INITIAL STATEMENT OF REASONS
TITLE 27, CALIFORNIA CODE OF REGULATIONS

PROPOSED AMENDMENTS TO
SECTION 25805(b), SPECIFIC REGULATORY LEVELS: CHEMICALS CAUSING REPRODUCTIVE TOXICITY

MAXIMUM ALLOWABLE DOSE LEVEL FOR
BISPHENOL A (BPA)
(DERMAL EXPOSURE FROM SOLID MATERIALS)

PURPOSE AND BACKGROUND OF PROPOSED AMENDMENT

PURPOSE

This proposed regulatory amendment is to adopt a maximum allowable dose level (MADL) for dermal exposure to bisphenol A (BPA) from contact with solid materials under Proposition 65[1] in Title 27, California Code of Regulations, section 25805(b) [2]. The proposed dermal MADL was derived using scientific methods outlined in Section 25803. The proposed MADL for BPA (dermal exposure from solid materials) is 3 micrograms per day. "Solid materials" are materials in solid form and include, but are not limited to items such as paper and plastics.

PROPOSITION 65 AND LISTING OF BPA

Proposition 65 was enacted as a ballot initiative on November 4, 1986. The Office of Environmental Health Hazard Assessment (OEHHA) within the California Environmental Protection Agency is the lead state entity responsible for the implementation of Proposition 65[3]. OEHHA has the authority to promulgate and amend regulations to further the purposes of the Act[4].

The Act requires businesses to provide a warning when they cause an exposure to a chemical listed as known to the state to cause cancer or reproductive

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[1] The Safe Drinking Water and Toxic Enforcement Act of 1986, codified at Health and Safety Code section 25249.5 *et. seq*., hereafter referred to as "Proposition 65" or "The Act".
[2] All subsequent citations are to Title 27, California Code of Regulations, unless otherwise noted.
[3] Health and Safety Code, section 25249.12(a) and Cal. Code of Regs., Title 27, section 25102(o).
[4] Health and Safety Code, section 25249.12(a).

toxicity. The Act also prohibits the discharge of listed chemicals to sources of drinking water. Warnings are not required and the discharge prohibition is not in force when exposures are sufficiently small, as specified in the Act[5].

On May 11, 2015, BPA was added to the Proposition 65 list as known to the state to cause reproductive toxicity (female endpoint). The listing is based on a decision by the Developmental and Reproductive Toxicant Identification Committee (DARTIC), the state's qualified experts for reproductive toxicity[6], made at a public meeting held on May 07, 2015. At that meeting, the DARTIC determined that BPA had been clearly shown through scientifically valid testing according to generally accepted principles to cause reproductive toxicity (female endpoint). To facilitate its review, the DARTIC was provided with extensive information on female reproductive toxicity[7]. This included a number of documents, reports, articles published in the scientific literature, and public comments submitted to the DARTIC in 2009 and in 2015, all as part of the Hazard Identification Materials for BPA[8].

STUDY SELECTION

Relevant studies that provide information on the female reproductive toxicity of BPA were identified from the Hazard Identification Materials provided to the DARTIC, and additional relevant studies published subsequent to preparation of those materials were identified through literature searches. OEHHA also reviewed these later studies as the possible basis for the MADL for dermal exposure to BPA from contact with solid materials. In the process of determining that BPA had been clearly shown through scientifically valid testing according to generally accepted principles to cause female reproductive toxicity, the DARTIC identified ovarian toxicity, including effects on follicle development, as endpoints of female reproductive toxicity contributing to their conclusion. Studies of these endpoints have been selected as the most sensitive studies providing a basis for the MADL[9].

[5] Health and Safety Code, section 25249.9(b) and 25249.10(c).
[6] Section 25102(c)(2).
[7] 2015 Hazard Identification Materials for Consideration of the Female Reproductive Toxicity of Bisphenol A available at http://www.oehha.ca.gov/prop65/hazard_ident/BPAhazardID2014.html
[8] *Ibid*.
[9] Section 25803(a)(5).

Human Studies

No human data that could be used with confidence to establish a dermal MADL based on the female reproductive effects of BPA were identified in the Hazard Identification Materials or in the subsequent literature search by OEHHA.

