Identifying BPA as a reproductive toxicant

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A comprehensive review of all the human literature exploring BPA and health effects

-91 studies
-75 showed effects
-Multiple adverse health effects
Outline

- What is listed
- Criteria for listing
- Scientific evidence on BPA

(Nov. 1993) CRITERIA FOR RECOMMENDING CHEMICALS FOR LISTING AS "KNOWN TO THE STATE TO CAUSE REPRODUCTIVE TOXICITY"
What is listed

Proposition 65 list

- Reproductive Toxicant
  - Developmental toxicity
  - Female reproductive toxicity
  - Male reproductive toxicity
    - Adverse effects on reproductive structure or function
      - Impaired reproductive performance
  - Carcinogen
For listing, ONE of these criteria has to be met:

1. Sufficient evidence of reproductive toxicity in humans

OR

2. Sufficient evidence of reproductive toxicity in animals (mammals)
Other considerations

1. Sufficient evidence of reproductive toxicity in humans

OR

2. Sufficient evidence of reproductive toxicity in animals (mammals)

Statistical considerations

Biological Plausibility
What is listed

- Proposition 65 list
  - Reproductive Toxicant
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    - Carcinogen
One example of reproductive effects in women

BPA disrupts fertility in women

- Endometrial Disorders
- Polycyclic Ovary Syndrome
- Miscarriage
- Preterm Birth
- Disrupted Ovulation and Oocyte Maturation
Adverse effects on **reproductive structure or function:**
Evidence of reproductive toxicity in humans

<table>
<thead>
<tr>
<th>Genetic damage to the ovum or its precursors</th>
<th>Alterations in ovulation, menstrual cycle/menstrual disorders</th>
<th>Impaired or altered endocrine function</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fujimoto 2011</strong> Reduced number mature oocytes</td>
<td><strong>Ehrlich 2012</strong> Poor ovulation response</td>
<td><strong>Mok-Lin 2010</strong> Low estrogen response</td>
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<td><strong>Ehrlich 2012</strong> Reduced number of mature and fertilized oocytes</td>
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<td><strong>Bloom 2011a</strong> Poor ovulation response</td>
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</table>

Adverse effects on reproductive structure include (but are not limited to):

Evidence of any one of these effects is sufficient for listing
Normal oocyte development
Normal ovulation

GnRH

Brain

pituitary

estrogen

fallopian tube

ovary

uterus

vagina

cervix

repro hormones
### Adverse effects on reproductive structure or function:

Evidence of reproductive toxicity in animals

<table>
<thead>
<tr>
<th>Effects</th>
<th>Research Reference</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genetic damage to the ovum</td>
<td>Zhang 2012</td>
<td>Mice: Disrupted oocytes and follicles</td>
</tr>
<tr>
<td></td>
<td>Hunt 2012</td>
<td>Macaques: Disrupted oocyte meiosis</td>
</tr>
<tr>
<td>Alterations in ovulation, menstrual cycle/ menstrual disorders</td>
<td>Ziv-Gal 2015</td>
<td>Mice: Delayed time of first estrus</td>
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<td>Nah 2011</td>
<td>Mice: Decreased estrus cycles and days</td>
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<tr>
<td>Impaired endocrine function</td>
<td>Kawai 2007</td>
<td>Mice: Alterations in estrogen receptor</td>
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Adverse effects on reproductive structure include (but are not limited to):

Evidence of any one of these effects is sufficient for listing.
Adverse effects on reproductive structure or function:
In vitro/mechanistic evidence showing biological plausibility

- Genetic damage to the ovum
  - Lenie 2008: Oocyte disruption and spindle aberrations (in vitro)
  - Can 2005: Oocyte cell cycle and spindle disruption (in vitro)

- Alterations in ovulation and estrous
  - Adewale 2009: Disruption of ovarian development but not brain hormone neurons (in vivo)

- Impaired endocrine function
  - Kitamura 2005: BPA binds to the estrogen and androgen receptors and has estrogenic and anti-androgenic activity (in vitro)

Adverse effects on reproductive structure include (but are not limited to):
Evidence of any one of these effects is sufficient for listing.
What is listed

Proposition 65 list

Reproductive Toxicant

Developmental toxicity

Female reproductive toxicity

Adverse effects on reproductive structure or function

Impaired reproductive performance

Carcinogen

Male reproductive toxicity
Impaired reproductive performance: Evidence of reproductive toxicity in humans

Adverse effects on reproductive structure include (but are not limited to):

- Increased pregnancy wastage (e.g., miscarriage)
  - Lathi 2014: Increased rates of miscarriage
  - Sugiura-Ogasawara 2005: Increased rates of miscarriage

- Inability/decreased ability to conceive
  - Ehrlich 2012: Increased implantation failure
  - Caserta 2013: Higher rates of infertility in women

- Adverse effects on sexual behavior, gestation, lactation, etc.
  - Cantonwine 2010: Increased premature delivery

Evidence of any one of these effects is sufficient for listing.
Impaired reproductive performance: Evidence of reproductive toxicity in animals

Adverse effects on reproductive structure include (but are not limited to):

Evidence of any one of these effects is sufficient for listing

- **Increased pregnancy wastage (e.g., miscarriage)**
  - *Kim 2001*
    Mice: Pregnancy failure and pre- and post-implantation failure
  - *George 2012*
    Rats: Increased fetal death and malformation

- **Inability/decreased ability to conceive**
  - *Cabaton 2011*
    Mice: Reduction in fertility in females

- **Adverse effects on sexual behavior, gestation, lactation, etc.**
  - *Farabollini 2002*
    Mice: Altered female sexual behavior
  - *Matsumoto 2004*
    Mice: Exposed mothers had reduced lactation
Impaired reproductive performance:
In vitro/mechanistic evidence showing biological plausibility

Adverse effects on reproductive structure include (but are not limited to):

Evidence of any one of these effects is sufficient for listing

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<tr>
<td><strong>Ozlem 2008</strong>&lt;br&gt;BPA is toxic to embryos (in vitro)</td>
<td><strong>Newbold 2007</strong>&lt;br&gt;Disruption of reproductive tract morphology (in vivo)</td>
<td><strong>Chun 2000</strong>&lt;br&gt;BPA alters prolactin (lactation hormone) release (in vitro)</td>
</tr>
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<td><strong>Hwang 1986</strong>&lt;br&gt;BPA is toxic to embryos (in vitro)</td>
<td></td>
<td><strong>Monje 2009</strong>&lt;br&gt;BPA altered brain mechanisms that drive female sexual behavior (in vivo)</td>
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What is listed

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Sufficient evidence of one of these impacts in either humans or animals or in combination
Conclusion

Unlike some other bodies that have reviewed BPA, the DART IC’s inquiry is focused on whether there is sufficient evidence of reproductive toxicity, guided by the criteria we just discussed:

- The scientific literature demonstrates **sufficient evidence of female reproductive toxicity**

The decision reflects the DART IC’s independent judgment as the State’s experts on the science and responding to Proposition 65’s specific criteria.

Risk and exposure issues are addressed at a later stage:

- The committee will have an opportunity to review and comment on OEHHA’s assessment of risk and exposure and any proposed action at that stage.