

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

K. Lily Wu, Ph.D.  
Associate Toxicologist



# Female Reproductive Studies in Humans

Study/Design	Population/Exposure Measure	Results
<i>Takeuchi and Tsutsumi, 2002</i> 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
<i>Takeuchi et al., 2004</i> 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
<i>Yang et al., 2006</i> Cross-sectional	172 men and women BPA in urine	No association with endocrine-related disorders



## Female Reproductive Studies in Humans (con't.)

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



# 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

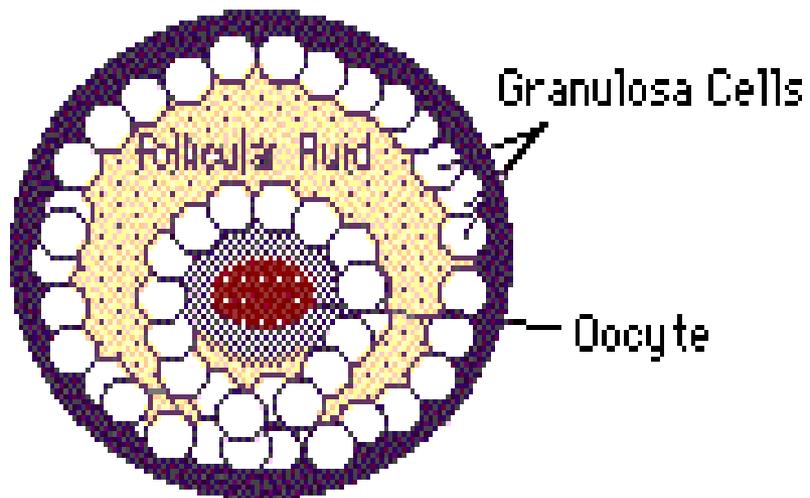
0.001 mg/kg-d ~ 700 mg/kg-d\*

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

$1 \times 10^{-10}$  M –  $4.38 \times 10^{-2}$  M

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