Laboratory Studies

In its identification of BPA as known to cause female reproductive toxicity[10], the DARTIC identified a number of effects, including in particular, effects on the ovaries. The ovarian effects identified by the DARTIC include meiosis errors in oocytes, oocyte nest breakdown, alterations in primordial follicle assembly, ovarian lesions, and other effects on ovarian development[11]. For example, *in vivo* studies in mammals investigating the effect of BPA exposure during oocyte maturation have demonstrated that BPA causes a range of effects indicative of poor oocyte quality. These effects include, for example:

- Disrupted follicle developmental trajectory (Veiga-Lopez et al., 2014)[12] and altered trajectory of fetal ovarian gene expression (Veiga-Lopez et al., 2013)[13] in sheep
- Decreased number of corpora lutea and increased number of atretic follicles in rats (Li et al., 2014)[14]

In addition to *in vivo* studies in mammals, several *in vitro* studies provide additional evidence that BPA causes ovarian and follicular effects, including the following examples of effects following BPA exposure:

- Fewer metaphase II (MII) oocytes and significantly increased abnormal spindle morphology and chromosome dispersal in mature bovine oocytes (Ferris et al., 2015)[15]

[10] Transcript of the Meeting of the Proposition 65 Developmental and Reproductive Toxicant Identification Committee May 7, 2015. Available at http://www.oehha.ca.gov/prop65/public_meetings/pdf/DARTIC5-21-2014MeetingTranscript.pdf.
[11] *Ibid.*
[12] Veiga-Lopez A, Beckett EM, Abi SB, Ye W and Padmanabhan V (2014). Developmental programming: prenatal BPA treatment disrupts timing of LH surge and ovarian follicular wave dynamics in adult sheep. *Toxicol Appl Pharmacol* **279**(2): 119-128.
[13] Veiga-Lopez A, Luense LJ, Christenson LK and Padmanabhan V (2013). Developmental programming: gestational bisphenol-A treatment alters trajectory of fetal ovarian gene expression. Endocrinology 154(5): 1873-1884
[14] Li Y, Zhang W, Liu J, Wang W, Li H, Zhu J, Weng S, Xiao S and Wu T (2014). Prepubertal bisphenol A exposure interferes with ovarian follicle development and its relevant gene expression. Reprod Toxicol 44: 33-40.

- Slowing of oocyte progression to MII and an increase in the percentage of oocytes that degenerated, or underwent spontaneous activation in cultured human oocytes (Machtinger et al., 2013)[16]
- Disturbances in oocyte genomic imprinting and modification of post-translational histone and centromere architecture in cultured mouse follicles (Trapphoff et al., 2013)[17]
- Impaired mouse primordial follicle assembly *in vitro* and severe impairment of folliculogenesis in BPA exposed ovaries after transplantation into the kidney capsules of immunodeficient mice (Zhang et al., 2014)[18]
- Inhibited follicle growth partially via the aryl hydrocarbon receptor pathway in antral follicles from wild-type and Ahr knock-out mice (Ziv-Gal et al., 2013)[19]

No studies investigating female reproductive toxicity after dermal exposure to BPA were identified. Studies of female reproductive toxicity of BPA resulting from routes of exposure that may potentially serve as a basis for establishment of a MADL for dermal exposure, such as subcutaneous (*s.c.*) and intraperitoneal (*i.p*.) injection, were therefore considered. Exposure by the *s.c.* route, where BPA is deposited directly under the skin, is considered to be more analogous to trans-dermal exposures in terms of distribution and metabolism than is *i.p*., since it is generally recognized that "subcutaneously and intramuscularly administered toxicants are usually absorbed at lower rates but enter directly into the general circulation", while "intraperitoneally administered compounds are absorbed primarily through the portal circulation and therefore must pass through the liver before reaching other organs"[20]. Similarly, oral administration is also less

[15] Ferris, J., L. A. Favetta and W. A. King (2015). "Bisphenol A Exposure during Oocyte Maturation in vitro Results in Spindle Abnormalities and Chromosome Misalignment in Bos taurus." *Cytogenetic and Genome Research* **145**(1): 50-58.
[16] Machtinger, R., C. M. Combelles, S. A. Missmer, K. F. Correia, P. Williams, R. Hauser and C. Racowsky (2013). "Bisphenol-A and human oocyte maturation in vitro." *Human Reproduction* (Oxford, England) **28**(10): 2735-2745.
[17] Trapphoff, T., M. Heiligentag, H. N. El, T. Haaf and U. Eichenlaub-Ritter (2013). "Chronic exposure to a low concentration of bisphenol A during follicle culture affects the epigenetic status of germinal vesicles and metaphase II oocytes." *Fertility and sterility* **100**(6): 1758-1767 e1751.
[18] Zhang, T., L. Li, X. S. Qin, Y. Zhou, X. F. Zhang, L. Q. Wang, F. M. De, H. Chen, G. Q. Qin and W. Shen (2014). "Di-(2-ethylhexyl) phthalate and bisphenol A exposure impairs mouse primordial follicle assembly in vitro." *Environmental and molecular mutagenesis* **55**(4): 343-353.
[19] Ziv-Gal, A., Z. R. Craig, W. Wang and J. A. Flaws (2013). "Bisphenol A inhibits cultured mouse ovarian follicle growth partially via the aryl hydrocarbon receptor signaling pathway." *Reproductive Toxicology* (Elmsford, N.Y.) **42**: 58-67.
[20] Lehman-McKeeman, L.D. (2008). Absorption, distribution and excretion of toxicants. Chapter 5 (P. 144), in: *Casarett and Doull's Toxicology: The Basic Science of Poisons.* Seventh edition. McGraw Hill

