 39:1-75.
Hengstler, JG; Roth, H; Gebel, T; Kramer, PJ; Lilienblum, W; Schweinfurth, H; Volkel, W; Wollin, KM; Gundert-Remy, U. 2011. "Critical evaluation of key evidence on the human health hazards of exposure to bisphenol A." *Crit. Rev. Toxicol.* 41(4):263-291.
3 Aungst, J; Anderson, S. [US Food and Drug Administration (US FDA), Bisphenol A Joint Emerging Science Working Group]. 2014. Memorandum to S. Ostroff (US FDA, Chemical and Environmental Science Council (CESC)) re: Final report for the review of literature and data on BPA (Draft). 2p., June 6. Accessed at http://www.fda.gov/downloads/Food/IngredientsPackagingLabeling/FoodAdditivesIngredients/UCM424011.pdf.

4 Adewale, HB; Jefferson, WN; Newbold, RR; Patisaul, HB. 2009. "Neonatal bisphenol-A exposure alters rat reproductive development and ovarian morphology without impairing activation of gonadotropin-releasing hormone neurons." *Biol. Reprod.* 81:690-699.
5 Tyl, RW; Myers, CB; Marr, MC; Sloan, CS; Castillo, NP; Veselica, MM; Seely, JC; Dimond, SS; Van Miller, JP; Shiotsuka, RS; Beyer, D; Hentges, SG; Waechter, JM Jr. 2008. "Two-generation reproductive toxicity study of dietary bisphenol A in CD-1 (Swiss) mice." *Toxicol. Sci.* 104(2):362-384.

"increased pup weight." However, increased pup body weight was not a consistent effect at any dose, and the only dose at which this effect occurred somewhat frequently was at the highest dose tested, 600 mg/kg-d, a dose at which significant systemic toxicity was observed. Peretz *et al.* (2014) do not even mention the null effects observed in Tyl *et al.* (2008). Specifically (from the Tyl *et al.*, 2008 abstract) that study notes that, "There were no BPA-related effects on adult mating, fertility or gestational indices, ovarian primordial follicle counts, estrous cyclicity, precoital interval, offspring sex ratios or postnatal survival, sperm parameters or reproductive organ weights or histopathology (including the testes and prostate)." In other words, Peretz *et al.* (2014) not only misrepresent the positive results found in the Tyl *et al.* (2008) study (one of the largest and most well conducted studies in the BPA database), they also disregard all its the null results.

In sum, Peretz *et al.* (2014) do not present a systematic, weight-of-evidence review of the relevant literature, and should not be considered as a primary study; studies that do should be given much more weight in the DART-IC evaluation.

BPA Epidemiology Studies Are Unreliable

Epidemiology studies have evaluated the association between BPA and various health effects, including premature birth, miscarriages, polycystic ovarian syndrome, and other reproductive endpoints.[6] These studies have methodological issues and cannot be used to evaluate causal associations.

Exposures to BPA in the general population are very low (often close to or below laboratory detection limits), and the range of exposures among individuals is small (in general, estimates of average and high exposure for various age groups differ by no more than a factor of three). Urinary measurements usually only include biologically inactive BPA, and the blood measurements of BPA reported in many studies are most likely due to contamination, rather than being reflective of actual exposure to BPA.[7] Also, most studies that rely on urine measurements use a one-time spot urine sample to estimate BPA exposure for each study participant. In light of how quickly BPA passes through the body after ingestion, the use of total BPA measurements from spot urine samples may over- or under-predict exposure.[8] This indicates that estimated BPA concentrations in epidemiology studies may not accurately represent each study participant's BPA exposure – over time or, particularly, at the time period of interest – and likely led to inaccurate estimates of the association between BPA exposure and health outcomes.

