Health Effects of Perinatal Exposure to Endocrine Disrupting Chemicals: State of the Science

Nicole Acevedo, Ph.D.
Tufts University School of Medicine, Boston, MA

Collaborative on Health and the Environment (CHE)-Alaska
December 10, 2014
THE ENDOCRINE SYSTEM

- Endocrine glands secrete molecules (hormones) directly into bloodstream to produce effects on distant target cells/tissues.

- Major hormone organs/systems include:
  - Hypothalamus
  - Pituitary
  - Stomach
  - Pancreas
  - Adipose Tissue
  - Adrenals
  - Cardiovascular
  - Thyroid/Parathyroid
  - Liver
  - Stomach
  - Mammary gland
  - Ovary/Uterus (female)
  - Testis/Prostate (male)
  - Placenta (female)
HORMONE ACTION ON TARGET TISSUES

- Hormones exert effects via binding to high affinity receptors in target tissues.
- In adults, hormones have transient effects on target tissues.
- Low concentrations sufficient to initiate large biological effects.
- Dose-responses to naturally circulating hormones are non-linear (non-monotonic):

![Graphs showing dose-response relationships](image)
Hormone actions during development program postnatal function of target tissues.

- Estrogen/androgen and reproductive axis
- Thyroid hormone and brain development

Impairment of proper hormone action during development can lead to irreversible health outcomes later in life.
LESSONS ON DEVELOPMENTAL EXPOSURE TO SYNTHETIC HORMONES: THE DES STORY

- Young women exposed in utero to DES have been diagnosed with reproductive tract malformations, infertility, and rare vaginal cancers.
- Recent studies show that as these exposed women reach the age where breast cancer is likely to manifest (≥ 40 years of age), they experience a 2.5-fold greater risk of developing cancer compared to age-matched women not exposed fetally to DES.
What are Endocrine Disrupting Chemicals (EDCs)?

- (1991) Wingspread Conference convened to review evidence for endocrine disruption in developing organisms via exposure to synthetic chemicals introduced into the environment by human activity since the mid-1950s.
  - Hypothesis: fetal exposure to hormonally-active chemicals may be contributing to increasing epidemiological trends in altered metabolism, reproduction, behavior, immune, cardiopulmonary, and brain function, as well as in rates of cancer.

- (1996) Executive order for the US EPA to develop the Endocrine Disruptor Screening Program (EDSP):
  - Test chemical substances for ability to produce effects similar to those produced by estrogen, androgen and thyroid systems.
What are Endocrine Disrupting Chemicals (EDCs)?

- **(2002):** World Health Organization (WHO)-International Programme on Chemical Safety:
  - Defined an endocrine disruptor as “an exogenous substance or mixture that alters function(s) of the endocrine system and consequently causes adverse health effects in an intact organism, or its progeny, or (sub) populations.”
  - Determined need for “broad, collaborative, and international research initiatives” to provide evidence for adverse human health effects following exposure to chemicals that can affect the endocrine system.

Categories of Some Known Endocrine Disruptors

- Pharmaceutical estrogens: diethylstilbestrol (DES).
- Phytoestrogens: plant-derived estrogens: genistein
- Persistent Organic Pollutants (POPs): by-products of burning process, chlorine bleaching, or manufacture of pesticides/herbicides or industrial chemicals.
  - Dioxins: classified human carcinogen.
  - Pesticides/Herbicides/Fungicides: i.e. DDT/DDE, atrazine, vinclozolin.
  - Organotins: Tributyltin (TBT)
  - Polybrominated diphenyl ethers (PBDEs): flame-retardant chemicals; used in many consumer products.
  - Perchlorate: additive for many industrial products; rocket fuel.
  - Perfluorinated chemicals (PFCs): non-stick cookware; completely resistant to biodegradation!
- Plasticizers: polyvinyl chloride (PVC) and polycarbonate plastics used for many consumer and medical device products.
  - Phthalates
  - Bisphenol A (BPA)
- Heavy Metals:
  - lead, cadmium, mercury, arsenic
Sensitivity of Endocrine Tissues to EDCs

Areas of potential disruption:

