Endocrine Disruptors and the Reproductive System

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Overview

- What is an endocrine disruptor?
- Which environmental exposures are associated with reproductive toxicity?
- How do endocrine disruptors cause damage?
What is an endocrine disruptor?
“Exogenous agent that interferes with the synthesis, storage/release, transport, metabolism, binding, action, or elimination of natural hormones”

Cooper and Kavlock, 1997
Endocrine System

- Pineal
- Hypothalamus
- Pituitary
- Thyroid
- Parathyroids
- Thymus
- Adrenals
- Pancreas
- Ovary
- Testes
Endocrine Disruptors

- Estrogens
- Androgens
- Anti-estrogens
- Anti-androgens
- Progestogens
- Adrenal toxins
- Thyrotoxic agents
- Aryl hydrocarbons
- Retinoids
Endocrine Disruptors

- Types of endocrine disruptors
  - Pharmaceutical agents
    - diethylstilbestrol, oral contraceptives
  - Pesticides
    - dichloro-diphenyl-trichloroethane (DDT), methoxychlor (MXC)
  - Flame retardants
    - polybrominated diphenyl ethers (PBDEs)
  - Plasticizers
    - phthalates, bisphenol A
  - Heavy metals
    - lead, mercury, arsenic
  - Environmental contaminants
    - dioxins, polychlorinated biphenyls (PCBs)
Pharmaceutical Agents:
Diethylstibestrol (DES)

Yes...

desPLEX to prevent abortion, miscarriage and premature labor

Recommended for routine prophylaxis in ALL pregnancies...
98 per cent live delivery with desPLEX in one series of 1300 patients...
- bigger and stronger babies, too...
- no gastric or other side effects with desPLEX
- in either high or low dosage...

Each desPLEX tablet contains 25 mg of diethylstibestrol, U.S.P., which is then ultracentrifuged to smooth and accelerate absorption and activity. A portion of this ultracentrifuged diethylstibestrol is even included in the tablet coating to assure prompt help in emergencies. desPLEX tablets also contain vitamin C and certain members of the vitamin B complex to aid detoxification in pregnancy and the aftermath of estrus.

For further data and a generous trial supply of desPLEX, write to:

Dr. Frank L. Halsey, M.D.
Grant Chemical Co., Inc.
New York 10, N.Y.

REFERENCES

After extensive clinical experience with des, Karnaky, Gitman and Koplowitz as well as countless other clinicians wholeheartedly endorse the sound therapeutic necessity for the use of des in threatened abortion, habitual abortion and premature labor.

In a most recent publication, Karnaky has demonstrated that des, in massive doses (275 milligrams daily) provides optimum therapeutic results with maximum safety.
DES versus Estradiol

Estradiol

DES
DES Story

• 1966-1969
  – 7 women between 15-22 developed clear cell adenocarcinoma of the vagina

• 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
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
- Nothing? A lot?
  - DES being used a prostate and breast cancer treatment in some countries
  - DES being used to treat dogs and cats with urinary incontinence
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
Methoxychlor

Sesame Control

MXC (64 mg/kg/day)

Borgeest et al., 2002
Methoxychlor

Borgeest et al., 2002
Hexachlorocyclohexane (HCH) and Miscarriage

Levels of HCH (ng/L)

- Women without miscarriage: 206 ± 106
- Women with miscarriage: 258 ± 105

Gerhard et al; 1999
Flame Retardants
Flame Retardants

PBDE levels in human tissues from Sweden, Canada and the U.S., 1992-2003

<table>
<thead>
<tr>
<th>Year</th>
<th>Total PBDEs (ng/g lipid; mean ±)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1992</td>
<td>50</td>
</tr>
<tr>
<td>1993</td>
<td>70</td>
</tr>
<tr>
<td>1994</td>
<td>90</td>
</tr>
<tr>
<td>1995</td>
<td>110</td>
</tr>
<tr>
<td>1996</td>
<td>130</td>
</tr>
<tr>
<td>1997</td>
<td>150</td>
</tr>
<tr>
<td>1998</td>
<td>170</td>
</tr>
<tr>
<td>1999</td>
<td>190</td>
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<td>2000</td>
<td>210</td>
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<td>2001</td>
<td>230</td>
</tr>
<tr>
<td>2002</td>
<td>250</td>
</tr>
<tr>
<td>2003</td>
<td>270</td>
</tr>
</tbody>
</table>

Sources: Data from Noren and Meironyte, 2000; Meironyte, 2002; Sjödin et al., 2003; Mazdai et al., 2003 (median value*); Schechter et al., 2003; She et al., 2002; EWG, 2004; and Northwest Environment Watch, 2004.