analogous to trans-dermal absorption because of first-pass metabolism in the liver.

The lowest observable effect levels (LOELs) and no observable effect levels (NOELs), if available, from studies of sufficient quality that may provide the basis for the establishment of the MADL are discussed below, as are the data and assumptions used to relate dermal exposures to the internal exposures resulting from administration of BPA by these routes.

Studies evaluating the reproductive effects of BPA *in vivo* included assessment of ovarian effects following prenatal exposure to BPA through the *s.c.* route of exposure in sheep. A study in rats following exposure through the *i.p.* route provided supporting information on female reproductive effects; however, the studies conducted in sheep through the *s.c.* route were considered more relevant for development of a dermal MADL, in part, because of the route used.

A study by Veiga-Lopez et al. (2014)[21] was identified as the most sensitive for identifying BPA as causing female reproductive toxicity though the *s.c.* route of exposure, which is a more appropriate route to examine potential toxicity from dermal exposure. OEHHA considers this study to be of sufficient quality for use in determining a MADL[22]. This study provides a LOEL of 0.05 milligrams BPA per kilogram body weight per day (mg/kg-day), for female reproductive toxicity. Because the LOEL corresponds to the lowest dose administered, a NOEL was not determined in this study.

Veiga-Lopez et al. (2014) investigated potential effects on female reproduction using the sheep animal model. The authors tested the hypothesis that prenatal BPA treatment disrupts ovarian follicular dynamics. Pregnant sheep were treated by the *s.c.* route of exposure daily from gestational day (GD) 30 to GD 90. Reproductive toxicity assessment was performed on female offspring at 19 month of age. Six to 12 estrous-synchronized female offspring per dose group were assessed. A significant effect of prenatal BPA treatment on the trajectory of follicle development was observed at all doses.

[21] Veiga-Lopez A, Beckett EM, Abi SB, Ye W and Padmanabhan V (2014). Developmental programming: prenatal BPA treatment disrupts timing of LH surge and ovarian follicular wave dynamics in adult sheep. *Toxicol Appl Pharmacol* **279**(2): 119-128.
[22] Section 25803(a)(6)

An earlier study in sheep by the same group[23] measured the effect of a single daily *s.c.* BPA dose (0.5 mg/kg-day) from GD 30 to GD 90 on gene expression of two steroidogenic enzymes in the fetal ovary at GD 65. The authors reported significant increases in gene expression of P450 aromatase (the enzyme that catalyzes the conversion of testosterone (T) to estradiol (E_2)) and 5α-reductase (the enzyme that catalyzes the conversion of T to the non-aromatizable androgen dihydrotestosterone) in the fetal ovary of treated animals.

The LOEL for this earlier study is 0.5 mg/kg-day, the only dose administered, based on effects on steroidogenic enzyme gene expression. The absence of other doses with which to evaluate potential dose response relationships makes it less relevant for MADL development, but the data are consistent with BPA altering fetal ovarian function by interfering with steroidogenesis. Further, the later 2014 study by the same group showed effects at lower doses. In the 2013 study, BPA was measured in blood from the umbilical artery of female fetuses at GD 90 in both control and treated animals. The BPA level in control animals was 0.43 ng/ml and in the treated animals was 2.6 ng/ml. Thus the treated animals received more BPA than untreated controls. However, this background BPA level in the earlier study may not be the same in the later study, which uses different experimental parameters such as diet.

A study by Li et al. (2014)[24] investigated the effects of pre-pubertal BPA exposure on ovarian follicle development and relevant gene expression in rats, and provides supporting evidence for ovarian effects. In this study, 28-day-old rats were randomly divided into four groups according to their body weights. Twelve rats per group were exposed to BPA by *i.p.* injection of 10 mg/kg-day, 40 mg/kg-day or 160 mg/kg-day for 7 days. Control group rats were injected daily with an equal volume of solvent (olive oil).