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6 Cantonwine, D; Meeker, JD; Hu, H; Sanchez, BN; Lamadrid-Figueroa, H; Mercado-Garcia, A; Fortenberry, GZ; Calafat, AM; Tellez-Rojo, MM. 2010. "Bisphenol A exposure in Mexico City and risk of prematurity: A pilot nested case control study." *Environ. Health* 9:62. doi: 10.1186/1476-069X-9-62.
Sugiura-Ogasawara, M; Ozaki, Y; Sonta, S; Makino, T; Suzumori, K. 2005. "Exposure to bisphenol A is associated with recurrent miscarriage." *Hum. Reprod.* 20(8):2325-2329. doi: 10.1093/humrep/deh888.
Takeuchi, T; Tsutsumi, O. 2002. "Serum bisphenol A concentrations showed gender differences, possibly linked to androgen levels." *Biochem. Biophys. Res. Commun.* 291:76-78.
Takeuchi, T; Tsutsumi, O; Ikezuki,Y; Takai, Y; Taketani, Y. 2004. "Positive relationship between androgen and the endocrine disruptor, bisphenol A, in normal women and women with ovarian dysfunction." *Endocr. J.* 51(2):165-169.
Hiroi, H; Tsutsumi, O; Takeuchi, T; Momoeda, M; Ikezuki, Y; Okamura, A; Yokota, H; Taketani, Y. 2004. "Differences in serum bisphenol A concentrations in premenopausal normal women and women with endometrial hyperplasia." *Endocr. J.* 51(6):595-600.
Yang, M; Kim, SY; Chang, SS; Lee, IS; Kawamoto, T. 2006. "Urinary concentrations of bisphenol A in relation to biomarkers of sensitivity and effect and endocrine-related health effects." *Environ. Mol. Mutagen.* 47:571-578.
7 Teeguarden, JG; Calafat, AM; Ye, X; Doerge, DR; Churchwell, MI; Gunawan, R; Graham, M. 2011. "24-hour human urine and serum profiles of bisphenol A during high dietary exposure." *Toxicol. Sci.* 123(1):48-57.
8 Ye, X; Wong, LY; Bishop, AM; Calafat, AM. 2011. "Variability of urinary concentrations of bisphenol A in spot samples, first morning voids, and 24-hour collections." *Environ. Health Perspect.* 119(7):983-988.
Christensen, KL; Lorber, M; Koch, HM; Kolossa-Gehring, M; Morgan, MK. 2012. "Population variability of phthalate metabolites and bisphenol A concentrations in spot urine samples versus 24- or 48-h collections." *J. Expo. Sci. Environ. Epidemiol.* 22(6):632-640. doi: 10.1038/jes.2012.52.

In addition, the vast majority of BPA epidemiology studies are cross-sectional in nature, meaning that BPA is measured at the same time as health effects are assessed. Thus, whether past BPA exposures were causally associated with the effects observed in these studies cannot be determined. Also, most studies do not fully evaluate all the factors that could have contributed to observed health effects (*e.g.*, lifestyle factors, dietary habits, *etc.*). At best, BPA epidemiology studies are hypothesis-generating, and none are sufficient to address possible health effects at typical human exposures.

Other Weight-of-Evidence Reviews Indicate BPA Is Not a Reproductive Toxicant

From Goodman *et al.* (2009):[2] "The weight of evidence does not support the hypothesis that low oral doses of BPA adversely affect human reproductive and developmental health."

From Hengstler *et al.* (2011):[2]

> Despite the fact that more than 5000 safety-related studies have been published on bisphenol A (BPA), there seems to be no resolution of the apparently deadlocked controversy as to whether exposure of the general population to BPA causes adverse effects due to its estrogenicity. Therefore, the Advisory Committee of the German Society of Toxicology reviewed the background and cutting-edge topics of this BPA controversy. The current tolerable daily intake value (TDI) of 0.05 mg/kg body weight [bw]/day, derived by the European Food Safety Authority (EFSA), is mainly based on body weight changes in two- and three-generation studies in mice and rats. Recently, these studies and the derivation of the TDI have been criticized. After having carefully considered all arguments, the Committee had to conclude that the criticism was scientifically not justified; moreover, recently published additional data further support the reliability of the two- and three-generation studies demonstrating a lack of estrogen-dependent effects at and below doses on which the current TDI is based. A frequently discussed topic is whether doses below 5 mg/kg bw/day may cause adverse health effects in laboratory animals. Meanwhile, it has become clear that positive results from some explorative studies have not been confirmed in subsequent studies with higher numbers of animals or a priori defined hypotheses…. Overall, the Committee concluded that the current TDI for BPA is adequately justified and that the available evidence indicates that BPA exposure represents no noteworthy risk to the health of the human population, including newborns and babies.