PBDEs Breast Milk and Fat Samples Around the World

<table>
<thead>
<tr>
<th>Country</th>
<th>Median Concentration ng/g lipid</th>
</tr>
</thead>
<tbody>
<tr>
<td>U.S. Indiana 2001</td>
<td>35</td>
</tr>
<tr>
<td>U.S. SF Bay Area Late 1990s</td>
<td>30</td>
</tr>
<tr>
<td>U.S. Texas 2002</td>
<td>25</td>
</tr>
<tr>
<td>Canada 2002</td>
<td>20</td>
</tr>
<tr>
<td>Germany 2000</td>
<td>15</td>
</tr>
<tr>
<td>Sweden 2000</td>
<td>10</td>
</tr>
<tr>
<td>Finland 1996</td>
<td>5</td>
</tr>
<tr>
<td>United Kingdom 2002</td>
<td>2</td>
</tr>
</tbody>
</table>

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

Figure 1. Individual serum estradiol concentrations (bars indicate means) of F₁ female offspring on PND38 after treatment with vehicle or PBDE-47 (140 or 700 μg/kg bw) to F₀ dams on GD6. PTU was administered on GD7–PND21. *p < 0.05, and **p < 0.01.

Talsness et al, 2008
Flame Retardants

**Figure 1.** Thyroid weights in male (A) and female (B) adult offspring after exposure to low and high doses of PBDE-99 or A1254. Data shown are mean ± SE (n = 8/group).

*p* < 0.05 compared with control.

Lilienthal et al., 2006
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

- Have both anti-androgenic and estrogenic effects on development and sexual differentiation of the brain

- 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
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**

Table 2. Median concentration [range (μg/L)] of six phthalate monoesters in human breast milk samples 1997–2001, collected as additive aliquots from 1 to 3 months postnatally.

<table>
<thead>
<tr>
<th>Phthalate</th>
<th>Denmark (n = 65)</th>
<th>Finland (n = 65)</th>
<th>p-Value</th>
<th>LOD (μg/L)</th>
<th>Detection rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>mMMP</td>
<td>0.10 (&lt; 0.01–5.53)</td>
<td>0.09 (&lt; 0.01–0.37)</td>
<td>0.355</td>
<td>0.01</td>
<td>95</td>
</tr>
<tr>
<td>mEP</td>
<td>0.93 (0.07–33.6)</td>
<td>0.97 (0.25–41.4)</td>
<td>0.976</td>
<td>0.01</td>
<td>100</td>
</tr>
<tr>
<td>mBP</td>
<td>4.3 (0.6–10,900)</td>
<td>12 (2.4–123)</td>
<td>0.0001</td>
<td>0.05</td>
<td>100</td>
</tr>
<tr>
<td>mBzP</td>
<td>0.9 (0.2–14)</td>
<td>1.3 (0.4–26)</td>
<td>0.0001</td>
<td>0.05</td>
<td>100</td>
</tr>
<tr>
<td>mEHP</td>
<td>9.5 (1.5–191)</td>
<td>13 (4.0–1,410)</td>
<td>0.001</td>
<td>0.10</td>
<td>100</td>
</tr>
<tr>
<td>miNP</td>
<td>101 (27–469)</td>
<td>89 (28–230)</td>
<td>0.056</td>
<td>0.50</td>
<td>100</td>
</tr>
</tbody>
</table>

Country differences were tested by Mann-Whitney U-test.

Hogberg et al, 2008
**Phthalates**

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

Swan et al., 2005
Phthalates

Estradiol Levels
(DEHP exposed follicles)

Gupta et al., unpublished
Phthalates

Gupta et al., unpublished

Atresia rating (DEHP)

- DMSO
- DEHP100
- E1nM
- E10nM
- DEHP100+E1nM
- DEHP100+E10nM

Gupta et al., unpublished
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
BPA is an endocrine disrupting chemical:
- Anti-androgenic effects
- Antagonistic effects on thyroid hormone receptor
- Agonist and antagonistic effects on estrogen receptors

Effects depend on the receptor subtype and cell type
Gender Specific Effects of BPA

- Reduced sperm production
- Altered prostate development
- Increased susceptibility to prostate cancer

- Altered mammary glands
- Decreased fertility
- Chromosomally abnormal oocytes
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
**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

www.ejnet.org/dioxin
Dioxins

Yushchenko endured dioxin poisoning, likely by political foes, which, along with nearly killing him, left his skin severely disfigured.
## TCDD and Sex Ratio