At 35 days of age, body weight (bw) and ovarian weight were recorded. Blood samples were collected and the animals were sacrificed. Estradiol and progesterone (P_4) were measured in serum. The number of developing follicles, atretic follicles, and corpora lutea (CL) were determined by ovarian histology. In addition, several genes involved in development of the reproductive system were assessed by real time polymerase chain reaction (RT-PCR). There were no

[23] Veiga-Lopez A, Luense LJ, Christenson LK and Padmanabhan V (2013). Developmental programming: gestational bisphenol-A treatment alters trajectory of fetal ovarian gene expression. *Endocrinology* 154(5): 1873-1884.
[24] Li Y, Zhang W, Liu J, Wang W, Li H, Zhu J, Weng S, Xiao S and Wu T (2014). Prepubertal bisphenol A exposure interferes with ovarian follicle development and its relevant gene expression. Reprod Toxicol 44: 33-40.

differences in bw between the BPA-exposed groups and the control group, but there was a dose-related ovarian weight reduction that reached statistical significance ($p<0.01$) at the two higher doses.

There was a statistically significant decrease in P_4 blood level at 40 and 160 mg/kg-day ($p<0.01$) and a non-statistically significant decrease in E_2 blood levels. There was a dose-related decrease in the number of total, pre-antral, and antral follicles in each BPA exposure group. Significant changes were observed at all BPA doses with $p<0.05$, $p<0.01$, and $p<0.01$ for the 10 mg/kg-day, 40 mg/kg-day and 160 mg/kg-day groups, respectively. Similarly, there was a dose-related decrease in the number of CL that was statistically significant at all doses ($p<0.05$ for the 10 mg/kg-day and $p<0.01$ for each of the two higher doses). There was also an increase in the number of atretic follicles that reached significance ($p<0.01$) at the two higher doses. Therefore, for reductions in the number of follicles (at various stages) and CL, the LOEL in this study is 10 mg/kg-day with no evident NOEL.

The follicle development promoting genes, germline alpha (FIGLA), and oocyte-specific histone H1 variant (H1FOO), were significantly down regulated by BPA treatment. H1FOO was down regulated at all doses ($p<0.01$), while FIGLA was down regulated at the higher dose ($p<0.05$) only. In contrast, a follicular development inhibitory gene, the anti-mullerian hormone (AMH), was up regulated at 40 mg/kg-day ($p<0.05$) and 160 mg/kg-day ($p<0.001$). The gene expression data is also consistent with the protein expression of these genes that was determined by western blot analysis. Therefore for ovarian development gene expression in this study, the LOEL is 10 mg/kg-day and there is no apparent NOEL.

Comparison of the studies above identifies 0.05 mg/kg-day in sheep as the LOEL for female reproductive toxicity of BPA, and no NOEL was identified. Hence, the study reported by Veiga-Lopez et al. (2014) is identified as the most sensitive study deemed to be of sufficient quality, and was conducted by subcutaneous injection, a route more relevant for dermal exposure, and therefore provides the basis for calculation of the MADL.

Study Basis for the MADL Calculation

The study by Veiga-Lopez et al. (2014) provides a LOEL of 0.05 mg/kg-day (the lowest dose used in the study) for female reproductive toxicity. This study tested the hypothesis that prenatal BPA treatment disrupts ovarian follicular dynamics using sheep as the animal model. Adult Suffolk sheep, 3 to 5 years of age, were

exposed to BPA at different doses: 0 (vehicle control), 0.05, 0.5 or 5 mg/kg-day. Pregnant sheep received daily *s.c.* injections from GD 30 to GD 90. In sheep, gonadal differentiation occurs around GD 30 and the completion of primordial follicle formation occurs around GD 90. At 19 months of age, 6 to 12 female sheep per group (F1 generation) were estrous synchronized for reproductive dynamic assessment.

No chemical-related maternal toxicity was reported. Ovaries were examined daily by ultrasonography for follicle and CL dynamics. Blood samples were collected every 2 hours for 5 consecutive days to assess pre-ovulatory luteinizing hormone (LH) and E_2 around the LH surge. Additional blood samples were collected daily to day 28 for P_4 determination.

