Effect of the Environment on Reproductive Health

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Overview

- Which environmental exposures are associated with reproductive toxicity?
- How do environmental exposures cause damage?
Environmental Exposures

- Pharmaceutical agents
  - diethylstilbestrol
- Pesticides
  - dichloro-diphenyl-trichloroethane (DDT), methoxychlor (MXC)
- Flame retardants
  - polybrominated diphenyl ethers (PBDEs)
- Plasticizers
  - phthalates, bisphenol A
- Environmental contaminants
  - dioxins, polychlorinated biphenyls (PCBs)
Pharmaceutical Agents: Diethylstibestrol (DES)
**DES Story**

- **1966-1969**
  - 8 women between 15-22 developed vaginal cancer (should be 0)
  - 7 of the 8 women were born to mothers who took DES during pregnancy

- **1969-current**
  - Serious adverse outcomes in male and female children of DES-exposed mothers
  - DES use limited; not manufactured in US
DES Events

• Females
  – Abnormalities of the reproductive tract
    • Uterus, Fallopian tubes
  – Infertility
  – Preterm labor
  – Fibroids
  – Cancer
    • Vagina, Breast
  – DES granddaughters

• Males
  – Cryptorchidism
  – Abnormal semen
  – Reduced fertility
  – Testicular cancer
  – Hypospadias
  – DES grandsons
What did we learn from the DES story?

- Placenta does not always protect the fetus
  - We must use care with drugs given to pregnant women
- Not all estrogens are good for all tissues, species
- Chemicals can have delayed, long-lasting effects
- Chemicals can have transgenerational effects
- We must take precautions when using DES
Pesticides

- Banned
  - Dichloro-diphenyl-trichloroethane (DDT)
  - Kepone
  - Hexachlorocyclohexane

- Current
  - Atrazine
  - Endosulfan
  - Lindane
  - Methoxychlor
Pesticides

- Used on crops, lawns, gardens, homes, and pets
- Contaminate food and water
- **Known reproductive toxicants in wildlife and humans**
  - eggshell thinning in birds (DDT)
  - abnormal reproductive organs in alligators (DDE)
  - masculinization of rodents (kepone, DDT, methoxychlor)
  - spontaneous abortion in women
  - endometriosis in women
  - low conception rates in women
  - infertility in men and women
  - altered sex ratio in humans and fish (more females)
Lake Apopka Disaster
Lake Apopka Disaster

Guillette et al., 1996; Toft et al, 2003
Effect of MXC on Antral Follicles

20 Day Treatment

Percent Atretic Follicles

20 Day Treatment

Control
8mg/kg MXC
16mg/kg MXC
32mg/kg MXC
64mg/kg MXC
8mg/kg KPN

* *
Flame Retardants

$$\text{Br}_m \quad \text{O} \quad \text{Br}_n$$
Flame Retardants

PBDEs Breast Milk and Fat Samples Around the World

Source: Figure 3 in Schecter et al (EHP, August 2003), Table 1 in Mazdai et al (EHP, July 2003), and Table 1 in Kalantzis et al (EHP, July 2004)
Flame Retardants

All Species
- 0
- 1 - 270
- 271 - 8202

Reduced eggshell mass
Delayed egg laying
Reduced fledging success
Consistent with peregrine data

American Kestrel

NOAA, 2009
Fernie et al., 2009
Plasticizers-Phthalates
Phthalates

- More than 18 billion pounds of phthalates are produced worldwide each year

- One of the top three contaminants present in human tissue (CDC report, 2005)

- Little to nothing is known about the health risks from everyday, environmental exposure
Phthalate Effects

- Chronic exposure in humans is associated with:
  - Decreased pregnancy rates
  - High rates of miscarriage
  - Pregnancy complications
    - Anemia
    - Toxemia
    - Preeclampsia

- Animal studies have shown that exposure inhibits ovarian and testicular synthesis of steroid hormones required for fertility
Prenatal Exposure to Phthalates

- Maternal exposure to phthalates results in a number of abnormalities of the male reproductive system
  - Reduced anogenital distance
  - Retained nipples
  - Undescended testes
  - Impaired reproductive behavior
Phthalates

Figure 1. Mean AGI (mm/kg) in relation to boys’ age at examination (months).

Swan et al., 2005
Effects of Phthalates on Antral Follicles

![Bar graph showing atresia rating for different samples: DMSO, DEHP1, DEHP10, DEHP100. The DEHP10 and DEHP100 samples have significantly higher atresia ratings compared to DMSO and DEHP1.](image)
Bisphenol A (BPA)

- BPA was originally synthesized in 1891 and intended for use as a chemical estrogen to help prevent miscarriage.

- Diethylstilbestrol (DES) was a more potent estrogen and used instead of BPA.