<table>
<thead>
<tr>
<th>Father’s concentrations of TCCD (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 Male</td>
<td>20 Female</td>
<td>51</td>
</tr>
<tr>
<td>&gt;15</td>
<td>&gt;15</td>
<td>96 Male</td>
<td>121 Female</td>
<td>217</td>
</tr>
<tr>
<td>&gt;15</td>
<td>Unexposed*</td>
<td>81 Male</td>
<td>105 Female</td>
<td>186</td>
</tr>
<tr>
<td>Unexposed*</td>
<td>&gt;15</td>
<td>120 Male</td>
<td>100 Female</td>
<td>220</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td>328 Male</td>
<td>346 Female</td>
<td>674</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
Polychlorinated biphenyls (PCBs)

- **Humans**
  - reproduction
    - intrauterine growth retardation
    - hyperplasia in tissues
    - birth defects
  - neurologic, behavior
    - impaired short-term memory
    - delayed psychomotor development
  - thyroid
    - altered activity
- **Animal models**
  - reproduction
    - small litter size
    - abortions
    - early puberty
  - neurologic, behavior
    - altered sex differentiation
    - cognitive deficits
  - thyroid
    - altered activity
PCBs
PCBs

LAKE ONTARIO BIOMAGNIFICATION OF PCBs

- Herring gull: 25,000,000x
- Lake trout: 2,600,000x
- Smelt: 835,000x
- Phytoplankton: 250x
- Zooplankton: 500x

Pollutionissues.com
PCBs

Total PCBs in 2005 Great Lakes Top Predator Fish
Lake trout (Walleye in Lake Erie only)

Wildlife protection value = .16ppm
### PCB Levels in Other Foods

<table>
<thead>
<tr>
<th>Food</th>
<th>PCB Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Butter, salted</td>
<td>70</td>
</tr>
<tr>
<td>Tuna, canned in oil</td>
<td>45</td>
</tr>
<tr>
<td>Chicken breast, roasted</td>
<td>32</td>
</tr>
<tr>
<td>Brown gravy, homemade</td>
<td>30</td>
</tr>
<tr>
<td>Salmon steak or fillet, baked</td>
<td>26*</td>
</tr>
<tr>
<td>Pancake, from mix</td>
<td>24</td>
</tr>
<tr>
<td>Meatloaf</td>
<td>23</td>
</tr>
<tr>
<td>Beef steak, pan-cooked</td>
<td>22</td>
</tr>
<tr>
<td>Pork chop, pan-cooked</td>
<td>21</td>
</tr>
<tr>
<td>Egg, fried</td>
<td>19</td>
</tr>
<tr>
<td>Pork roast, baked</td>
<td>18</td>
</tr>
<tr>
<td>Popcorn, popped in oil</td>
<td>17</td>
</tr>
<tr>
<td>Biscuit, refrigerated dough, baked</td>
<td>16</td>
</tr>
<tr>
<td>Veal cutlet, pan-cooked</td>
<td>13</td>
</tr>
<tr>
<td>Cornbread</td>
<td>11</td>
</tr>
<tr>
<td>Chuck roast, baked</td>
<td>10</td>
</tr>
<tr>
<td>English muffin, plain, toasted</td>
<td>10</td>
</tr>
<tr>
<td>Raisin</td>
<td>10</td>
</tr>
<tr>
<td>Chicken, fried</td>
<td>9</td>
</tr>
<tr>
<td>Caramel candy</td>
<td>6</td>
</tr>
</tbody>
</table>

*Puget Sound salmon tested higher.

Source: FDA

**Note:** Few foods are immune from contamination by PCBs, which have spread worldwide despite bans in the United States and most other countries. These foods have been tested by the Food and Drug Administration. Figures in parts per billion.
### PCBs

