April 10, 2013

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Dear Ms. Vela:

Thank you for the opportunity to comment on the proposed Maximum Allowable Dose Level (MADL) of 290 micrograms per day for exposures to bisphenol A (BPA). BPA is a high production volume chemical, it is used in a wide variety of consumer products, and biomonitoring studies in the US and elsewhere have shown that exposure to BPA is ubiquitous. Therefore, we strongly support the establishment of a MADL by the Office of Environmental Health Hazard Assessment (OEHHA). As the agency wrote in its notice of proposed rulemaking, this establishment of a MADL should "encourage businesses to lower the amount of the listed chemical in their products to a level that does not cause a significant exposure. This in turn may reduce exposures to chemicals that cause reproductive harm." As scientists, academics, health professionals, health advocates and others who work to improve public health, we strongly support this goal.

We also strongly support the timing of proposing this MADL, simultaneous with the proposed Proposition 65 (Safe Drinking Water and Toxic Enforcement Act) listing of BPA.

At the same time, we recommend that OEHHA reconsider recent research about the developmental effects of exposure to low doses of BPA. In the table on the following pages, we summarize the results of ten studies published during the last year that found developmental effects of BPA at dose levels significantly below the No Observable Effect Level on which the proposed MADL is based (5 mg/kg/day). The Lowest Observable Adverse Effect Levels (LOAEL) in these studies ranges from .00005x the NOEL on which the MADL is based to .08x that NOEL. The studies include research on three types of laboratory animals, including primates in addition to the rodent species commonly used as test animals. The research we summarize identifies a wide variety of developmental endpoints in both male and female offspring.

There is an enormous amount of research about developmental effects of BPA and this amount is rapidly expanding. The studies we have summarized are not meant to be an exhaustive list, but rather are examples of significant recent research.

Based on this research, we strongly recommend establishment of a health-protective MADL no higher than .08x the proposed MADL (23.2 ug/day). Further, given the LOAELs in the studies we summarize, we recommend OEHHA consider an even lower MADL.

The Initial Statement of Reasons for the proposed MADL indicates that the administrative (“authoritative bodies”) process used to identify BPA as a chemical known to cause reproductive harm poses some constraints for establishment of a MADL. However, we believe that setting a MADL that is consistent with current science and is health-protective is urgent and of utmost importance.
<table>
<thead>
<tr>
<th>Test Animal</th>
<th>Developmental Endpoint</th>
<th>Lowest Observable Adverse Effect Level (LOAEL)*</th>
<th>LOAEL relative to the No Observable Effect Level (NOEL) used to determine proposed safe harbor level</th>
<th>Citation</th>
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<tbody>
<tr>
<td>Rhesus Macaque</td>
<td>Brain development in offspring</td>
<td>.4 mg/kg/day</td>
<td>.08x</td>
<td>John D. Elsworth et al. Prenatal exposure to bisphenol A impacts midbrain dopamine neurons and hippocampal spine synapses in non-human primates. NeuroToxicology 35 (2013) 113–120.</td>
</tr>
<tr>
<td>Rhesus Macaque</td>
<td>Development of mammary glands in female offspring</td>
<td>.4 mg/kg/day</td>
<td>.08x</td>
<td>Andrew P. Tharp et al. Bisphenol A alters the development of the rhesus monkey mammary gland. PNAS (2012) 109(21): 8190-8195.</td>
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<tr>
<td>Rhesus Macaque</td>
<td>Development of ovary in female fetuses</td>
<td>.4 mg/kg/day</td>
<td>.08x</td>
<td>Patricia A. Hunt et al. Bisphenol A alters early oogenesis and follicle formation in the fetal ovary of the rhesus monkey. PNAS (2012) 109(43): 17525–17530.</td>
</tr>
<tr>
<td>Rat</td>
<td>Demasculinization of behaviors in male offspring</td>
<td>.005 mg/kg/day</td>
<td>.001x</td>
<td>Bryan A. Jones, Neil V. Watson. Perinatal BPA exposure demasculinizes males in measures of affect but has no effect on water maze learning in adulthood. Hormones and Behavior 61 (2012) 605–610.</td>
</tr>
<tr>
<td>Rat</td>
<td>Development of sexually dimorphic brain structure in male offspring</td>
<td>.0025 mg/kg/day</td>
<td>.0005x</td>
<td>Zhen He. Low oral doses of bisphenol A increase volume of the sexually dimorphic nucleus of the preoptic area in male, but not female, rats at postnatal day 21. Neurotoxicology and Teratology 34 (2012) 331–337.</td>
</tr>
<tr>
<td>Rat</td>
<td>Development of brain estrogen receptors in offspring</td>
<td>.0025 mg/kg/day</td>
<td>.0005x</td>
<td>Patisaul, Heather et al. 2013. Prenatal Bisphenol A (BPA) Exposure Alters Sex Specific Estrogen Receptor Expression in the Neonatal Rat Hypothalamus and Amygdala. Toxicological Sciences, in press.</td>
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<tr>
<td>Mouse</td>
<td>Increased anxiety in female offspring</td>
<td>.4 mg/kg/day</td>
<td>.08x</td>
<td>Xiaohong Xu et al. Gestational and lactational exposure to bisphenol-A affects anxiety- and depression-like behaviors in mice. Hormones and Behavior 62 (2012) 480–490.</td>
</tr>
<tr>
<td>Mouse</td>
<td>Increased anxiety and reduced exploratory behavior in female offspring</td>
<td>.01 mg/kg/day</td>
<td>.002x</td>
<td>Laura Gioiosa et al. The Effects of Bisphenol A on Emotional Behavior Depend upon the Timing of Exposure, Age and Gender in Mice. Hormones and Behavior. Accepted February 2013.</td>
</tr>
<tr>
<td>Mouse</td>
<td>Altered morphology of mammary glands in male offspring</td>
<td>.00025 mg/kg/day</td>
<td>.00005x</td>
<td>Laura N. Vandenberg et al. The male mammary gland: A target for the xenoestrogen bisphenol A. Reproductive Toxicology 37 (2013) 15–23.</td>
</tr>
</tbody>
</table>

