

Hazard Identification Materials for Consideration of the Female Reproductive Toxicity of Bisphenol A

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Office of Environmental Health Hazard Assessment
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Introduction

On July 15, 2009, bisphenol A (BPA) was considered for listing under Proposition 65 by the Developmental and Reproductive Toxicant Identification Committee (DARTIC), a committee of the Office of Environmental Health Hazard Assessment's (OEHHA) Science Advisory Board and the state's qualified experts regarding findings of reproductive toxicity. At that time, the DARTIC voted unanimously that BPA had not been clearly shown to cause developmental, female reproductive or male reproductive toxicity. However, the committee requested the opportunity to re-visit consideration of BPA if additional epidemiological or other specific types of data on reproductive and developmental toxicity became available¹.

In August 2014, a scientific review of BPA and reproductive health was published in the journal *Environmental Health Perspectives* (EHP)². The review noted that in 2007 an expert panel reviewed associations between BPA exposure and reproductive health outcomes and that, since then, new studies have been conducted on the impact of BPA on reproduction. The objective of the review was to summarize the data obtained since 2007, focusing on: 1) findings from human and animal studies, 2) the effects of BPA on a variety of reproductive toxicity endpoints and 3) mechanisms of BPA action. The review identifies substantial new epidemiological and toxicological data on female reproductive toxicity that have become available subsequent to the DARTIC's consideration of BPA in 2009. OEHHA has therefore assembled materials on the female reproductive toxicity of BPA for DARTIC consideration.

¹ Meeting transcript and synopsis available at:
http://www.oehha.org/Prop65/public_meetings/dart071509synop.html

² Peretz J., Vrooman L., Ricke W.A., Hunt P.A., Ehrlich S., Hauser R., Padmanabhan V., Taylor H.S., Swan S.H., VandeVoort C.A. and Flaws J.A., *Environmental Health Perspectives* 122(8): 775-786 (2014). (available online at: <http://ehp.niehs.nih.gov/1307728/>)

The DARTIC is scheduled to deliberate at public meetings to be held on May 7 and, if necessary, May 21, 2015, on whether or not BPA has been “clearly shown by scientifically valid testing according to generally accepted principles to cause female reproductive toxicity”.³

Hazard Identification Materials on the Female Reproductive Toxicity of BPA

The following materials are being provided to the DARTIC in electronic form:

- The 2014 EHP review: Peretz, J., L. Vrooman, W.A. Ricke, P.A. Hunt, S. Ehrlich, R. Hauser, V. Padmanabhan, H.S. Taylor, S.H. Swan, C.A. VandeVoort, and J.A. Flaws (2014). “Bisphenol A and Reproductive Health: Update of Experimental and Animal Evidence, 2007 – 2013,” EHP 122(8): 775-786. [available online at: <http://ehp.niehs.nih.gov/1307728/>]
- Supplemental material to the 2014 EHP review [available online at <http://ehp.niehs.nih.gov/1307728/>].
- Articles cited in the 2014 EHP review that directly pertain to female reproductive toxicity.
- Studies of bisphenol A relevant to female reproductive toxicity which were conducted in mammals and published after the 2014 EHP review was submitted for publication.
- The hazard identification materials provided to the DARTIC in 2009:
 1. OEHHA, “Evidence on the Developmental and Reproductive Toxicity of Bisphenol A.” October 2009.
This document provides an integrative review of the data available in 2009.
 2. National Toxicology Program -- Center for the Evaluation of Risks to Human Reproduction (NTP-CERHR, 2008). “NTP-CERHR Monograph on the Potential Human Reproductive and Developmental Effects of Bisphenol A.” NTP, US Department of Health and Human Services, Research Triangle Park, NC, NIH Publication No. 08-5994.
 3. European Union (EU). “European Union (EU) Risk Assessment Report: 4,4'-isopropylidenediphenol (bisphenol-A).” Final Report, 2003
 4. EU Update of the Risk Assessment of 4,4'-Isopropylidenediphenol (Bisphenol-A), Final Human Health Draft for publication, 2008.
 5. Public comments submitted to the DARTIC in 2009 regarding possible listing of BPA.

Articles and reports available to OEHHA and cited in OEHHA (2009), NTP-CERHR, (2008), EU (2003) and (EU 2008) that directly pertain to female

³ Health and Safety Code section 25249.8(b) and Title 27, Cal. Code of Regs., section 25305(b)(1)

reproductive toxicity are also being provided, as is a list of the articles and reports that OEHHA was unable to obtain.

Hazard identification materials (other than those protected by copyright) are available to the public on OEHHA's website (at http://www.oehha.ca.gov/prop65/hazard_ident/BPAhazardID2014.html). Copyrighted materials may be requested through OEHHA or from the copyright holder.

Portions of Provided Documents Relevant to Female Reproductive Toxicity

To assist the committee and public, the relevant pages from the 2014 EHP review and the OEHHA, NTP, and EU documents that are directly relevant to female reproductive toxicity in mammals are identified below.

