Environmental Chemicals and their Impact on Child Health: A Focus on Endocrine Disrupting Chemicals.

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Objectives

- Define ‘endocrine disrupting chemicals’ (EDCs) and their properties.
- Identify the most common and/or problematic EDCs.
- Appreciate that EDC exposure can generate phenotypes that persist ≥ 3 generations.
- Employ strategies to minimize exposure and risk.

Perfluorooctane sulfonate (PFOS) exposure

Environmental Health Perspectives  May 2007  115:A251-256
Conflicts/Disclosures

- I have no financial conflicts or disclosures
- I will not discuss use of unapproved/experimental devices
Endocrine Disrupting Chemicals (EDCs): Definitions

- **US EPA:** “An exogenous agent that interferes with the production, release, transport, metabolism, binding, action, or elimination of natural hormones in the body responsible for the maintenance of homeostasis and the regulation of developmental processes”

- **WHO/UNEP:** “An exogenous substance or mixture that alters the function(s) of the endocrine system and consequently causes adverse effects in intact organisms, or its progeny or (sub) population”

- **EU:** “Exogenous substance that causes adverse health effects in an intact organism, or its progeny, secondary to changes in endocrine function”

- **Endocrine Society (2015):** “An exogenous chemical, or mixture of chemicals, that interfere with any aspect of hormone action”
Four lines of EDC research:

(Gore et. al. Endocrine Reviews 2015;36:E1-E150)

- Animal studies:
  - Consequences of EDC exposure on development and physiology in animal models.

- Mechanistic studies
  - Effects in cells or tissues from exposed animals looking at gene expression, epigenetic changes, molecular events etc.

- Epidemiological studies in humans:
  - Comparing body burden of EDCs and disease propensity in humans.
  - Prospective studies

- Occupational/Acute exposure in humans
  - Investigation of humans with known occupational or acute exposure.
Strong evidence for role of EDCs in:

(Gore et. al. Endocrine Reviews 2015;36:E1-E150)

- Obesity and diabetes
- Female reproductive system
- Male reproductive system
- Hormone-sensitive cancers in females
- Prostate gland
- Thyroid gland function
- Neurodevelopment and neuroendocrine system
EDCs are highly heterogeneous:

- >85,000 registered chemicals in use
  - >1,000 of those tested act as EDCs

- Synthetic chemicals
  - Solvents/lubricants and byproducts
    - Polychlorinated biphenyls (PCBs), dioxins
  - Fuels/explosives
    - Perchlorate, Jet fuel
  - Flame retardants
    - Polybrominated diphenyl ethers (PBDEs)
  - Plastics and plasticizers
    - Bisphenol A (BPA), BPS, phthalates
  - Pesticides/insecticides
    - Methoxychlor, chlorpyriphos, parathion, dichlorodiphenyltrichloroethane (DDT)
  - Fungicides
    - Vinclozalin, organotins (tributyltin), mane
EDCs are highly heterogeneous:

- Natural compounds, drugs, personal care products
  - Phytoestrogens (especially soy and soy products)
    - Genestein, Coumestrol
  - Nicotine
  - Pharmaceuticals
    - Diethylstilbestrol (DES), phthalates
  - Personal care products
    - Detergents: nonylphenol
    - UV screens: 4-methylbenzlidine camphor
    - Lotions/fragrances: phthalates
    - Antibacterial sanitizer: triclosan
EDCs have special characteristics...

- May be toxic at high levels but at low levels behave more like a drug or a hormone
  - Complex dose-response curves
  - Active at very low concentrations
- May have long latency period between exposure and effect
  - In utero exposure can lead to adult disease
- May act synergistically at low level
  - xenoestrogens
- Multiple windows of susceptibility
  - Fetal, early childhood, adolescence, post menopausal
- Gender, genetics, nutrition, stress etc. modulate effects
- Effects of some EDCs can be transmitted to further generations via germ-line epigenetic modifications
  - ≠ DNA mutation
How regulatory agencies determine reference (safe) dose (amount/kg day$^{-1}$)

Reference Dose ($\approx$ safe)  Lowest Observed Adverse Effect Level (LOAEL)

$10^{-3}$
How EDCs behave: non-monotonic and non-predictable dose response curves

Reference Dose (≈ safe)  Lowest Observable Adverse Effect Level (LOAEL)
Toxic and endocrine disruption dose response curves for BPA are distinct.
Gestational exposure to EDCs potentially directly exposes 3 generations

Nicotine:
1<sup>st</sup> anorexia in mother
2<sup>nd</sup> child’s phenotype?
Effect of maternal smoking during pregnancy on offspring overweight (n= 84,563, @ 3-33 years of age)

