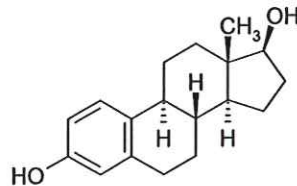




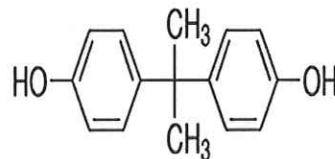
BPA Hazard Assessment as a Basis for Public Health Protection

Gary Ginsberg Ph.D.
Toxicologist
CT Dept Public Health

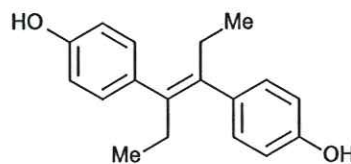
Estradiol



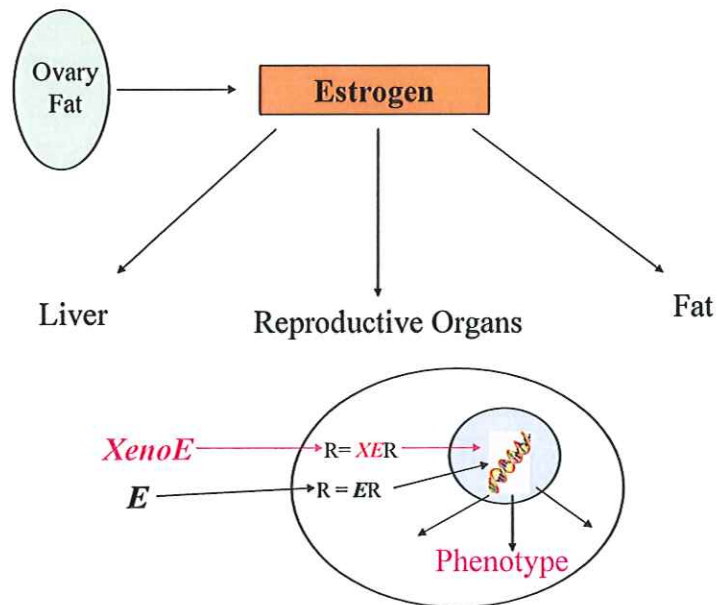
BPA



DES



1950's: BPA makes great plastic but



What Drives Policy? Hazard vs Risk Assessment

- Risk Assessment preferred if moderate uncertainty and moderate toxicity
- Hazard Assessment may be preferred if high uncertainty or high toxicity
- BPA represents both high uncertainty and potential for high toxicity
- Exposure is quite common
 - Breast milk
 - Canned food
 - Plastic cookware and water bottles
 - Cash register receipts

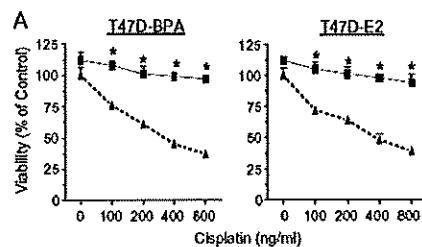
Why is BPA Hazard Potential High

- Endocrine disruptor – estrogen mimic
- Mechanism not just thru estrogen receptor
 - Potency to bind ER much less than DES or E-2
 - Yet effective at comparable concentrations in some systems
- Multiple effects
 - Increased susceptibility to breast cancer
 - Breast cancer resistance to chemotherapy
 - At physiologic concentrations in adults
 - Prostate effects and other anti-male effects
 - Sexually dimorphic behaviors
 - Obesity from perinatal exposure in rats and mice
 - BPA increases insulin secretion
 - BPA increases body weight and adipocyte number
 - Implications for metabolic syndrome/diabetes/ht dx

Other Features of BPA Profile

- Non-monotonic dose-response
 - Complex receptor mechanism – up/down regulation
- Early life exposure more sensitive than later
 - Effects may be manifest at sexual maturity or senescence
- Exposures may already be at an effect level?
- Transgenerational epigenetic effects?
 - Heritable methylation patterns or chromosomal change across age-span and generations
- Interaction with natural hormones and other EDCs

Bisphenol A and estradiol are equipotent in antagonizing cisplatin-induced cytotoxicity in breast cancer cells. LaPensee et al. Cancer Lett 2010



Breast cancer cells pretreated with 1 nM BPA or E-2

Will BPA's Impact on the Male Sex Drive Finally Spur a National Ban?