- Bisphenol A and Reproductive Health: Update of Experimental and Human Evidence, 2007–2013 (Peretz *et al.*, *Env. Hlth. Perspect.*, 2014, 122(8): 775-786) [2014 EHP Review]
 - Abstract (Page 775)
 - Early oogenesis and ovarian follicle formation (Pages 776-777)
 - Steroidogenesis in females (Page 777)
 - Oocytes: quantity, quality, and fertilization (Pages 777-778)
 - Polycystic ovarian syndrome (Page 778)
 - Oviduct (Page 778)
 - Uterine morphology (Page 778)
 - Uterine endometrium (Pages 778-779)
 - Uterine receptivity and implantation (Page 779)
 - Placenta (Page 779)
 - Pregnancy outcomes (Pages 779-780)
 - Puberty and sexual receptivity (Pages 782-783)
 - Sexual dysfunction (Page 783)
 - Conclusions (Page 783)

- Evidence on the Developmental and Reproductive Toxicity of Bisphenol A (OEHHA, 2009)
 - Executive Summary (Pages 11-12)
 - Female reproductive studies in humans (Pages 65-67)
 - Female reproductive studies in laboratory rodents (Pages 68-119)
 - Uterine weight effects (Page 68)
 - Uterine cell morphology (Page 69)
 - Uterine protein expression (Page 70)

Effects on gravid uteri (Page 71)
Long-term uterine effects of neonatal exposure (Page 71)
Effects on the ovary (Pages 82-84)
Effects on the ovarian follicles and oocytes (Pages 84)
Effects on the estrous cycle (Pages 93-98)
Altered estrous cycle patterns and lengths (Pages 93-94)
Alteration of estrous cycle onset (Pages 95-98)
Effects on fertility (Page 99)
Multi-generation studies (Pages 99-100)
Reproductive Assessment by Continuous Breeding (RACB) biosassay (Page 101)
Effects on the vagina (Pages 101-106)
Effects on the mammary gland (Pages 107-113)
Maternal behavior (Page 118)
Summary and human health relevance (Pages 119-120)
Appendix 1: Female Reproductive Toxicity Studies (Pages A1-7 – A1-16)

- NTP-CERHR Monograph on the Potential Human Reproductive and Developmental Effects of Bisphenol A (2008) [Attachment to OEHHA, 2009]
 - Can Bisphenol A Affect Human Development or Reproduction? (Pages 6-9)
 - Human studies (Page 15)
 - Reproductive studies in animals (developmental pertaining to female reproductive toxicity endpoints) (Pages 16-17)
 - Mammary gland (Pages 21-24)
 - Puberty and Sexual Maturation (Pages 26-29)
 - Other Effects Considered (Pages 29-30)
 - Evaluation of reproductive organ data (BDR⁴ Pages 239, 241, 245-246)
 - Rat—oral exposure postnatally with or without prenatal exposure. Reproductive studies. (BDR Pages 247-252, 254-255, 258-260, 263-264, 268-269, 271-272, 273-274, 278-279, 281-283, 285-286, 288, 292-293, 294-295, 299)
 - Mouse—parenteral exposure postnatally with or without prenatal exposure. Female reproductive endpoints. (BDR Pages 303-305)
 - Sheep (BDR Pages 307-308)
 - Development pertaining to reproductive toxicity (BDR Pages 321-325)

⁴ The Expert Panel Report is appended to the NTP-CERHR Monograph in the form of a paper published in the journal Birth Defects Research, so page numbers for this portion of the Monograph refer to the journal's pagination.

- Reproductive system development (BDR Pages 328-339)
 - Reproductive toxicity data: human female (BDR Pages 330-332)
 - Reproductive toxicity: female experimental animals (BDR Pages 333-338)
 - Reproductive toxicity: male and female (BDR Pages 357-371, 374-378)
 - Utility of reproductive toxicity data: (BDR Pages 378-379)
 - Summary of reproductive toxicity data (BDR Pages 379-381)
 - Summaries, Conclusions, and Critical Data Needs: Reproductive Toxicity (BDR Page 381)
- EU Risk Assessment Report: 4,4'-isopropylidenediphenol (bisphenol-A). Final Report (2003) [Attachment to OEHHA, 2009]
 - In the section “Toxicity to Reproduction”
 - Studies investigating endocrine modulating activity: in vitro systems (Pages 197-198, 201-212)
 - Effects on fertility (Pages 212-220)
 - Effects on development pertaining to reproduction (Pages 223-226)
 - Summary of toxicity to reproduction (Pages 231-233)
 - EU “Updated European Risk Assessment Report 4,4'-Isopropylidenediphenol (bisphenol-A). Environment Addendum of February 2008 (to be read in conjunction with published EU RAR of Bisphenol A, 2003).” [Attachment to OEHHA, 2009]
 - In the section “Reproductive Toxicity”
 - Summary of original risk assessment report (Pages 84-86)
 - Updated information (Pages 86-90, 91-92, 96-97, 100, 103-104)
 - Developmental effects on female reproductive tract expressed in old-age (Pages 120-121)
 - Human case control study (Page 121)
 - Impact of new information and summary of reproductive toxicity (Pages 122, 127-129)