**Table 3.** Summary of epidemiologic results on perinatal PCB or dietary fish exposure in relation to neurodevelopmental outcomes.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Age outcome measured</th>
<th>Location of population studied (reference)</th>
<th>Effect of ↑ PCB intake</th>
<th>Exposure measure used</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neonatal reflexes</td>
<td>60 hr</td>
<td>Michigan (119)</td>
<td>Hyporeflexia</td>
<td>Fish</td>
</tr>
<tr>
<td></td>
<td>60 hr</td>
<td>Michigan (119)</td>
<td>None</td>
<td>Measured PCBs</td>
</tr>
<tr>
<td></td>
<td>72 hr</td>
<td>North Carolina (120)</td>
<td>Hyporeflexia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>14 days</td>
<td>Netherlands (121)</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td></td>
<td>36 hr</td>
<td>New York (122)</td>
<td>Abnormal reflexes</td>
<td></td>
</tr>
<tr>
<td>Neonatal muscle tone</td>
<td>60 hr</td>
<td>Michigan (119)</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td></td>
<td>72 hr</td>
<td>North Carolina (120)</td>
<td>Hypotonia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>14 days</td>
<td>Netherlands (121)</td>
<td>Hypotonia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>36 hr</td>
<td>New York (122)</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Psychomotor development&lt;sup&gt;4&lt;/sup&gt;</td>
<td>6 months</td>
<td>North Carolina (123)</td>
<td>Delayed</td>
<td></td>
</tr>
<tr>
<td></td>
<td>36 months</td>
<td>North Carolina (124)</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3 months</td>
<td>Netherlands (125)</td>
<td>Delayed</td>
<td></td>
</tr>
<tr>
<td>Mental development</td>
<td>6 months</td>
<td>North Carolina (123)</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3 months</td>
<td>Netherlands (125)</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>IQ</td>
<td>11 years</td>
<td>Michigan (127)</td>
<td>Decreased</td>
<td></td>
</tr>
<tr>
<td>Visual recognition memory</td>
<td>7 months</td>
<td>Michigan (128)</td>
<td>Decreased</td>
<td></td>
</tr>
<tr>
<td>Short-term memory</td>
<td>4 years</td>
<td>Michigan (129)</td>
<td>Decreased</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4 years</td>
<td>North Carolina (130)</td>
<td>None</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: IQ, intelligence quotient; PCBs, polychlorinated biphenyls. <sup>4</sup>Representative findings are shown from each study; for brevity all results from each study are not included. <sup>4</sup>A relation with "neonatal optimality score," comprising reflex and tone components, was found for breast-fed children with PCBs measured in breast milk. However, with PCBs in cord blood as the exposure measure in the entire study group, including children who were not breast fed, however, a relation was not present. <sup>4</sup>True only in breast-fed children, with PCBs measured in breast milk. <sup>4</sup>Dutch neurologic exam findings for children (not neonates) are classified with psychomotor development results in this table.

Brouwer et al., 1999
### Table 3. Neuropsychological outcomes of human PCB studies.