Ovarian examination: Significant differences in follicular count trajectories were found in all BPA-treated groups and in all three follicular size classes (2–3 mm, p=0.0001; 4–5 mm, p=0.001; and ≥6 mm, p=0.05). Specifically, posthoc analyses of the 2–3 mm follicular count trajectory found significant differences between controls and each of the 3 BPA dose groups (p=0.01, p=0.001, and p=0.006 for the 0.05, 0.5, and 5 mg/kg-day BPA dose groups, respectively). Similarly, the trajectory of the 4–5 mm follicular count was also significantly different in control vs. BPA groups (p=0.006, p=0.002, and p=0.04 for the 0.05, 0.5, and 5 mg/kg-day BPA dose groups, respectively). However, the effect on the trajectory of ≥6 mm follicular count was observed only in the highest BPA dose (p=0.04).

There were no differences in CL count or P_4 circulating levels. The F1 control animals showed normal hormone cycles (LH, E_2, and P_4). BPA treatment induced a 4 h delay (not statistically significant) in the E_2 rise, and also a non-statistically significant delay in LH surge. No alteration in P_4 profiles was observed.

The dose of 0.05 mg/kg-day was identified as the LOEL. Regulations specify that "when data do not allow the determination of a NOEL, the lowest observed effect level in a study shall be divided by 10 to establish a NOEL for purposes of assessment"[25]. Accordingly, a NOEL of 0.005 mg/kg-day for the female reproductive effects of BPA in this study was calculated.

[25] Section 25803(a)(8).

Extrapolation from Subcutaneous Doses to Dermal Exposures

OEHHA has not identified any studies that directly relate dermal and subcutaneous BPA exposures to each other. For the purpose of MADL development, OEHHA assumes that the amount absorbed trans-dermally is toxicologically equivalent to the same amount injected subcutaneously.

Bodies such as the European Food Safety Authority (EFSA)[26,27] have estimated dermal absorption of BPA. EFSA assumed that the dermal absorption fraction for solid BPA from thermal paper was 0.1 (10%).

EFSA reviewed five studies of percutaneous penetration of BPA[28], four using human skin and one using pig skin. These studies were also reviewed by OEHHA. On the basis of these studies, EFSA stated that:

> "Demierre et al. (2011) [sic, the cited paper is dated 2012] … showed that 8.6% of the applied dose passed through the human skin within 24 h. Given the uncertainties around this value, and taking the evidence from the other dermal absorption studies into account, a dermal absorption fraction of 10% was assumed in the present opinion for the exposure scenarios with dermal contact to thermal paper."

OEHHA has reviewed the information relied upon by EFSA and concurs with the absorption fraction identified by EFSA for contact with solid materials such as thermal paper. OEHHA notes that the same absorption fraction from contact with

[26] Scientific Opinion on the risks to public health related to the presence of bisphenol A (BPA) in foodstuffs: Part I – Exposure assessment. EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (CEF). European Food Safety Authority (EFSA), Parma, Italy. EFSA Journal 2015;13(1):3978

[27] Scientific Opinion on the risks to public health related to the presence of bisphenol A (BPA) in foodstuffs: Part II - Toxicological assessment and risk characterization. EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (CEF). European Food Safety Authority (EFSA), Parma, Italy. EFSA Journal 2015;13(1):3978

[28] Kaddar N, Harthe C, Dechaud H, Mappus E and Pugeat M (2008). Cutaneous penetration of bisphenol A in pig skin. *J Toxicol Environ Health A* **71**(8): 471-473.
Morck TJ, Sorda G, Bechi N, Rasmussen BS, Nielsen JB, Ietta F, Rytting E, Mathiesen L, Paulesu L and Knudsen LE, 2010. Placental transport and in vitro effects of Bisphenol A. *Reprod Toxicol*, 30, 131-137.
Marquet F, Payan JP, Beydon D, Wathier L, Grandclaude MC and Ferrari E (2011). In vivo and ex vivo percutaneous absorption of [14C]-bisphenol A in rats: a possible extrapolation to human absorption? *Arch Toxicol* **85**(9): 1035-1043.
Zalko D, Jacques C, Duplan H, Bruel S and Perdu E (2011). Viable skin efficiently absorbs and metabolizes bisphenol A. *Chemosphere* **82**(3): 424-430.
Demierre AL, Peter R, Oberli A and Bourqui-Pittet M (2012). Dermal penetration of bisphenol A in human skin contributes marginally to total exposure. *Toxicol Lett* **213**(3): 305-308.

solid materials such as thermal paper has also been assumed by the European Chemicals Bureau of the European Union[29] and the Danish Environmental Protection Agency[30].