1. Increased adipogenic commitment
   - BADGE
   - Firemaster 550
   - Fludioxonil
   - Quinoxyfen
   - Tributyltin
   - Triflumizole

2. Increased adipocyte differentiation
   - Acetamiprid
   - BADGE
   - BDE-47
   - BPA
   - DES
   - Dioxin
   - Fludioxonil
   - Forchlorfenuron
   - PCB-77
   - Pymetrozine
   - Quinoxyfen
   - Spirodiclofen
   - Tebupirimfos
   - Triphenyltin

3. Increased adipocyte proliferation (in vivo)
   - BPA
   - DES
   - Nicotine
   - PCB-77
   - Tributyltin

4. Increased lipid uptake (in vivo)
   - BPA
   - Nicotine
   - PCB-77
   - Tributyltin

Mesenchymal Stem Cell (MSC) → Preadipocyte → Normal adipocytes → Hyperplastic adipocytes → Hypertrophic adipocytes
# Metabolism Disruptors and Metabolic Disruption (Heindel 2016)

<table>
<thead>
<tr>
<th></th>
<th>Obesity</th>
<th>Diabetes</th>
<th>Fatty Liver</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bisphenol A (BPA)</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Phthalates (DEHP)</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
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<tr>
<td>Tributyl Tin (TBT)</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Nicotine/smoking</td>
<td>+++</td>
<td>++</td>
<td>+++</td>
</tr>
<tr>
<td>Air Pollution (PAH)</td>
<td>++</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>PCBs</td>
<td>+</td>
<td>+++</td>
<td>+++</td>
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<tr>
<td>Arsenic</td>
<td>++</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>DDT/DDE</td>
<td>+++</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>PFOA</td>
<td>++</td>
<td></td>
<td>+++</td>
</tr>
<tr>
<td>PFOS</td>
<td>+</td>
<td></td>
<td>+++</td>
</tr>
<tr>
<td>Dioxin (TCDD)</td>
<td>++</td>
<td></td>
<td>+++</td>
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<tr>
<td>Others</td>
<td></td>
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</tbody>
</table>
Gestational exposure to EDCs potentially directly exposes 3 generations

1\textsuperscript{st} DES = anti-nausea in mother
2\textsuperscript{nd} Adenocarcinoma in daughter
3\textsuperscript{rd} 20 x RR Hypospadias in grandson
Transient gestational exposure to EDCs causes trans-generational inheritance of reproductive disease
Manikkah M et al 2012 PLoS ONE 7(2)e31901.

<table>
<thead>
<tr>
<th>Generation</th>
<th>Pesticides Permethrin and DEET</th>
<th>Plastics BPA and Phthalate mix</th>
<th>Dioxin</th>
<th>Hydrocarbons jet fuel/JP8</th>
</tr>
</thead>
<tbody>
<tr>
<td>gen 1 or F₀ “Great GM”</td>
<td>Transient exposure to EDC during early embryonic gonadal sex determination</td>
<td>Reproduce with no EDC exposure</td>
<td>Reproduce with no EDC exposure</td>
<td></td>
</tr>
<tr>
<td>gen 2 or F₁ “Grandmother”</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>gen 3 or F₂ “Mother”</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>gen 4 or F₃ “Child”</td>
<td>Normal puberty ↓ pool of primordial follicles</td>
<td>Early puberty ♀ ↓ pool of primordial follicles PCOS</td>
<td>Early puberty ♀ ↓ pool of primordial follicles</td>
<td>Early puberty ♀ ↓ pool of primordial follicles ↑ Sperm apoptosis</td>
</tr>
</tbody>
</table>
Female reproductive disease in 3rd generation removed from exposure to low dose plastic mix (BPA, DEHP, DBP – Skinner)
Visceral fat in 3rd generation removed from exposure to low dose plastic mix (BPA, DEHP, DBP – Skinner et al)
Regulation of Gene Expression through Epigenetic Processes

2008;359:61-73
Mesenchymal Stem Cell (MSC)

1. Increased adipogenic commitment
   - BADGE Quinoxyfen
   - Firemaster 550 Tributyltin
   - Fludioxonil Triflumizole

2. Increased adipocyte differentiation
   - Acetamiprid Flusilazole Triphenyltin
   - BADGE Forchlorfenuron Triflumizole
   - BDE-47 PCB-77
   - BPA Pymetrozine
   - DES Quinoxyfen
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Preadipocyte

