Prostate

Prostate Gland – "Low" Dose Effects

- 2 studies reported effects on the prostate at 10 μg/kg/day
  - "Preneoplastic" prostatic intraepithelial neoplasia (PIN) lesions (Ho *et al.* 2006)
  - Morphometric effects (Timms *et al.* 2005)
- New study reports prostate as a target tissue (Ogura *et al*. 2007)
- Findings interpreted as potentially predisposing prostate to disease later in life

Prostate Gland PIN Lesions (Ho *et al*. 2006)

- Sprague-Dawley rats
- 10 μg/kg BPA (sc injection to neonate on PND 1,3,5; 15-16 litters/group)
- Adult treatment with E2 and T to induce PIN
- Increased PIN score

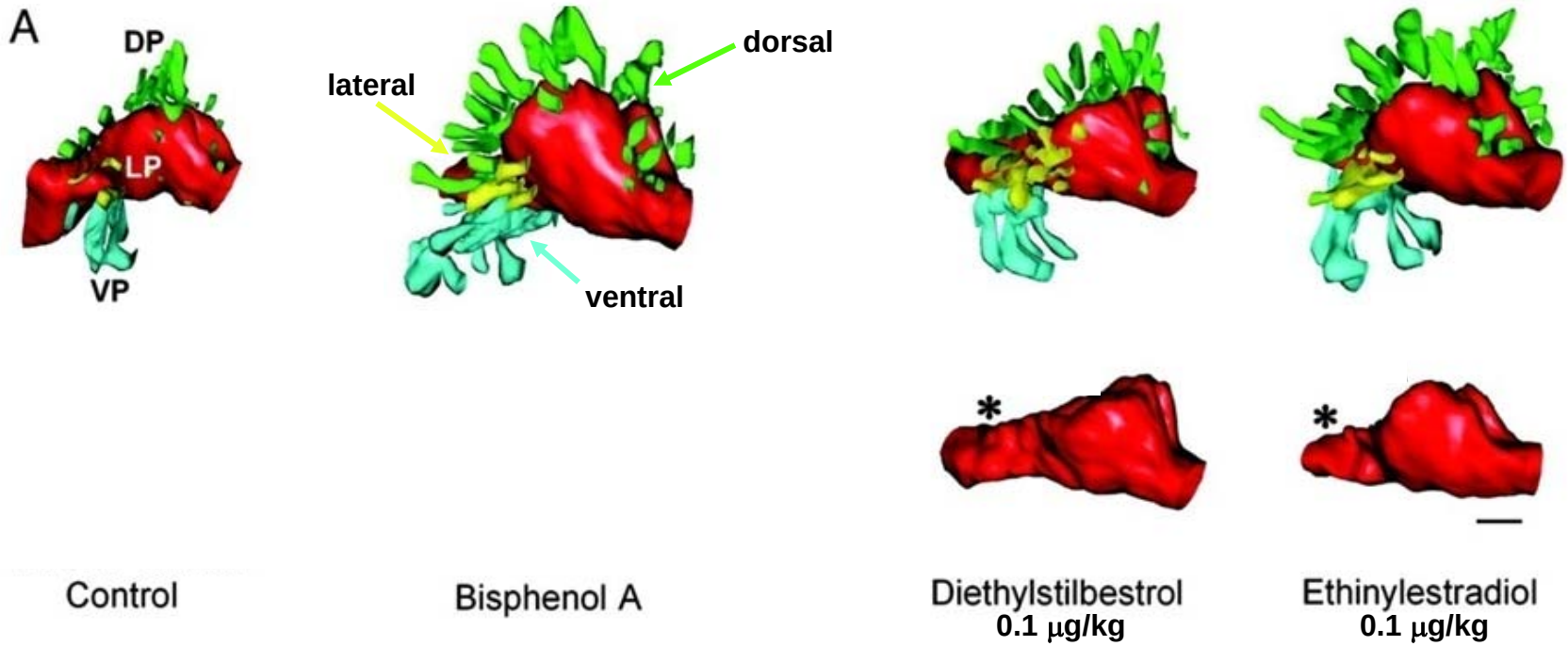
Incidence and Grade of Doral Prostate Intraepithelial Neoplasia (PIN)				
Adult - T + E2	**Low Grade PIN**	**High Grade PIN**	**Total PIN**	**PIN Score**
Oil	2/10 (20%)	2/10 (20%)	4/10 (40%)	0.52
BPA	3/10 (30%)	7/10 (70%)	10/10 (100%)	1.3*
2500 μg/kg **EB**	3/8 (38%)	5/8 (38%)	8/8 (100%)	1.3*
0.1 μg/kg **EB**	3/10 (30%)	2/10 (30%)	5/10 (50%)	~0.6