- Hormone synthesis.
- Receptor function (affinity vs potency).
  - Simultaneous interaction with multiple hormone receptors.
- Interference with developmental programming of tissues/organs.
  - Prenatal exposure may alter response of a tissue to hormone exposures in adulthood.
- Epigenetic processes that produce heritable transgenerational effects.
- Effects of mixtures with endogenous hormones and/or other EDCs.
# EDCs and Reproductive Health

Documented endocrine disruption in human, primate, or rodent models

<table>
<thead>
<tr>
<th>Female</th>
<th>Male</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset of puberty (dioxins)</td>
<td>Reduced semen quality (phthalates, dioxins, PCBs)</td>
</tr>
<tr>
<td>Altered endogenous estradiol (phytoestrogens, phthalates, chlorinated pesticides)</td>
<td>Altered endogenous testosterone (DES, dioxins)</td>
</tr>
<tr>
<td>Reduced fertility/fecundity (DES, TBT, phthalates, dioxins, BPA)</td>
<td>Cryptorchidism (DES, phthalates, dicarboximide fungicides)</td>
</tr>
<tr>
<td>Adverse pregnancy outcomes (TBT)</td>
<td>Hypospadias (phthalates, chlorinated pesticides, dicarboximide fungicides)</td>
</tr>
<tr>
<td>Ovarian abnormalities (DES, chlorinated pesticides, phytoestrogens, BPA)</td>
<td>Reduced anogenital distance (phthalates, chlorinated pesticides, dioxins, PCBs, dicarboximide fungicides)</td>
</tr>
<tr>
<td>Uterine abnormalities (DES, phytoestrogens, phthalates, dioxins, BPA)</td>
<td>Altered sexual behavior (PCBs)</td>
</tr>
<tr>
<td>Endometriosis (phthalates)</td>
<td>Erectile dysfunction (BPA, phytoestrogens)</td>
</tr>
<tr>
<td></td>
<td>Accessory sex organ abnormalities (dicarboximide fungicides)</td>
</tr>
</tbody>
</table>

(UNEP State of the Science of Endocrine Disrupting Chemicals (2012))
Implications of EDCs on other developmental endpoints

**Impaired Neurodevelopment**
- General cognitive deficits (PCBs, PBDEs, perchlorate)
  - Thyroid hormone insufficiency (PCBs)
- Attention deficit disorders (PCBs, BPA, PBDEs, phthalates)
- Altered organization of sexually dimorphic regions in the brain (BPA, phthalates)

**Metabolic Dysregulation**
- Obesity (TBT, phytoestrogens, PFCs, PBDEs, BPA, PCBs, DES)
- Type 2 diabetes (PCBs, DDE, dioxin, pesticides, arsenic, flame-retardants)

**Impaired Immune Function**
- Allergies (triclosan)
- Endometriosis (phthalates, possibly PCBs and dioxins)
- Auto-immune thyroid disease (PCBs)
- Asthma (phthalates)
- Inflammation (BPA)

(WHO-UNEP State of the Science of Endocrine Disrupting Chemical (2012))
EDCs and Hormone-related cancers

- Breast Cancer: DES, BPA
- Endometrial Cancer: DES
- Prostate Cancer: pesticides, arsenic
- Testicular Cancer: POPs

Major challenges regarding determination of carcinogenic potential of EDCs:

- Human epidemiological studies cannot easily examine effects of single chemicals.
- Valid animal models are not currently available for investigation of most endocrine-mediated cancers in humans.

(WHO-UNEP State of the Science of Endocrine Disrupting Chemical (2012))
Major challenges regarding identification of EDCs and determination of adverse health effects

- Inherent limitations of current testing methods for identification of EDCs.
  - Process further complicated by the ideological conflict between toxicologists and endocrinologists regarding possible low-dose effects and non-monotonic responses of EDCs.

- Incomplete assessment of all windows of susceptibility and routes of exposure for known and possible EDCs.

- Very little data is available on the health impacts of chemical mixtures.

- Need for widely-accepted system to evaluate the strength of evidence of exposures to possible EDCs and adverse health outcomes.

- Lack of consistent international regulatory standards for the manufacture and regulation of chemicals leads to exponential increases in the global burden of chemicals.
RESOURCES


• The Endocrine Disruption Exchange (TEDX) website: excellent resource for up-to-date information on the state of endocrine disruptor research.
  http://endocrinedisruption.org/

• US EPA Endocrine Disruptor Screening Program (EDSP) homepage:
  http://www.epa.gov/endo/