MADL CALCULATION

The following calculations were performed in accordance with Section 25803 to derive the MADL for dermal exposure to BPA from contact with solid materials:

- Calculation of the subcutaneous NOEL dose for a 58 kg woman:
  0.005 mg/kg-day × 58 kg = 0.29 mg/day

- Calculation of the subcutaneous (i.e., trans-dermally absorbed) maximum allowable dose level for BPA by dividing the subcutaneous NOEL expressed in mg/day by one thousand (Section 25801(b)(1)):
  0.29 mg/day ÷ 1000 = 0.29 micrograms/day

- Derivation of the MADL for dermal exposure to BPA from contact with solid materials by dividing the trans-dermally absorbed maximum allowable dose level by the dermal absorption fraction for contact with solid materials:

$$\textbf{MADL}_{\textbf{dermal exposure from solid materials}} = 0.29 \text{ micrograms/day} \div 0.1$$
$$= 2.9 \text{ micrograms/day,}$$
which rounds to **3 micrograms/days**

PROPOSED REGULATORY AMENDMENT

The proposed change to Section 25805(b) is provided below in underline:

Chemical name	*Level (micrograms per day)*
…	
Bisphenol A (BPA)	3 (dermal exposure from solid

[29] European Chemicals Bureau**.** Updated Risk Assessment of 4,4'-IsopropylideneDiphenol (Bisphenol-A) CAS Number: 80-05-7 EINECS Number: 201-245-8 Final human health draft for publication (to be read in conjunction with published EU RAR of BPA, 2003) April 2008

[30] Lassen C, Mikkelsen SH and Brandt UK (2011). Migration of bisphenol A from cash register receipts and baby dummies. Danish Ministry of the Environment, Environmental Protection Agency. Survey of Chemical Substances in Consumer Products, No. 110 2011

materials)

PROBLEM BEING ADDRESSED BY THIS PROPOSED RULEMAKING

Proposition 65 does not provide guidance regarding how to determine whether a warning is required or a discharge is prohibited. OEHHA is the implementing agency for Proposition 65 and has the authority and expertise to examine the scientific literature and calculate a level of exposure, in this case a MADL, that does not require a warning or at which a discharge is not prohibited.

NECESSITY

This proposed regulatory amendment would adopt a MADL that conforms with the Proposition 65 implementing regulations and reflects the currently available scientific knowledge about BPA. The MADL provides assurance to the regulated community that exposures or discharges at or below it are considered not to pose a significant risk of developmental or reproductive harm. Exposures at or below the MADL are exempt from the warning and discharge requirements of Proposition 65[31].

BENEFITS OF THE PROPOSED REGULATION

See "Benefits of the Proposed Regulation" under ECONOMIC IMPACT ANALYSIS below.

TECHNICAL, THEORETICAL, AND/OR EMPIRICAL STUDIES, REPORTS, OR DOCUMENTS

In determining the evidence and standards that formed the basis for listing BPA under Proposition 65, OEHHA reviewed the transcript of the May 7, 2015 meeting of the DARTIC[32] and the hazard identification materials reviewed by the DARTIC for that meeting[33]. These hazard identification materials, which include the public comments received, included numerous studies of the effects of BPA on the female reproductive system, including *in vivo* studies in experimental animals and *in vitro* studies that provide additional evidence of female reproductive toxicity.

[31] Health and Safety Code sections 25249.9(b) and 25249.10(c)
[32] Transcript of the Meeting of the Proposition 65 Developmental and Reproductive Toxicant Identification Committee, May 7, 2015. Available at http://www.oehha.ca.gov/prop65/public_meetings/pdf/DARTIC5-21-2014MeetingTranscript.pdf.
[33] 2015 Hazard Identification Materials for Consideration of the Female Reproductive Toxicity of Bisphenol A available at http://www.oehha.ca.gov/prop65/hazard_ident/BPAhazardID2014.html

OEHHA relied on the study by Veiga-Lopez et al. (2014) [34] that provides a subcutaneous LOEL of 0.05 milligrams BPA per kilogram body weight per day (mg/kg-day), for female reproductive toxicity. This study was determined to be the most sensitive of those relevant to the dermal route of exposure. OEHHA also reviewed a related subcutaneous injection study by Veiga-Lopez et al. (2013)[35] and a supporting intraperitoneal injection study by Li et al. (2014)[36]. OEHHA also reviewed several *in vitro* studies that provided additional evidence of female reproductive toxicity[37].