Kaiser Permanente 5 Year Study of 497 Chinese BPA Workers

(Li et al. J Andrology 2010)

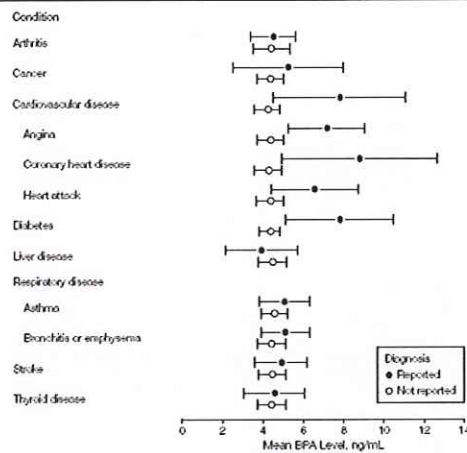
Table 3. Urine Bisphenol-A Concentration¹ and Male Sexual Function in Workers with no previous exposure to other chemicals or heavy metals.

| Sexual Function in the Past 6 Months | N | Adjusted ² β Coefficient for BPA | p-value |
|--|-----|---|---------|
| <u>Sexual Desire</u> | | | |
| Level of sex drive ³ | 271 | -0.018 ⁵ | 0.001 |
| <u>Erectile function</u> | | | |
| Ability to have an erection ⁴ | 271 | -0.032 | 0.04 |
| Ability to have an erection hard enough for penetration ⁴ | 270 | -0.032 | 0.06 |
| Difficulty level of having an erection ⁵ | 268 | 0.020 ⁵ | 0.01 |
| <u>Orgasmic function</u> | | | |
| Difficulty level of ejaculating ⁵ | 245 | 0.011 ⁵ | 0.14 |
| Level of ejaculation strength ³ | 245 | -0.014 ⁵ | 0.01 |
| <u>Overall satisfaction with sex life</u> | | | |
| Level of satisfaction ² | 243 | -0.013 ⁵ | 0.009 |

NIOSH Repeating this Study in US Workers

Association of Urinary Bisphenol A Concentration With Medical Disorders and Laboratory Abnormalities in Adults. Lang et al. JAMA 2008

Figure. Estimated Mean Bisphenol A (BPA) Concentrations in Relation to Reported Diseases and Conditions



Estimates adjusted for age and sex. Error bars indicate 95% confidence intervals.

Based upon NHANES 2003 results for 1455 adults

Standard Repro Testing

- Tyl et al. Multi-gen studies in rats and mice
- BPA no direct effects, not even estrogenic
 - Estrogen as + control in the mouse study
- Thus, standard tox guideline studies fail to show a functional effect on male/female reproduction
- How would BPA test in animal models of endocrine dx - Endometriosis? Polycystic ovary (PCOS)?

Bisphenol A Exposure In Utero Disrupts Early Oogenesis in the Mouse Susiarjo et al. PLoS Genetics 2007

Table 4. Aneuploidy Analysis

| Group | Number of Mice | Number of Cells | Total Chromosomes | | | |
|---------|----------------|-----------------|-------------------|-----|------|------|
| | | | 20 | ≥21 | 20.5 | 19.5 |
| Placebo | 10 | 57 | 56 | 1 | 0 | 0 |
| BPA | 16 | 56 | 43 | 10 | 2 | 1 |

Metaphase II cells were classified as normal (20 chromosomes) or hyperploid (with ≥ 21 chromosomes or 20 chromosomes plus one or more prematurely separated sister chromatid). Hypoploid cells were excluded from the analysis, although a single cell with 19 chromosomes and one prematurely separated sister chromatid (19.5) was observed in the BPA exposed group and has been included in the table.
doi: 10.1371/journal.pgen.0030005.t004

- Disruption of oocyte meiosis in fetus at 20 ug/kg/d x 1 week gestation
- Transgen Effect – maternal exposure alters grandkid chromosomes
- Effect mediated by interference with ERbeta
- Implications – abnormal ova, shorter lifespan, shorter period of fertility

Commentary
**Does Rapid Metabolism Ensure Negligible
Risk from Bisphenol A?**

Gary Ginsberg¹, Deborah C. Rice²
EHP 117: Nov 2009

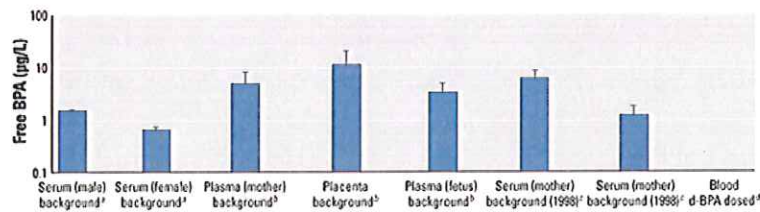


Figure 2. Free BPA in humans from background exposure or after BPA dosing.

¹Data from Takeuchi et al. (2002). ²Data from Schönfelder et al. (2002). ³Data from Yamada et al. (2002). ⁴Data from Völkel et al. (2002); LOD = 2.3 µg/L.

