

# **Consideration of Bisphenol A (BPA) as Known to Cause Reproductive Toxicity, Based on Female Reproductive Toxicity**

**Developmental and Reproductive Toxicant  
Identification Committee Meeting**

**May 7, 2015**

**Reproductive and Cancer Hazard Assessment Branch  
Office of Environmental Health Hazard Assessment  
California Environmental Protection Agency**



# Prior Consideration of BPA

- On July 15, 2009, the Developmental and Reproductive Toxicant Identification Committee (DARTIC) considered whether BPA had been clearly shown by scientifically valid testing according to generally accepted principles to cause reproductive toxicity (male reproductive, female reproductive and developmental)
- Unanimous vote on all categories that BPA had not been clearly shown to cause reproductive toxicity
- DARTIC requested the opportunity to revisit consideration of BPA if additional epidemiological or other specific types of data on reproductive and developmental toxicity became available.

# 2009 Hazard Identification Materials

- Materials provided to the DARTIC in 2009: Four reviews
  - OEHHA, *"Evidence on the Developmental and Reproductive Toxicity of Bisphenol A."* (2009). Provided an integrative review of the data available in 2009, including PK and mechanistic data.
  - National Toxicology Program - Center for the Evaluation of Risks to Human Reproduction (NTP-CERHR). *"Monograph on the Potential Human Reproductive and Developmental Effects of Bisphenol A."* (2008)
  - European Union (EU). *"European Union (EU) Risk Assessment Report: 4,4'-isopropylidenediphenol (bisphenol-A)."* Final Report (2003).
  - EU *Update of the Risk Assessment of 4,4'-Isopropylidenediphenol (Bisphenol-A)*, Final Human Health Draft for publication (2008).
  - Public comments submitted to the DARTIC in 2009 regarding possible listing of BPA.

# Consideration of Female Reproductive Toxicity of BPA

- Substantial new epidemiological and toxicological data on BPA and female reproductive toxicity have become available since 2009
  - exemplified by 2014 review by Peretz et al.
- Only female reproductive toxicity is being considered at this time because of the volume and complexity of the data
- Other endpoints (e.g., male reproductive toxicity) may be considered at future meetings

# 2015 Hazard Identification Materials (HIM)

- A description of the HIM for consideration of the female reproductive toxicity of BPA prepared by OEHHA.
- 2014 EHP review: Peretz, et al.,(2014). *"Bisphenol A and Reproductive Health: Update of Experimental and Animal Evidence, 2007 – 2013"*.
- Supplemental material to the 2014 EHP review.
- Articles cited in the 2014 EHP review that directly pertain to female reproductive toxicity.
- Studies of BPA relevant to female reproductive toxicity which were conducted in mammals and published after the 2014 EHP review was submitted for publication.
- 2009 HIM (includes public comments received in 2009).
- Articles and reports available to OEHHA and cited in OEHHA (2009), NTP-CERHR, (2008), EU (2003) and (EU 2008) that directly pertain to female reproductive toxicity.
- Additional public comments on updated HIM (includes 2014 USFDA and 2015 EFSA safety assessments).

# Scope of Data on Female Reproductive Toxicity of BPA

- 320 papers and reports relevant to female reproductive toxicity provided to DARTIC
  - 290 papers and reports cited in the 5 review documents (EHP, OEHHA, NTP-CERHR, EU, EU update)\*
  - 30 papers published subsequent to the EHP review

\* Additional 41 reports relevant to female reproductive toxicity cited in the OEHHA, NTP-CERHR and EU documents not available to OEHHA or provided to DARTIC

# Additional Studies of Female Reproductive Toxicity in Peretz et al., 2014 (published after 2009)

Ovarian and oviductal outcomes, and steroidogenesis in experimental studies	26
Female human reproductive outcomes	13
Human pregnancy and birth outcomes	8
Uterine outcomes in experimental studies	16
Pregnancy outcomes in experimental studies	8
Sexual function outcomes in experimental studies	2

# Additional Studies Published After Peretz et al., 2014 Review

Cell Signaling and Mode of Action	2
Endocrine	1
Epidemiologic	10
Epigenomic	2
Mammary Gland	2
Neurobehavioral and Neurobiology	2
Ovary	9
Sexual Development	2
Vagina	1

# Female Reproductive Toxicity

## US EPA Guidelines for Reproductive Toxicity Risk Assessment (1996)

Table 5. Female-specific endpoints of reproductive toxicity

Organ weights	Ovary, uterus, vagina, pituitary
Visual examination and histopathology	Ovary, uterus, vagina, pituitary, oviduct, mammary gland
Estrous (menstrual*) cycle normality	Vaginal smear cytology
Sexual behavior	Lordosis, time to mating, vaginal plugs, or sperm
Hormone levels*	LH, FSH, estrogen, progesterone, prolactin
Lactation*	Offspring growth, milk quantity and quality
Development	Normality of external genitalia*, vaginal opening, vaginal smear cytology, onset of estrous behavior (menstruation*)
Senescence	Vaginal smear cytology, ovarian histology (menopause*)

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\*Endpoints that can be obtained relatively noninvasively with humans.

# Female Reproductive Toxicity (cont.)

## United Nations Globally Harmonized System of Classification and Listing of Chemicals (2011)

- Alterations to the female reproductive system
- Adverse effects on the onset of puberty
- Gamete production and transport
- Reproductive cycle normality
- Sexual behavior
- Fertility
- Parturition
- Pregnancy outcomes
- Premature reproductive senescence
- Modification of other functions that are dependent on the integrity of the reproductive system
- Adverse effects on or via lactation

# Relationship of Pregnancy Outcome to Female Reproductive Toxicity

## US EPA Guidelines for Reproductive Toxicity Risk Assessment (1996)

Table 2. Couple-mediated endpoints of reproductive toxicity

### Multigeneration studies

Mating rate, time to mating (time to pregnancy\*)  
Pregnancy rate\*  
Delivery rate\*  
Gestation length\*  
Litter size (total and live)  
Number of live and dead offspring (fetal death rate\*)  
Offspring gender\* (sex ratio)  
Birth weight\*  
Postnatal weights\*  
Offspring survival\*  
External malformations and variations\*  
Offspring reproduction\*

### Other reproductive endpoints

Ovulation rate  
Fertilization rate  
Preimplantation loss  
Implantation number  
Postimplantation loss\*  
Internal malformations and variations\*  
Postnatal structural and functional development\*

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\*Endpoints that can be obtained with humans.