In determining the appropriate factor for extrapolation from subcutaneous to dermal exposure, OEHHA reviewed documents published by EFSA[38,39], the European Chemicals Bureau of the European Union[40] and the Danish

[34] Veiga-Lopez A, Beckett EM, Abi SB, Ye W and Padmanabhan V (2014). Developmental programming: prenatal BPA treatment disrupts timing of LH surge and ovarian follicular wave dynamics in adult sheep. *Toxicol Appl Pharmacol* **279**(2): 119-128.

[35] Veiga-Lopez A, Luense LJ, Christenson LK and Padmanabhan V (2013). Developmental programming: gestational bisphenol-A treatment alters trajectory of fetal ovarian gene expression. *Endocrinology* 154(5): 1873-1884.

[36] Li Y, Zhang W, Liu J, Wang W, Li H, Zhu J, Weng S, Xiao S and Wu T (2014). Prepubertal bisphenol A exposure interferes with ovarian follicle development and its relevant gene expression. *Reprod Toxicol* 44: 33-40.

[37] Ferris, J., L. A. Favetta and W. A. King (2015). "Bisphenol A Exposure during Oocyte Maturation in vitro Results in Spindle Abnormalities and Chromosome Misalignment in Bos taurus." *Cytogenetic and Genome Research* **145**(1): 50-58.
Machtinger, R., C. M. Combelles, S. A. Missmer, K. F. Correia, P. Williams, R. Hauser and C. Racowsky (2013). "Bisphenol-A and human oocyte maturation in vitro." *Human Reproduction* (Oxford, England) **28**(10): 2735-2745.
Trapphoff, T., M. Heiligentag, H. N. El, T. Haaf and U. Eichenlaub-Ritter (2013). "Chronic exposure to a low concentration of bisphenol A during follicle culture affects the epigenetic status of germinal vesicles and metaphase II oocytes." *Fertility and sterility* **100**(6): 1758-1767 e1751.
Zhang, T., L. Li, X. S. Qin, Y. Zhou, X. F. Zhang, L. Q. Wang, F. M. De, H. Chen, G. Q. Qin and W. Shen (2014). "Di-(2-ethylhexyl) phthalate and bisphenol A exposure impairs mouse primordial follicle assembly in vitro." *Environmental and molecular mutagenesis* **55**(4): 343-353.
Ziv-Gal, A., Z. R. Craig, W. Wang and J. A. Flaws (2013). "Bisphenol A inhibits cultured mouse ovarian follicle growth partially via the aryl hydrocarbon receptor signaling pathway." *Reproductive Toxicology* (Elmsford, N.Y.) **42**: 58-67.

[38] Scientific Opinion on the risks to public health related to the presence of bisphenol A (BPA) in foodstuffs: Part I – Exposure assessment. EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (CEF). European Food Safety Authority (EFSA), Parma, Italy. EFSA Journal 2015;13(1):3978

[39] Scientific Opinion on the risks to public health related to the presence of bisphenol A (BPA) in foodstuffs: Part II - Toxicological assessment and risk characterization. EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (CEF). European Food Safety Authority (EFSA), Parma, Italy. EFSA Journal 2015;13(1):3978

[40] European Chemicals Bureau**.** Updated Risk Assessment of 4,4'-IsopropylideneDiphenol (Bisphenol-A) CAS Number: 80-05-7 EINECS Number: 201-245-8 Final human health draft for publication (to be read in conjunction with published EU RAR of BPA, 2003) April 2008

Environmental Protection Agency[41]. OEHHA also reviewed relevant publications cited in the EFSA documents[42].

Copies of these documents and studies reviewed in development of the MADL will be included in the regulatory file for this action, and are available from OEHHA upon request.

OEHHA also relied on the attached Economic Impact Analysis in developing this proposed regulation.

REASONABLE ALTERNATIVES TO THE REGULATION AND THE AGENCY'S REASONS FOR REJECTING THOSE ALTERNATIVES

The MADL provides a "safe harbor" value that aids businesses in determining if they are complying with the law. The alternative to the amendment to Section 25805(b) would be to not promulgate a MADL for the chemical. Failure to promulgate a MADL would leave the business community without a safe harbor level to assist businesses in determining compliance with Proposition 65. No alternative that is less burdensome yet equally as effective in achieving the purposes of the regulation in a manner that achieves the purposes of the statute has been proposed.