- BPA was then employed by plastics manufacturers, and remains so today.
Plastics is the country's third-largest manufacturing industry, producing nearly $379 billion worth of goods each year (Society for the Plastics Industry)
BPA

- BPA is released from polycarbonate plastics and resins by:
  - Exposure to light
  - Heating
  - Aging
  - Coming into contact with acids and bases in cleaning products
BPA

- BPA is found in 95% of human urine samples
  - it is rapidly metabolized and excreted

- BPA has been detected in ovarian follicular fluid, suggesting the follicle may be a source of BPA exposure for the early fetus

- BPA is able to rapidly cross the placenta and enter fetal organs in rats
Prenatal Exposure to BPA in Rodents

- BPA causes long-term adverse effects
  - Multiple cystic follicles in the ovary
  - Altered cyclicity
  - Impaired ovulation in adult life
  - Altered sexual differentiation of reproductive tissues
  - Early puberty onset
  - Weight gain
  - Decreased anogenital distance
  - Premature breast development
Effect of BPA on Fertility Over Time (F1)
Effect of BPA on Fertility Over Time (F2)
Effect of BPA on Fertility Over Time (F3)
BPA

- BPA not banned in the US, but bans are being proposed
- FDA has approved BPA as a food additive, but this has been extensively criticized
- Marketing for baby bottles has been changed
  - BPA free or glass bottles
Environmental Contaminants

- Dioxins (TCDD)
  - paper bleaching
  - pesticide manufacturing
Dioxins

Humans
  - reproduction
    • possible birth defects
    • change in sex ratio (more females than males)
    • endometriosis
  - other
    • chloracne

Animal models
  - reproduction
    • malformations
    • decreased sperm count
    • delayed puberty
    • endometriosis
  - behavior
    • demasculinized sexual behaviors
    • decreased reflexes
    • increased locomotor activity
  - other
    • wasting syndrome
Dioxins
## TCDD and Sex Ratio

<table>
<thead>
<tr>
<th>Father’s concentrations of TCDD (ppt)</th>
<th>Mother’s concentrations of TCDD (ppt)</th>
<th>Number of children</th>
<th>Total children</th>
<th>Sex ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unexposed*</td>
<td>Unexposed*</td>
<td>31</td>
<td>20</td>
<td>51</td>
</tr>
<tr>
<td>&gt;15</td>
<td>&gt;15</td>
<td>96</td>
<td>121</td>
<td>217</td>
</tr>
<tr>
<td>&gt;15</td>
<td>Unexposed*</td>
<td>81</td>
<td>105</td>
<td>186</td>
</tr>
<tr>
<td>Unexposed*</td>
<td>&gt;15</td>
<td>120</td>
<td>100</td>
<td>220</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>Total</strong></td>
<td><strong>328</strong></td>
<td><strong>346</strong></td>
<td><strong>674</strong></td>
</tr>
</tbody>
</table>

*People living outside A, B, and R zones on July 10, 1976, and people living in these zones with serum TCDD concentrations less than or equal to 15 ppt. †Different from expected sex-ratio value of 0.514 at p=0.03.

Mocarelli et al., 2000
Environmental Contaminants

- Polychlorinated biphenyls (PCBs)
  - banned in 1970s
    - electrical transformers
    - capacitators
    - hydraulic fluids
    - plasticizers
    - adhesives
  - persist in fish
**PCBs**

*Total PCBs in 2005 Great Lakes Top Predator Fish*

Lake trout (Walleye in Lake Erie only)

- Concentration (ppm)
  - Superior: 0.2
  - Michigan: 1.0
  - Huron: 0.6
  - Erie: 0.2
  - Ontario: 1.2

*Wildlife protection value = 0.16 ppm*

US EPA website, 2005
Polychlorinated biphenyls (PCBs)

- Humans
  - reproduction
    - intrauterine growth retardation
    - hyperplasia in tissues
    - birth defects
  - neurologic, behavior
    - impaired short-term memory
    - delayed psychomotor development
  - thyroid
    - inhibited activity

- Animal models
  - reproduction
    - small litter size
    - abortions
    - early puberty
  - neurologic, behavior
    - altered sex differentiation
    - cognitive deficits
  - thyroid
    - inhibited activity
PCBs

Guillette et al., 1998
How do agents disrupt the reproductive system?
Mechanisms of Damage

- Endocrine Disruption
  - mimic hormones
  - block hormones
  - trigger inappropriate hormone action
Mechanisms of Toxicants

- Toxicant
  - Tissue
    - Detoxification: No Damage
    - No Detoxification: Damage
    - Bioactivation: Damage
What can we do to avoid endocrine disruption?

- Awareness
- Screen and Regulate chemicals
  - prevention
- Regulate food and water
  - prevention
- Mechanistic studies
  - treatment
Summary

• We are exposed to many environmental chemicals
• Environmental chemicals may affect reproduction in wild-life and humans
• We need more studies to determine which chemicals affect reproduction and how such chemicals act
  – Prevention
  – Treatment
  – Policies