Bisphenol A: Human and Laboratory Animal Data on Female Reproductive Effects

K. Lily Wu, Ph.D.
Associate Toxicologist
# Female Reproductive Studies in Humans

<table>
<thead>
<tr>
<th>Study/Design</th>
<th>Population/Exposure Measure</th>
<th>Results</th>
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</thead>
</table>
| **Takeuchi and Tsutsumi, 2002** Cross-sectional | 14 healthy women, 11 healthy males, 16 women with polycystic ovary syndrome (PCOS) BPA in blood | ↑ BPA in normal men vs. normal women  
↑ BPA in PCOS group vs. normal women  
Positive correlation with testosterone |
| **Takeuchi et al., 2004** Cross-sectional | 26 healthy women, 19 women with PCOS, 7 women with hyperprolactinemia  
21 women with hypothalamic amenorrhea  
BPA in blood | ↑ BPA in women with PCOS and in obese healthy women  
Positive correlation with testosterone, androstenedione and dehydroepiandrosterone sulfate |
| **Yang et al., 2006** Cross-sectional | 172 men and women  
BPA in urine | No association with endocrine-related disorders |
## Female Reproductive Studies in Humans (con’t.)

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<tbody>
<tr>
<td><strong>Hiroi et al., 2004</strong></td>
<td>11 healthy women, 19 women w/ endometrial hyperplasia, 7 women w/ endometrial carcinoma</td>
<td>↓ BPA in women w/ endometrial cancer or complex endometrial hyperplasia</td>
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<tr>
<td>Cross-sectional</td>
<td>BPA in blood</td>
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<tr>
<td><strong>Itoh et al., 2007</strong></td>
<td>140 infertile women</td>
<td>No association with endometriosis</td>
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<tr>
<td>Cross-sectional</td>
<td>BPA in urine</td>
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<tr>
<td><strong>Wolff et al., 2008</strong></td>
<td>192 healthy 9-year-old girls</td>
<td>No association with pubertal status</td>
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<td>Cross-sectional</td>
<td>BPA in urine</td>
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<tr>
<td><strong>Sugiura-Ogasawara et al., 2005</strong></td>
<td>45 women with recurrent miscarriages, 32 controls</td>
<td>↑ BPA in women with recurrent miscarriages</td>
</tr>
<tr>
<td>Case-control</td>
<td>BPA in blood</td>
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</tbody>
</table>
Uterus

27 studies: 14 in rats, 13 in mice
oral or s.c. injection
0.00025 mg/kg-d – 800 mg/kg-d
prenatal, perinatal, and adult (pregnancy)

• changes in uterine weight (12 out of 12)
  – ~1.2 mg/kg-d – 800 mg/kg-d
  – 0.1 – 4 mg/kg-d

• altered cell morphology (7 out of 8)
  – 0.00025 mg/kg-d – 50 mg/kg-d

• altered expression of genes and proteins (8 out of 8)
  – 0.5 mg/kg-d – 600 mg/kg-d
Ovary

6 studies: 2 in rats, 4 in mice
oral or s.c. injection

0.001 mg/kg-d ~ 700 mg/kg-d*

prenatal, perinatal, and adult (including pregnancy)

• histological alterations (3 out of 3)
  – 0.001 mg/kg-d ~ 700 mg/kg-d*

• changes in weight (3 out of 4)
  – 0.1 mg/kg-d 0.0002 ~ 700 mg/kg-d*
Follicles / Oocytes

6 in vivo studies
oral, s.c. injection, implant
0.02 mg/kg-d ~700 mg/kg-d*

- perturbation of the meiotic cell cycle (2 out of 2)
  - 0.13 mg/kg-d*

- increased polyploidy and chromosome misalignment (2 out of 2)
  - 0.04 mg/kg-d – 0.5 mg/kg-d