Health Canada Review (2008 to 2010)

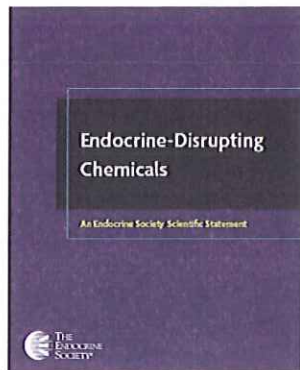
- "Health Canada considers that sufficient evidence relating to human health has been presented to justify the conclusion that bisphenol A is harmful to human life and should be added to Schedule 1"
- No Polycarbonate baby bottles, no BPA formula cans
 - But no warnings about canned food and other exposures

NTP Review

- Sept 3 2008 BPA report
- John Bucher – considerable uncertainty
 - “But we have concluded that the possibility that BPA may affect human development cannot be dismissed.”
 - “some concern” for effects on development of the prostate gland and brain and for behavioral effects in fetuses, infants and children
 - “If parents are concerned, they can make the personal choice to reduce exposures of their infants and children to BPA.”

FDA Review

- “However, on the basis of results from recent studies using novel approaches to test for subtle effects, both the National Toxicology Program at the National Institutes of Health and FDA have some concern about the potential effects of BPA on the brain, behavior, and prostate gland in fetuses, infants, and young children. “
- NIEHS spending 30 million on 10 new BPA studies
- Helping industry move away from BPA in baby bottles, infant formula cans and other types of canned food



- The evidence for adverse reproductive outcomes (infertility, cancers, malformations) from exposure to endocrine disrupting chemicals is strong, and there is mounting evidence for effects on other endocrine systems, including thyroid, neuroendocrine, obesity and metabolism, and insulin and glucose homeostasis.
- The Precautionary Principle is key to enhancing endocrine and reproductive health, and should be used to inform decisions about exposure to, and risk from, potential endocrine disruptors.

Endocrine Society Summary of BPA Effects on Reproductive Organs

MALE

| | | | |
|-----|---|---|---|
| BPA | <p>Increased prostate size (469) Aberrant development of prostate and urethra (470) Prostate cancer (122) Increased anogenital distance Altered periductal stroma in the prostate (471)</p> | <p><small>FETAL TESTS LIMITED</small></p> | <p>Increased ERα expression in hypothalamus (42) Increased AR expression in prostate (469)</p> |
|-----|---|---|---|

FEMALE

| | | | |
|-----|---|---------------------|--|
| BPA | <p>Inhibited mammary duct development and increased branching (145) Increased mammary gland density, Increased number of terminal ends (146) Reduced weight of vagina (473) Endometrial stimulation (473) Early puberty (474, 475)</p> | <p>Miscarriages</p> | <p>Inhibition of apoptotic activity in breast (145) Increased number of progesterone receptor-positive epithelial cells Reduced sulfotransferase inactivation of estradiol (45, 46) Nongenomic activation of ERK1/2 (476)</p> |
|-----|---|---------------------|--|



Pregnant Women and Families with Young Children Warned About Bisphenol A (BPA)

Baby Bottles, Plastic Containers and Canned Food Can Contain Chemical

FOR IMMEDIATE RELEASE
January 28, 2010

Connecticut Department of Public Health
Contact: William Gerrish
(860) 509-7270



- Choose breastfeeding over bottle-feeding.
- If you bottle-feed your baby:
- Use BPA-free baby bottles
- Consider powdered rather than liquid formula
- Limit your intake of canned food and drinks
- Do not microwave food in plastic containers
- Avoid drinking out of hard clear plastic water bottles
- Do not use plastic containers that are scratched.

<http://www.ct.gov/dph/cwp/view.asp?Q=454694&A=3865>

Public Act 09-103 bans BPA from baby bottles, infant formula cans and reusable food containers beginning October 1, 2011 in CT



What are the most important sources of exposure?

DPH planning biomonitoring intervention study

Summary of Evidence for Low Dose Effects

- **Animals: Extensive testing, MIXED results**
 - Standard protocols – negative results
 - Specialized designs – positive results, some reproduced
- **Humans: Limited study but Positive results**
 - Male reproductive
 - Female
 - Heart Dx/diabetes
- **Mechanistic: Positive**
 - Activating much more than just ER; blocking ER_{beta}?
- **Implications for:**
 - Cancer, Obesity, Diabetes, Reproductive health
- **Response of Governmental Authorities**
 - Health Canada – Toxic chemical, has taken action
 - NTP – Some concern
 - EFSA – low concern
 - FDA – Some concern, still evaluating
 - CT – taken action on all types of canned foods and baby bottles
 - Advisory in the interim

Policy Implications

- **BPA as new TSCA submission?** 
 - But BPA already widely used – diff cost/benefit equation
- **BPA as existing TSCA chem?** 
 - BPS as BPA replacement?
 - Already widely used – not much data
- **TSCA reform – clean up inventory**
 - REACH approach??