The most robust evaluations are the multigeneration studies conducted with Sprague-Dawley rats[9] and CD-1 Swiss mice,[10] and these have not shown low-dose reproductive effects. The United States Food and Drug Administration (US FDA) recently conducted a 90-day sub-chronic study in Sprague-Dawley rats to address concerns that negative study results could have been due to rat strain, the number of low doses evaluated, or issues that could have been resolved with positive controls. In that study, Delclos *et al.* (2014)[11] reported no consistent findings of biologically significant effects in either sex at doses up to 2.7 mg/kg-day, indicating these concerns were unfounded. This study was also used to inform dose levels for a chronic (life-long)

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9 Ema, M; Fujii, S; Furukawa, M; Kiguchi, M; Ikka, T; Harazono, A. 2001. "Rat two-generation reproductive toxicity study of bisphenol A." *Reprod. Toxicol.* 15:505-523.
Tyl, RW; Myers, CB; 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. 2002. "Three-generation reproductive toxicity study of dietary bisphenol A in CD Sprague-Dawley rats." *Toxicol. Sci.* 68:121-146.
10 Tyl, RW; Myers, CB; Marr, MC; Sloan, CS; Castillo, NP; Veselica, MM; Seely, JC; Dimond, SS; Van Miller, JP; Shiotsuka, RS; Beyer, D; Hentges, SG; Waechter, JM Jr. 2008. "Two-generation reproductive toxicity study of dietary bisphenol A in CD-1 (Swiss) mice." *Toxicol. Sci.* 104(2):362-384.
11 Delclos, KB; Camacho, L; Lewis, SM; Vanlandingham, MM; Latendresse, JR; Olson, GR; Davis, KJ; Patton, RE; da Costa, GG; Woodling, KA; Bryant, MS; Chidambaram, M; Trbojevich, R; Juliar, BE; Felton, RP; Thorn, BT. 2014. "Toxicity evaluation of bisphenol A administered by gavage to Sprague Dawley rats from gestation day 6 through postnatal day 90." *Toxicol. Sci.* 139(1):174-197. doi: 10.1093/toxsci/kfu022.

exposure study being conducted by US FDA's National Center for Toxicological Research, which should be completed this year.

All of the robust studies utilized a large number of animals exposed to a wide range of oral doses and examined a wide variety of hormonally sensitive endpoints. Reproductive effects occurred only at the highest doses tested (*e.g.*, above 100 mg/kg-day), and, at these doses, significant maternal toxicity was also observed, indicating that maternal toxicity is most likely the critical determinant of observed embryo/fetal offspring toxicity. Effects at lower doses were observed only sporadically (*e.g.*, in only one generation, with no dose-response pattern) and were not considered to be treatment-related.

Over the last decade, regulatory and international bodies have evaluated the safety of BPA – sometimes multiple times – and concluded that the current uses of BPA do not result in health risks, including for women specifically. The bodies that have performed these evaluations include Food Standards Australia New Zealand,[12] US FDA,[13] the Japanese Research Institute of Science for Safety and Sustainability,[14] EFSA,[15] Health Canada,[16] the World Health Organization/Food and Agriculture Organization of the United Nations,[17] the California Developmental and Reproductive Toxicant Identification Committee,[18] and the German Federal Institute for Risk Assessment.[19]

Both US FDA and EFSA have reaffirmed the safety of BPA. US FDA (Aungst and Anderson, 2014)[13] states:

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12 Food Standards Australia New Zealand (FSANZ). 2012. "FSANZ Activities in Relation to Bishpenol A." 27p. Accessed at http://www.foodstandards.gov.au/science/monitoring/surveillance/documents/BPA%20paper%20October%202010%20FINAL.pdf.
13 Aungst, J; Anderson, S. [US Food and Drug Administration (US FDA), Bisphenol A Joint Emerging Science Working Group]. 2014. Memorandum to S. Ostroff (US FDA, Chemical and Environmental Science Council (CESC)) re: Final report for the review of literature and data on BPA (Draft). 2p., June 6. Accessed at http://www.fda.gov/downloads/Food/IngredientsPackagingLabeling/FoodAdditivesIngredients/UCM424011.pdf.
14 National Institute of Advanced Industrial Science and Technology (AIST), Research Institute of Science for Safety and Sustainability (RISS). 2011. "Updated Hazard Assessment of Bisphenol A." 80p., July. Accessed at http://www.aist-riss.jp/projects/RAD/download01/download01.cgi?RISS_BPA_e_110815.
15 European Food Safety Authority (EFSA). 2015a. "Scientific opinion on the risks to public health related to the presence of bisphenol A (BPA) in foodstuffs: Part I – Exposure assessment." Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (CEF). *EFSA J.* 13(1):3978. Accessed at http://www.efsa.europa.eu/en/efsajournal/pub/3978.htm.
European Food Safety Authority (EFSA). 2015b. "Scientific Opinion on the risks to public health related to the presence of bisphenol A (BPA) in foodstuffs: Part II - Toxicological assessment and risk characterisation." Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (CEF). *EFSA J.* 13(1):3978. Accessed at http://www.efsa.europa.eu/en/efsajournal/pub/3978.htm. European Food Safety Authority (EFSA). 2011. "Scientific opinion of the EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (CEF): Statement on the ANSES reports on Bisphenol A." *EFSA J.* 9(12):2475.
European Food Safety Authority (EFSA). 2008. "Toxicokinetics of Bisphenol A: Scientific Opinion of the Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food (AFC) (Question No EFSA-Q-2008-382)." *EFSA J.* 759:1-10, July 9. European Food Safety Authority (EFSA). 2006. "Opinion of the Scientific Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food on a request from the Commission related to 2,2-bis(4-hydroxyphenyl)propane (bisphenol A): Question number EFSA-Q-2005-100." *EFSA J.* 428:1-75. Accessed at http://www.efsa.europa.eu/EFSA/efsa_locale-1178620753812_1178620772817.htm.
16 Health Canada. 2012. "Health Canada's Updated Assessment of Bisphenol A (BPA) Exposure from Food Sources." 6p., September. Accessed at http://www.hc-sc.gc.ca/fn-an/securit/packag-emball/bpa/bpa_hra-ers-2012-09-eng.php.
Health Canada. 2010. "Bisphenol A." 3p., December 8. Accessed at http://www.hc-sc.gc.ca/fn-an/securit/packag-emball/bpa/index-eng.php. Health Canada. July 2009. "Survey of Bisphenol A in Bottled Water Products." Bureau of Chemical Safety, Food Directorate, Health Products and Food Branch. 10p.
Health Canada. 2008. "Draft Screening Assessment for Phenol, 4,4' -(1-methylethylidene)bis-(Bisphenol A), Chemical Abstracts Service Registry Number 80-05-07." 106p., April.
17 Joint FAO/WHO Expert Committee on Food Additives (JECFA). 2010. "Toxicological and Health Aspects of Bisphenol A: Report of a Joint FAO/WHO Expert Meeting (2-5 November 2010) and Report of Stakeholder Meeting on Bisphenol A (1 November 2010)." World Health Organization (WHO) 59p. Accessed at http://whqlibdoc.who.int/publications/2011/97892141564274_eng.pdf.
18 California Office of Environmental Health Hazard Assessment (CalOEHHA). 2009. "Meeting synopsis and slide presentations for Developmental and Reproductive Toxicant Identification Committee meeting held July 15, 2009." Proposition 65 Developmental and Reproductive Toxicant Identification Committee. Accessed at http://www.oehha.org/prop65/public_meetings/dart071509synop.html.
19 BfR. 2008. "New studies on bisphenol A do not challenge earlier risk assessment." BfR Information No. 036/2008. 1p.. September 19. Accessed at http://www.bfr.bund.de/cm/349/new_studies_on_bisphenol_a_do_not_challenge_earlier_risk_assessment.pdf.

> In the fall of 2014, FDA experts from across the agency, specializing in toxicology, analytical chemistry, endocrinology, epidemiology, and other fields, completed a four year review of more than 300 scientific studies. The FDA review has not found any information in the evaluated studies to prompt a revision of FDA's safety assessment of BPA in food packaging at this time.

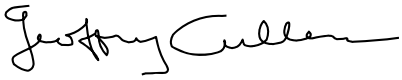
EFSA's conclusion[20] was virtually identical:

> By comparing this t-TDI [temporary-Tolerable Daily Intake] with the exposure estimates, the CEF Panel concluded that there is no health concern for any age group from dietary exposure and low health concern from aggregated exposure.

Conclusion

It is evident that BPA is not a female reproductive toxicant and that listing BPA under Proposition 65 will not result in a public health benefit. Please contact me at 202-232-4677 or gcullen@cancentral.com with any questions.

Sincerely,



Geoffrey Cullen
Vice President of Government Relations, CMI

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20 European Food Safety Authority (EFSA). 2015a. "Scientific opinion on the risks to public health related to the presence of bisphenol A (BPA) in foodstuffs: Part I – Exposure assessment." Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (CEF). *EFSA J.* 13(1):3978. Accessed at http://www.efsa.europa.eu/en/efsajournal/pub/3978.htm.
European Food Safety Authority (EFSA). 2015b. "Scientific Opinion on the risks to public health related to the presence of bisphenol A (BPA) in foodstuffs: Part II - Toxicological assessment and risk characterisation." Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (CEF). *EFSA J.* 13(1):3978. Accessed at http://www.efsa.europa.eu/en/efsajournal/pub/3978.htm.