- cystic follicles (1 out of 1)
  - ~180 ~ 700 mg/kg-d*

- disruption of early oogenesis (“grandmaternal” effect) (1 out of 1)
  - 0.02 mg/kg-d
Follicles / Oocytes

5 in vitro studies
0 – 12 days
$1 \times 10^{-10} \text{ M} – 4.38 \times 10^{-2} \text{ M}$

- perturbation of the meiotic cycle (2 out of 2)
  - $1 \times 10^{-5} \text{ M} – 4.38 \times 10^{-2} \text{ M}$
- increased chromosomal misalignment (3 out of 3)
  - $4.38 \times 10^{-2} \text{ M}$
- increased irregular pattern of Ca$^{+2}$ oscillations (1 out of 1)
  - $1 \times 10^{-8} \text{ M} – 0.1 \text{ M}$
- decreased granulosa cell viability (2 out of 2)
  - $1 \times 10^{-10} \text{ M} – 1 \times 10^{-4} \text{ M}$
Estrous Cycle

11 studies: 8 in rats, 3 in mice
oral or s.c. injection
0.0002 mg/kg-d ~ 700 mg/kg-d*
in utero, perinatal, postnatal

- altered pattern (6 out of 8)
  - 0.02 mg/kg-d ~ 700 mg/kg-d*
- changed length (4 out of 6)
  - 50 mg/kg-d – 100 mg/kg-d
- altered onset (2 out of 2)
  - 0.02 mg/kg-d
Fertility

Multi-generation & Reproductive Assessment by Continuous Breeding (RACB) studies

**diet**

0.001 mg/kg-d – 600 mg/kg-d

pre-breeding, mating, gestation, lactation, weaning, post-weaning

- Reduced trends in:
  - number of total pups/litter
  - live birth index
  - number of live pups/litter
Vagina

16 studies: 9 in rats, 7 in mice
oral, s.c. injection, s.c. implant, i.p. injection
0.00025 mg/kg-d – 800 mg/kg-d
prenatal, perinatal, postnatal

• vaginal epithelial cell morphology (5 out of 6)
  – 0.004 mg/kg-d – 200 mg/kg-d

• age at vaginal opening (8 out of 9)
  – 0.02 mg/kg-d – 800 mg/kg-d, via s.c. route (6)
  – 0.1 mg/kg-d – 500 mg/kg-d, via oral route (2)

• vaginal weight (1 out of 1)
  – 0.00025 mg/kg-d
Mammary Gland

11 studies: 4 in rats, 7 in mice
oral, s.c. injection, s.c. implant
0.00025 mg/kg-d – 54 mg/kg-d
prenatal, perinatal, juvenile

• accelerated cell cycle (5 out of 5)
  - terminal end buds, terminal ducts
    – 0.00025 mg/kg-d – 0.25 mg/kg-d

• acceleration of mammary gland development (4 out of 4)
  - timing of developmental events within the epithelium & stroma
    – 0.00025 mg/kg-d – 54 mg/kg-d

• reduction of milk production in mothers (1 out of 2)
  – 1000 mg/kg-d
Maternity

- Maternal behavior
  - reduced duration and frequency of licking-grooming, anogenital licking and arched-back posture
  - reduced nursing behavior

- Maternal-fetal transfer
  - follicular fluid, placenta, amniotic fluid
  - milk (lactation)
Female Reproductive Effects of BPA Summary

• Effects found from human studies
  – Limited data; miscarriages possibly consistent with animal data

• Effects found from lab animal studies
  – **Uterus**: alterations in weight, cell morphology, expression of genes and proteins
  – **Ovary**: alterations in histology and in weight
  – **Follicles /Oocytes**: perturbation of meiotic cell cycle, chromosome misalignment, cystic follicles
  – **Estrous Cycle**: altered pattern, length and onset
  – **Vagina**: altered epithelial cell morphology, altered age of vaginal opening
  – **Mammary Gland**: accelerated cell cycle, accelerated mammary gland development, reduction of milk production