3. Increased adipocyte proliferation (in vivo)
   - BPA
   - DES
   - Nicotine
   - PCB-77
   - Tributyltin

Normal adipocytes

Hypertrophic adipocytes

4. Increased lipid uptake (in vivo)
   - BPA
   - Nicotine
   - PCB-77
   - Tributyltin
Bisphenol A
vom Saal and Hughes EHP 2005;113:926-33

- Building block of polycarbonate
  - Bottles, can liners, carbonless receipts, dental resins
  - 6.4 billion pounds/year

- Readily leaches
  - Extremes of pH, temperature and age, detergents

- Potent “endocrine disruptor”
  - Gestational exposure (maternal consumption of ppb):
    - permanent androgen mediated prostate hypertrophy in rodents
    - Decreased sperm count
    - aneuploidy
    - Intraductal hyperplasia and carcinoma in situ in rats

- Other effects
  - Cognitive-behavioral
    - Excessive aggression in males
    - Hyperactive/inattentive
Bisphenol A
vom Saal and Hughes EHP 2005;113:926-33

- **Common in humans**
  - 95% of urine samples +
  - Maternal/fetal plasma, placenta, breast milk
  - Amniotic fluid levels 5X maternal plasma
  - Median BPA levels in humans exceed levels required to cause adverse effects in mice
    - 94/115 published in vivo studies demonstrate biological effects at low levels (below the LOAEL of 50 mg/kg/day)
    - 40/115 show effects below reference value (50 ug/kg/d)

- **Evidence supports effects in humans:**
  - Obesity, in adults and children
  - PCOS, ASD, ADD and other externalizing behaviors
Phthalates

- Commonly used
  - Plasticizers that are non covalently bound to substrates
  - Plastics, cosmetics, shampoos, toys, pacifiers, meds, blood bags
  - Common in people
    - 75% US adults ≥ 5 urinary metabolites
    - Present in breast milk, formula
    - NICU infants – from medical equipment

- Known endocrine disruptors
  - Anti-androenergetic in fetus
  - Levels in cord blood and breast milk positively associated with:
    - cryptorchidism and hypospadius
    - reduced sperm count and testosterone levels are correlated

- Low testosterone in men associated with:
  - Obesity
  - Insulin resistance
  - Diabetes
Number of phthalate metabolites in infant urine

Sathyanarayana S. *Pediatrics* 2008;121;e261-268

Percent of infants

Number of phthalate metabolites in infant urine
Perfluoroalkyl Acids (PFAAs)

Environmental Health Perspectives  May 2007 115:A251-256

- PFAAs
  - Surfactants/components in > 200 applications
    - Water/stain repellents
- Perfluorooctanoic acid (PFOA)
  - Teflon etc
- Perfluoroocatonyl sulfonate (PFOS)
  - Scotchguard, Stainmaster
  - Long t½ in humans (4-7 yrs!)
- Sources
  - Food
    - Wrappers – eg. Microwave popcorn!
  - Cook-ware
  - Soil/dust
    - DuPont sites in NC
  - Water
    - Cape Fear River (GenX c-6 version)
  - Breast milk
Gestational Exposure to PFOA and Body Composition at 80 Weeks

Environmental Health Perspectives  May 2007 115:A251-256
A Role for Perfluorinated Chemicals (PCAs) in Human Obesity and Metabolic Disease?

Ubiquitous
- > 90% adults have PCAs
  - PFOS @ 30.4 ppb
  - PFOA @ 5.2 ppb
- Cord blood
  - ≈ 10% maternal serum levels
  - 100% with PFOS
  - 99% with PFOA
- Breast milk
  - ≈ 1% maternal serum levels
  - 200 ngm/day to infant

Correlations
- Decrease in infant birth weight
  - - 69 gms for PFOS
  - - 104 gms for PFOA
- Obesity at age 20 in women exposed in utero
  - Prospective study

Apelberg et al., *EHP* 2007 115;1670-1676, Halldorsson TI et al EHP 2012;120:668-673
PBDE and OP Associated IQ Loss, Intellectual Disability and Costs of European Children Born in 2010

**Polybrominated Diphenyl Ether (PBDE) flame retardants**

- Strong Toxicological Evidence

**Organophosphate (OP) Pesticides**

Moderate/High Epi Evidence

**70-100% probability:**

- 0.3 – 1.9 loss IQ points
- € 1.4 – 19.4 x 10^9 per yr.
- 544 – 8,080 attributable cases intellectual disability
- € 0.1 – 1.2 x 10^9 per yr.

**70-100% probability:**

- 1.7 – 7.0 loss IQ points
- € 40.8 – 164 x 10^9 per yr.
- 16,500 – 84,400 attributable cases intellectual disability
- € 5.9 – 30.5 x 10^9 per yr.