EB = 17ß-estradiol benzoate

Modified from Figure 1 from Ho SM *et al*. (2006) *Cancer Res.* Developmental exposure to estradiol and bisphenol A increases susceptibility to prostate carcinogenesis and epigenetically regulates phosphodiesterase type 4 variant 4. 66(11): 5624-5632.

Prostate and Urethra Morphometric Changes

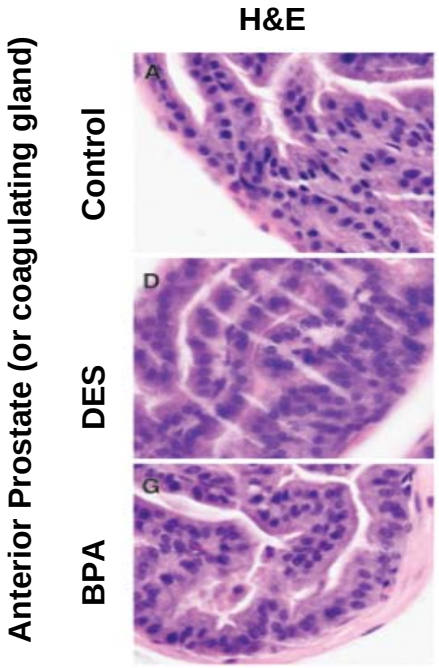
- CD-1 mice
- 10 μg/kg BPA (oral to dam GD14 – PND18; 5-6 litters/group)
- Increased duct number, increased duct volume, decreased volume of cranial urethra



Modified Figure 2 from Timms BG *et al*. (2005) Estrogenic chemicals in plastic and oral contraceptives disrupt development of the fetal mouse prostate and urethra. Proc Natl Acad Sci U S A 102(19):7014-7019.

Prostate – New Supporting Literature (Ogura *et al*. 2007)

- BALB/c mice
- 20μg/kg/day BPA or 0.2 μg/kg/day DES (oral to dam GD13 – PND18; 3 litters)
- Increased CK10 staining in basal epithelial cells ("squamous differentiation")



Modified Figure 6 from Ogura Y *et al.* (2007) *Differentiation.* Bisphenol A induces permanent squamous change in mouse prostatic epithelium. 75(8): 745-756.

Prostate - Reproducibility

- These effects would not likely not have been detected in guideline compliant multigenerational studies
  - No morphometric analysis
  - PIN lesions may not be detected with “conventional” rodent models
  - Some estrogenic effects not detected by H&E staining
- NTP 2-year bioassay did not report tumors in BPA-treated rats or mice
  - NTP bioassay has never identified a prostate carcinogen
  - Did not include perinatal exposure

Prostate - Data Limitations

- Long-term consequences of morphometric changes unclear
  - Are effects permanent and/or adverse?
- Unclear if PIN lesions progress to cancer
  - CERHR Expert Panel noted that PIN lesions observed following E2 and T treatment often progress to adenocarcinoma
- Unexpectedly high potency of BPA relative to positive control response in PIN incidence and score

Weight of Evidence for Prostate

- **Two key studies identified prostate as target**
- **Reported effects not assessed or expected to be detected in guideline studies**
- **New supportive data on prostate**
- **New data related to sc injection in neonate**

- **Progression of PIN lesions?**
- **Long-term implications of morphometric findings**

Clear evidence of adverse effects

Some evidence of adverse effects

Limited evidence of adverse effects

Insufficient evidence for a conclusion

Limited evidence of no adverse effects

Some evidence of no adverse effects

Clear evidence of no adverse effects

CERHR Expert Panel

- The CERHR Expert Panel expressed “minimal concern” for effects on the prostate based on Ho *et al*. 2006 and Timms *et al*. 2005
  - Considered research need
- NTP “elevated” to “some concern” based on new data and consideration of daily intakes in infants

Serious concern for adverse effects

Concern for adverse effects

Some concern for adverse effects

Minimal concern for adverse effects

Negligible concern for adverse effects

Questions and Discussion