<table>
<thead>
<tr>
<th>Test Description</th>
<th>Age 1</th>
<th>Age 2</th>
<th>Outcome 1</th>
<th>Outcome 2</th>
<th>Exposure Variable</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congener-specific studies</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oswego cohort</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NBAS</td>
<td>Birth</td>
<td></td>
<td>↓ Autonomic</td>
<td>↓ Habituation</td>
<td>7–9 chlornated PCBs</td>
<td>Stewart et al. (2003)</td>
</tr>
<tr>
<td>Fagan</td>
<td>6 months</td>
<td></td>
<td>↓ Fixation time</td>
<td></td>
<td>7–9 chlornated PCBs</td>
<td>Darvill et al. (2000)</td>
</tr>
<tr>
<td></td>
<td>12 months</td>
<td></td>
<td>↓ Fixation time</td>
<td></td>
<td>Cord blood PCBs, 7–9 chlornated PCBs</td>
<td>Darvill et al. (2000)</td>
</tr>
<tr>
<td>German cohort</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fagan</td>
<td>7 months</td>
<td></td>
<td>No effect</td>
<td></td>
<td>Cord blood PCBs</td>
<td>Winneke et al. (1998)</td>
</tr>
<tr>
<td>Bayley scales</td>
<td>7 months</td>
<td></td>
<td>↓ MDI</td>
<td></td>
<td>In $\Sigma$PCBs (138, 153, and 160) breast milk</td>
<td>Winneke et al. (1998)</td>
</tr>
<tr>
<td></td>
<td>18 months</td>
<td></td>
<td>No effect</td>
<td></td>
<td>In $\Sigma$PCBs (138, 153, and 160) breast milk</td>
<td>Walkowiak et al. (2001)</td>
</tr>
<tr>
<td></td>
<td>30 months</td>
<td></td>
<td>↓ MDI</td>
<td></td>
<td>In $\Sigma$PCBs (138, 153, and 160) breast milk</td>
<td>Walkowiak et al. (2001)</td>
</tr>
<tr>
<td>Kaufman ABC</td>
<td>42 months</td>
<td></td>
<td>↓ Mental processing composite index</td>
<td></td>
<td>In $\Sigma$PCBs (138, 153, and 160) breast milk</td>
<td>Walkowiak et al. (2001)</td>
</tr>
<tr>
<td>Faroe islands cohort</td>
<td></td>
<td></td>
<td>↓ Performance</td>
<td></td>
<td>Cord blood PCBs</td>
<td>Grandjean et al. (2001)</td>
</tr>
<tr>
<td>Boston Naming Test</td>
<td></td>
<td></td>
<td>↑ Auditory thresholds</td>
<td></td>
<td>Cord blood PCBs</td>
<td>Grandjean et al. (2001)</td>
</tr>
<tr>
<td>Auditory function</td>
<td></td>
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<td>Michigan cohort</td>
<td></td>
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<tr>
<td>Birth size/growth</td>
<td>Birth</td>
<td></td>
<td>↓ Birth weight</td>
<td></td>
<td>Cord blood PCBs</td>
<td>Fein et al. (1984)</td>
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<tr>
<td></td>
<td>5 months</td>
<td></td>
<td>↓ Head circumference</td>
<td></td>
<td>Cord blood PCBs</td>
<td>Jacobson and Jacobson (1988)</td>
</tr>
<tr>
<td></td>
<td>7 months</td>
<td></td>
<td>No effect</td>
<td></td>
<td>Cord blood PCBs</td>
<td>Jacobson and Jacobson (1988)</td>
</tr>
<tr>
<td></td>
<td>4 years</td>
<td></td>
<td>↓ Verbal memory</td>
<td></td>
<td>Cord blood PCBs, breast milk PCBs</td>
<td>Jacobson et al. (1990)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>↓ Numerical memory</td>
<td></td>
<td>Cord blood PCBs, breast milk PCBs</td>
<td>Jacobson et al. (1990)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>↓ Visual discrimination</td>
<td></td>
<td>Cord blood PCBs, breast milk PCBs</td>
<td>Jacobson et al. (1990)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>↓ Short term memory</td>
<td></td>
<td>Cord blood PCBs</td>
<td>Jacobson and Jacobson (1988)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>↓ Full-scale IQ</td>
<td></td>
<td>Total cord PCBs</td>
<td>Jacobson et al. (1990)</td>
</tr>
<tr>
<td></td>
<td>11 years</td>
<td></td>
<td>↓ Verbal IQ</td>
<td></td>
<td>Child's total PCBs</td>
<td>Jacobson and Jacobson (1996)</td>
</tr>
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<td>North Carolina cohort</td>
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<tr>
<td>NBAS</td>
<td>Birth</td>
<td></td>
<td>↓ Muscle tone</td>
<td></td>
<td>Breast milk PCBs</td>
<td>Rogan et al. (1968)</td>
</tr>
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<td></td>
<td>6 months</td>
<td></td>
<td>↓ Activity</td>
<td></td>
<td>Breast milk PCBs</td>
<td>Gladen et al. (1988)</td>
</tr>
<tr>
<td></td>
<td>12 months</td>
<td></td>
<td>↓ Reflexes</td>
<td></td>
<td>Breast milk PCBs</td>
<td>Gladen et al. (1988)</td>
</tr>
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<td></td>
<td>18 months</td>
<td></td>
<td>No effect</td>
<td></td>
<td>Breast milk PCBs</td>
<td>Rogan and Gladen (1991)</td>
</tr>
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<td></td>
<td>24 months</td>
<td></td>
<td>↓ PDI</td>
<td></td>
<td>Breast milk PCBs</td>
<td>Rogan and Gladen (1991)</td>
</tr>
<tr>
<td></td>
<td>3–5 years</td>
<td></td>
<td>No effect</td>
<td></td>
<td>Breast milk PCBs</td>
<td>Rogan and Gladen (1991)</td>
</tr>
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</table>

Abbreviations: ↓, decrease; ↑, increase. Bayley scales, Bayley Scales of Infant Development; Fagan, Fagan Test of Infant Intelligence; Kaufman ABC, Kaufman Assessment Battery for Children; McCarthy scales, McCarthy Scales of Children’s Abilities; NBAS, Brazelton Neonatal Behavioral Assessment Scale; WISC-R, Wechsler Intelligence Scales for Children—Revised. *A Dutch cohort is summarized in Table 2.*

Schantz et al., 2003
PCBs

Guillette et al., 1998
PCBs and Normal Time to Conception

Courval et al; 1999
How do agents disrupt/modulate the endocrine system?
Mechanisms of Damage

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

Agent A

Cells

Hormonal Response

Agent B

hormone

No response
Mechanisms of Toxicants

- Toxicant
  - Tissue
    - Detoxification: No Damage
    - No Detoxification: Damage
    - Bioactivation: Damage
Mechanisms of Damage

- Damage reproductive tissues
  - ovary
  - uterus
  - oviducts
  - cervix
  - vagina
  - testes
  - epididymis
  - prostate
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 endocrine disrupting agents
- Endocrine disruptors 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