* BPA administered orally in all studies except Vandenberg, et al in which subcutaneous administration was used.

The importance of a health protective MADL is increased because epidemiological studies have correlated prenatal BPA exposure with adverse outcomes in infants/children, suggesting developmental effects of BPA in humans. These studies measured BPA concentration in the urine or serum of pregnant women exposed to BPA from environmental sources (i.e. not occupationally exposed), and measured outcomes in their offspring. The chart below (and on the next page) summarizes the relevant studies.

<table>
<thead>
<tr>
<th>Categories</th>
<th>Study</th>
<th>Study Type#</th>
<th>N</th>
<th>Population Type</th>
<th>BPA Conc. ±</th>
<th>Results</th>
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</thead>
<tbody>
<tr>
<td>Birth Weight/Fetal Growth</td>
<td>Chou et al. 2011[1]</td>
<td>Pros. cohort</td>
<td>97</td>
<td>Taiwanese mother-infant pairs.</td>
<td>0.5-2.5±</td>
<td>Higher serum BPA was significantly associated with lower birth weight and smaller size for gestational age in male infants, but not female infants.</td>
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<tr>
<td>Sex Hormone Concentrations</td>
<td>Fénelch et al. 2012 [3]</td>
<td>Pros. cohort</td>
<td>152</td>
<td>Newborn boys born with or without cryptorchidism.</td>
<td>1.1-1.3±</td>
<td>There was a significant positive correlation between cord blood BPA and total testosterone and inhibin.</td>
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<td>Thyroid Function</td>
<td>Chevrier et al. 2013 [4]</td>
<td>Long birth  cohort</td>
<td>364</td>
<td>Mother-child pairs</td>
<td>1.1-1.2c</td>
<td>Maternal BPA was negatively associated with neonatal TSH in boys.</td>
</tr>
<tr>
<td>Child Wheeze/Asthma</td>
<td>Spanier et al. 2012 [5]</td>
<td>Pros. birth  cohort</td>
<td>365</td>
<td>Mother-infant pairs</td>
<td>2.4c</td>
<td>Higher maternal urinary BPA was associated with increased odds of wheeze in the child at 6 months of age, but this association was diminished by 3 years of age.</td>
</tr>
<tr>
<td>Child Behavior</td>
<td>Perera et al. 2012</td>
<td>Pros. birth  cohort</td>
<td>198</td>
<td>Mother-child pairs</td>
<td>1.96a</td>
<td>Among boys, high prenatal BPA exposure was associated with more problems on Emotionally Reactive and Aggressive Behavior syndromes. Among girls, higher exposure was associated with lower scores on Anxious/Depressed and Aggressive Behavior syndromes.</td>
</tr>
</tbody>
</table>

*, Mean or geometric mean BPA of participants. Ranges of BPA indicate several reported means/medians (i.e. for different groups) or a reported range.

a, ug/L, urinary BPA adjusted for specific gravity (SG).
b, ug/L, serum BPA.
c, ug/g, urinary BPA adjusted for creatinine (Cr).
d, ug/L, unadjusted urinary BPA.

References


Thank you for consideration of our comments.

Sincerely,

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