REASONABLE ALTERNATIVES TO THE PROPOSED REGULATORY ACTION THAT WOULD LESSEN ANY ADVERSE IMPACT ON SMALL BUSINESSES

OEHHA is not aware of significant cost impacts that small businesses would incur in reasonable compliance with the proposed action. Use of the proposed MADL by businesses is voluntary and therefore does not impose any costs on small businesses. In addition, Proposition 65 is limited by its terms to businesses with 10 or more employees (Health and Safety Code, section 25249.11(b)) so it has no effect on very small businesses.

EVIDENCE SUPPORTING FINDING OF NO SIGNIFICANT ADVERSE ECONOMIC IMPACT ON BUSINESS

Because the proposed MADL provides a "safe harbor" level for businesses to use when determining compliance with Proposition 65, OEHHA does not

[41] Lassen C, Mikkelsen SH and Brandt UK (2011). Migration of bisphenol A from cash register receipts and baby dummies. Danish Ministry of the Environment, Environmental Protection Agency. Survey of Chemical Substances in Consumer Products, No. 110 2011

anticipate that the regulation will have a significant statewide adverse economic impact directly affecting businesses, including the ability of California businesses to compete with businesses in other states.

EFFORTS TO AVOID UNNECESSARY DUPLICATION OR CONFLICTS WITH FEDERAL REGULATIONS CONTAINED IN THE CODE OF FEDERAL REGULATIONS

Proposition 65 is a California law that has no federal counterpart. There are no federal regulations addressing the same issues and, thus, there is no duplication or conflict with federal regulations.

ECONOMIC IMPACT ANALYSIS
Gov. Code section 11346.3(b)

It is not possible to quantify any monetary values for this proposed regulation because its use is entirely voluntary and it only provides compliance assistance for businesses subject to the Act.

Impact on the Creation, Elimination, or Expansion of Jobs/Businesses in California: This regulatory proposal will not affect the creation or elimination of jobs within the State of California. Proposition 65 requires businesses with ten or more employees to provide warnings when they expose people to chemicals that are known to cause cancer or developmental or reproductive harm. The law also prohibits the discharge of listed chemicals into sources of drinking water. BPA is listed under Proposition 65; therefore, businesses and individuals who manufacture, distribute or sell products with BPA in the state must provide a warning if their product or activity exposes the public or employees to this chemical.

Impact on the Creation of New Businesses or Elimination of Existing Businesses within the State of California

This regulatory action will not impact the creation of new businesses or the elimination of existing businesses within the State of California. The regulatory proposal does not create additional compliance requirements, but instead provides a “safe harbor” value that aids businesses in determining if they are complying with the law with respect to skin contact with solid materials such as thermal paper and hard plastics that contain BPA.

Impact on Expansion of Businesses within the State of California

This regulatory action will not impact the expansion of businesses within the State of California. The regulatory proposal does not create additional compliance requirements, but instead provides a "safe harbor" value that aids businesses in determining if they are complying with the law.

Benefits of the Proposed Regulation: The MADL provides a "safe harbor" value that aids businesses in determining if they are complying with the law. Some businesses may not be able to afford the expense of establishing a MADL and therefore may be exposed to litigation for a failure to warn or for a prohibited discharge of the listed chemical. Adopting this regulation will save these businesses those expenses and may reduce litigation costs. By providing a safe harbor level, this regulatory proposal does not require, but may encourage, businesses to lower the amount of the listed chemical in their product to a level that does not cause a significant exposure, thereby providing a public health benefit to Californians.

Problem being addressed by this proposed rulemaking: Proposition 65 does not provide specific guidance regarding how to determine whether a warning is required or a discharge is prohibited. OEHHA is the implementing agency for Proposition 65 and has the resources and expertise to examine the scientific literature and calculate a level of exposure that does not require a warning or trigger the discharge prohibition.

How the proposed regulation addresses the problem: The proposed regulation would adopt a specific regulatory level for a listed chemical to provide compliance assistance for businesses that are subject to the requirements of the Act. While OEHHA is not required to adopt such levels, adopting them provides a "safe harbor" for businesses and provides certainty that they are complying with the law if the exposures or discharges they cause are below the established level.

Reasonable alternatives to the proposed regulation: OEHHA determined that the only alternative to the proposed regulation would be to not adopt a MADL for this chemical. This alternative was rejected because it would fail to provide businesses with the certainty that the MADL can provide.

Results: By providing a MADL for dermal exposure, this regulatory proposal spares businesses the expense of calculating their own MADL for dermal

exposure and may also enable them to reduce or avoid litigation costs. In addition, the MADL does not require, but may encourage, businesses to lower the amount of the listed chemical in their product to a level that does not cause a significant exposure, thereby providing a public health benefit to Californians.