An Introduction to Endocrine Disrupting Chemicals

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Disclosures / Conflicts of Interest

• My spouse is employed by CVS Health
• My work is funded by the National Institutes of Health, the Allen Family Foundation, the Great Neck Breast Cancer Coalition, and the Cornell Douglas Foundation.
• I have received travel reimbursements from NGOs, industry, and academic organizations to speak about endocrine disrupting chemicals
Objectives

1) Explain endocrine disrupting chemicals (EDCs)

2) Examine endocrine disease trends

3) Apply the principles of endocrinology to the study and understanding of EDCs
What are Endocrine Disrupting Chemicals (EDCs)?

EDCs are exogenous chemicals or chemical mixtures that interfere in some way with hormone action.
Hormone action

- Synthesis
- Secretion
- Transport
- Binding
- Action
- Elimination
Suspected EDCs:

- Metals
- Industrial Chemicals
- Personal care products
- Pesticides
- Plastics
- Natural estrogens & Phytoestrogens
- Hormonally active drugs
- Synthetic hormones

Sources of exposure
Daily exposures to many of these chemicals are typically low – and often unsuspected.
We often hear: “But we’ve all been exposed and we’re all fine!”
We are not fine

Left: Tanner, Anderson & Must
Right: Levine et al., Hum Reprod Update. (2017)
We are not fine

Top: Richiardi et al., Cancer Epidem. Biomark. (2004);
Bottom: based on data from http://data.euro.who.int/hfadb/
We are not fine

Left: Neison, Environ Health (2014);
Right: Wang et al., Epidemiol & Psychiatry (2017)
We are not fine

Top: Sun et al., PLoS One (2014);
Bottom (L&R): Dabelea, Diabetes Care (2018)
Environment ↔ Genetics ↔ Diseases ↑
Applying the principles of endocrinology to the study & understanding of EDCs
1. The endocrine system coordinates the tissues & organs of the body
2. The endocrine system is important at all stages of life, from conception until death

“From the day of conception until an individual is born or hatched, the development of each stage of life is fully under the control of hormones.

Changes that happen during development are far less reversible [than those occurring in an adult]; you can't go back and rewire the brain”.

-Theo Colborn, zoologist, writer
<table>
<thead>
<tr>
<th>Early Prenatal</th>
<th>Mid-Late Prenatal</th>
<th>Postnatal</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Central nervous system</strong> (3wks - 20 years)</td>
<td><strong>Ear</strong> (4-20 wks)</td>
<td><strong>Birth</strong> – 25 years</td>
</tr>
<tr>
<td><strong>Heart</strong> (3-8)</td>
<td><strong>Kidneys</strong> (4-40 wks)</td>
<td></td>
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<tr>
<td><strong>Limbs</strong> (4-8wks)</td>
<td><strong>Immune system</strong> (8-40 wks; competence &amp; memory birth-10yrs)</td>
<td></td>
</tr>
<tr>
<td><strong>Skeleton</strong> (1-12 wks)</td>
<td><strong>Lungs</strong> (3-40 wks; alveoli birth-10yrs)</td>
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<td><strong>Reproductive system</strong> (7-40wks; maturation in puberty)</td>
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<tr>
<th>Week 1-16</th>
<th>Week 17-40</th>
<th>Birth – 25 years</th>
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3. Hormones act at low doses

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Free concentration (females)</th>
<th>Total concentration (females)</th>
<th>Free concentration (males)</th>
<th>Total concentration (males)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estradiol</td>
<td>0.5 – 9 pg/ml (adult female)</td>
<td>&lt; 20 pg/ml (prepubertal) 20 - 800 pg/ml (premenopausal) &lt; 30 pg/ml (postmenopausal)</td>
<td></td>
<td>10 - 60 pg/ml (adult)</td>
</tr>
<tr>
<td>Progesterone</td>
<td>0.2 – 0.55 ng/ml (prepubertal) 0.02 – 0.80 ng/ml (follicular phase) 0.90 – 4 ng/ml (luteal phase) &lt; 0.5 ng/ml (postmenopausal)</td>
<td></td>
<td>0.1 – 0.4 ng/ml (prepubertal) 0.2 – 2 ng/ml (adult)</td>
<td></td>
</tr>
<tr>
<td>Insulin</td>
<td>0 – 250 pmol/L</td>
<td></td>
<td>0 – 250 pmol/L</td>
<td></td>
</tr>
<tr>
<td>Prolactin</td>
<td>0 – 15 ng/ml</td>
<td></td>
<td>0 – 10 ng/ml</td>
<td></td>
</tr>
<tr>
<td>Testosterone</td>
<td>9 – 150 pg/ml (adult)</td>
<td>0.3 – 250 ng/ml</td>
<td></td>
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<tr>
<td>Thyroid hormone</td>
<td>8 – 30 pg/ml (10-35 pM)</td>
<td>8 – 30 pg/ml (10-35 pM)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TSH</td>
<td>0.5 – 5 μU/ml</td>
<td>0.5 – 5 μU/ml</td>
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</table>
DES and Obesity

Newbold et al. 2009

- 1000 ppb exposures cause weight loss (not shown here)
- 1 ppb exposures cause extreme obesity
Atrazine: disruptions to sexual development

Hayes et al. 2010
4. Hormones have very specific interactions with receptors

- Hormone receptors are the “business end” of hormones.
- EDCs interfere in some way with the ability of hormone to activate its receptor.
Response can be modulated by changing receptor number, hormone concentration, etc.
5. The relationship between hormones and effect is rarely linear, and often non-monotonic

Houshmand et al. 2009
Odds of type II diabetes

Lee et al. 2014

Sextiles of summary measure of 31 POPs

$P_{\text{quadratic}} = 0.04$
There is a strong case that EDCs affect human health.

Even low exposures to EDCs can induce adverse health effects.

Human and animal studies support causal relationships between EDCs & disease.

Many endocrine diseases are increasing in prevalence.

Animal studies have helped to identify the mechanisms by which EDCs cause harm.
More educational materials available from the Endocrine Society

- [www.endocrine.org/edc](http://www.endocrine.org/edc)

- Scientific statements:
  - Diamanti-Kandarakis et al., *Endo Reviews* 2009
  - Gore et al., *Endo Reviews* 2015

- Position statements:
  - Zoeller et al., *Endocrinology* 2012

- Policy perspectives:
  - Vandenberg, *Endocrinology* 2016

- More:
  - Vandenberg et al., *Endo Reviews* 2012