Bellanger M et al. JCEM 2015;100:1256-66.
## Attributable Cases and Cost of EDC-Associated Neurodevelopment Disorders

<table>
<thead>
<tr>
<th></th>
<th>Toxicological Evidence</th>
<th>Epidemiologic Evidence</th>
<th>Probability</th>
<th>Attributable Cases Cost per yr.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Autism</strong></td>
<td>Moderate</td>
<td>Low</td>
<td>20-39%</td>
<td>126 – 631 € 79 – 399 mil</td>
</tr>
<tr>
<td><strong>ADHD OP</strong></td>
<td>Strong</td>
<td>Low-Moderate</td>
<td>20-69%</td>
<td>19,388 – 31,154 € 1.2 – 2.9 bil</td>
</tr>
<tr>
<td><strong>PBDE</strong></td>
<td></td>
<td></td>
<td></td>
<td>22,600 € 1.4 – 2.1 bil</td>
</tr>
</tbody>
</table>

Legler J et al. JCEM 2015;100:1278-1288.
## Attributable Cases and Cost of EDC-Associated Obesity and Diabetes

<table>
<thead>
<tr>
<th>Exposure/Outcome</th>
<th>Toxicological Evidence</th>
<th>Epidemiologic Evidence</th>
<th>Probability of causation</th>
<th>Attributable Cases Cost per year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prenatal BPA Obesity at 10 yr.</td>
<td>Strong</td>
<td>Low</td>
<td>20-69%</td>
<td>42,200 € 1.5 bil</td>
</tr>
<tr>
<td>Prenatal DDE Obesity at 10 yr.</td>
<td>Moderate</td>
<td>Moderate</td>
<td>40-69%</td>
<td>1,555 € 24.6 mil</td>
</tr>
<tr>
<td>Adult Phthalate Adult Obesity</td>
<td>Strong</td>
<td>Low</td>
<td>40-69%</td>
<td>53,900 € 12.6 bil</td>
</tr>
<tr>
<td>Adult DDE Adult diabetes</td>
<td>Moderate</td>
<td>Low</td>
<td>20-39%</td>
<td>28,200 € 835 mil</td>
</tr>
<tr>
<td>Adult Phthalate Adult diabetes</td>
<td>Strong</td>
<td>Low</td>
<td>40-69%</td>
<td>20,500 € 1.5 mil</td>
</tr>
</tbody>
</table>

Bellanger M et al. JCEM 2015;11:1256.
Conclusions

- “The evidence for adverse reproductive outcomes from EDCs is strong, and there is mounting evidence for effects on other endocrine systems including thyroid, neuroendocrine, obesity and metabolism”

- Key issues are age at exposure, latency from exposure, mix of EDCs and other factors, dose response dynamics and the ability to transmit effects to future generations via germline epigenetic modifications
Epidemiologic evidence demonstrates associations between early life exposure to pesticides and pediatric cancers, decreased cognitive function, and behavioral problems. Related animal toxicology studies provide supportive biological plausibility for these findings.

Prospective contemporary birth cohort studies in the United States link early-life exposure to organophosphate insecticides with reductions in IQ and abnormal behaviors associated with attention-deficit/hyperactivity disorder and autism.

Strong evidence documenting a role in human disease for many EDC is still lacking and may be difficult to generate as is a complete scientific consensus.
HEALTH EFFECTS FROM ENDOCRINE DISRUPTING CHEMICALS COST THE EU 157 BILLION EUROS EACH YEAR. This is the tip of the iceberg: Costs may be as high as €270B.

€157B Cost by Health Effect

- Male Reproductive Disorders: €4B
- Premature Death: €6B
- Obesity & Diabetes: €15B
- Neurological Impacts (including ADHD): €132B

NOTE: The economic estimates do not include all costs associated with these conditions.

€157B Cost by EDC Type

- Pesticides: €120B
- Plastic, Cans: Phthalates & BPA: €26B
- Flame Retardants: €9B
- Other: €2B

Endocrine Disrupting Chemicals (EDCs) interfere with hormone action to cause adverse health effects in people.

"THE TIP OF THE ICEBERG"
The data shown to the left are based on fewer than 5% of likely EDCs. Many EDC health conditions were not included in this study because key data are lacking. Other health outcomes will be the focus of future research.

SOME EDC-RELATED HEALTH OUTCOMES NOT INCLUDED:
- Breast Cancer
- Prostate Cancer
- Immune Disorders
- Female Reproductive Disorders
- Liver Cancer
- Parkinson’s Disease
- Osteoporosis
- Endometriosis
- Thyroid Disorders

SOME EDCs NOT INCLUDED:
- Atrazine
- 2, 4-D
- Styrene
- Triclosan
- Nonylphenol
- Polycyclic Aromatic Hydrocarbons
- Bisphenol S
- Cadmium
- Arsenic
- Ethylene glycol

See Trasande et al. The Journal of Clinical Endocrinology & Metabolism
http://press.endocrine.org/edc
Minimize Risk: Pesticides

- **Diet**
  - Scrub and wash produce with water
  - Throw away outer leaves
  - Trim and discard skin and fat from meats
  - Eat lower fat foods and lower on the food chain
  - Purchase organic
  - Follow “Dirty Dozen and Clean 15” approach
    - [http://www.ewg.org/foodnews](http://www.ewg.org/foodnews)

- **Home, School, Day Care**
  - Use non/least toxic pest-control methods
    - Traps > baits > spray > fogger/bombs
  - Vacuum regularly to reduce dust/dirt
  - Wash child's hands
Minimize Risk: BPA/Phthalates

- Avoid plastics marked:
  - 3 = PVC (phthalates and organotin)
  - 6 = Polystyrene
  - 7 = Other (polycarbonate can contain BPA)
    - Select glass or polypropylene (#5 softer more opaque)
    - Polycarbonate baby bottles eliminated in US July 2012

- If polycarbonate is used:
  - Avoid high temperature and harsh detergents
  - Leaching accelerates after 50-100 washes

- Choose BPA free containers
  - Stainless or glass vs. “BPA-free” plastic
  - BPS – a regrettable substitution?

- Wash hands after handling receipts (BPA)
- Avoid recycled paper products for food (BPA)
Minimize Risk: BPA/Phthalates

- Look for PVC-free products
  - Consider high quality wooden toys
    - Look for approval by EU on label
- Limit infant care products and unless medically necessary avoid lotions and powders (phthalates)
  - Look for “phthalate free” products
- Avoid scented personal care products and cosmetics
  - Cologne, lotion, personal care products (phthalates)
  - Cosmetic safety [www.ewg.org/skindeep](http://www.ewg.org/skindeep)
- Avoid scented household products (phthalates)
  - Glade plugins, car air fresheners etc.
- Minimize inhalation and hand-mouth ingestion
  - Vacuuming with HEPA filter, frequent wet (not dry) dusting
    - Especially important for flame retardants PBDE/Organohalogens
  - Routine house-hold filter maintenance
Minimize Risk: BPA/Phthalates

- Minimize inhalation and hand-mouth ingestion
  - Vacuuming with HEPA filter, not sweeping or dry dusting
  - Routine filter maintenance

- Never heat food in plastic containers
  - Microwave in ceramic or glass containers
  - Don’t let cling wrap touch food – use paper towel

- Avoid micro waving in grease or water resistant paper packaging (perfluoroalkyl acids)
  - Microwave popcorn, pot pies etc.

- Avoid food in plastic wrap
  - Pliable cling wrap contains phthalates as plasticizer
  - Especially avoid meats and cheeses in cling wrap
    - Buy @ deli and have wrapped in paper (PFAAs??)
  - Cut away portion in contact with wrap
Minimize risk: BPA/other

- Avoid canned foods (BPA from lining)
  - Single soda per day ↑ odds of obesity
  - Glass, frozen or fresh
  - Do not store at high temperatures or for long times
  - Do not heat food in the can

- Avoid ready to feed and concentrated formula in cans (BPA)

- Avoid smoking and ETS exposures
  - Nicotine replacement contraindicated in pregnancy

- Use filtered tap water
  - Reverse osmosis > activated carbon filter
  - Don’t reuse bottled water bottles
Major References and Resources


- American Academy of Pediatrics (AAP)
  - Pediatrics 2012 130;e1757
Major References and Resources

- **Collaborative on Health and the Environment**
  - A reputable group of scientists, organizations with a concern for the environmental influences on health (ECU’s PHWRTC is a member of the diabetes-obesity working group)
  - Lots of reasonable handouts and information for the layperson
  - [www.healthandtheenvironment.org](http://www.healthandtheenvironment.org)
Major References and Resources

- **Pediatric Environmental Health Specialty Units**
  - Coordinated by Association of Occupational and Environmental Clinics to provide free academically based consultation for health care providers
  - Anticipatory guidance by age
  - Lots of good links
  - Endorsed by AAP
  - [http://peht.ucsf.edu/index.php](http://peht.ucsf.edu/index.php)