Overview of Endocrine Disruptor Action: Should We Be Concerned?

Jerrold J. Heindel, PhD
National Institute of Environmental Health Sciences
National Institutes of Health/DHHS

heindelj@niehs.nih.gov
We all Carry a Chemical Body Burden

- 287 chemicals in cord blood
- 47 chemicals in every pregnant woman tested
- In breast milk (PCBs, dioxins, pesticides, mercury, flame retardants)
- Of people tested by CDC:
  - BPA in 93%
  - Phthalates 50-97%
  - PFCs in 91-99%
  - PBDEs in 100%
  - Triclosan in 80%
  - PCBs in 100%

The presence of chemicals in the womb does not mean that they are causing harm.

However, it does mean that we have accepted a strategy whereby every pregnant woman is contaminated with hundreds of man made chemicals …without her consent….with the potential to cause harm.
Endocrine Disruptor Definition

An Endocrine Disruptor is an exogenous chemical, or mixture of chemicals, that interferes with any aspect of hormone action.

Endocrine Disrupting Chemicals

**HERBICIDES**
- Alachlor
- Amitro
- Atrazine
- Trifluralin

**FUNGICIDES**
- Benomyl
- Ethylene thiourea
- Fenarimol
- Hexachlorobenzene
- Mancozeb
- Maneb
- Metiram
- Tri-butyl-tin
- Vinclozolin
- Zineb

**INSECTICIDES**
- Aldicarb
- beta-HCH
- Carbaryl
- Chlordane
- Chlordecone
- DBCP
- Dieldrin
- DDT and metabolites
- Endosulfan
- Heptachlor / H-epoxide
- Lindane (gamma-HCH)
- Malathion
- Methomyl
- Methoxychlor
- Oxychlordane
- Parathion
- Synthetic pyrethroids
- Transnonachlor
- Toxaphene
- Plastics
- Bisphenol-A
- Polycarbonates
- Butylhydroxyanisole
- Cadmium
- Chloro & Bromo-diphenyl
- Dioxins
- Furans
- Lead
- Manganese
- Methyl mercury
- Nonylphenol
- Octylphenol
- PBDEs
- PCBs
- Pentachlorophenol
- Pent- to Nonylphenols
- Perchlorate
- PFOA
- p-tert-Pentylphenol
- Phthalates
- Styrene

**METALS**
- Tris
- Zinc

**INDUSTRIAL CHEMICALS**
- Bisphenol-A
- Polycarbonates
- Butylhydroxyanisole
- Cadmium
- Chloro & Bromo-diphenyl
- Dioxins
- Furans
- Lead
- Manganese
- Methyl mercury
- Nonylphenol
- Octylphenol
- PBDEs
- PCBs
- Pentachlorophenol
- Pent- to Nonylphenols
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**OVER 900 EDCs**

**Testosterone synthesis inhibitor**
**Thyroid hormone disruptor**
**Estrogen receptor agonist**
**Androgen receptor antagonist**
Principles of Endocrine Disruptor Action

• Many EDCs act via **Receptors:**
  – EDC response depends on concentration, receptor affinity and co-regulatory proteins.
  – EDC responses are **tissue specific.**
  – Receptor cross talk at high doses.
• EDCs can act at **Low Doses** throughout the lifespan.
• EDCs can show **Non-Monotonic Dose-Response Curves.**
• EDC effects are **Life-Stage Specific**
EDC Action is Life-stage Specific

Developmental Effects (Organizational)
- Most sensitive exposure window
- Stage and tissue specific
- Lack of feedback mechanisms
- Immature metabolic capability
- Epigenetic directed differentiation
- Functional changes leading to persistent and latent effects
- Increased disease risk later in life

Adult Effects (Activational)
- Usually higher doses
- Effects as long as EDC present
- Can augment developmental effects

A bad start...lasts a lifetime!
Epigenetics

• Epigenetics provides cells the capability to sense, interpret, and act upon environmental stimuli by modifying gene expression.

• Epigenetics provides plasticity that allows adaptation during times of early environmental stressors such as prenatal nutrition, stress and environmental chemical exposures…many positive adaptive effects.

• Epigenetic changes can be persistent across cell divisions and generations but are also dynamic across a lifetime.

Why is Development a Sensitive Window?
Disease Risk Increased by Developmental Exposures to EDCS (Human)

**Reproductive/Endocrine**
- Breast/prostate cancer (BPA)
- Endometriosis (Dioxin, PCBs)
- Infertility (Phthalates, Estrogens, Pesticides)
- Diabetes/metabolic syndrome (BPA)
- Early Puberty (Estrogens, BPA)
- Obesity (BPA, Tributyl Tin, Organochlorine Pesticides)

**Immune/Autoimmune**
- Susceptibility to infections (Dioxin, Perfluorinated compounds, Arsenic)
- Autoimmune Disease (Dioxin)

**Pulmonary/Cardiovascular**
- Asthma (Air Pollution)
- Heart disease/hypertension (BPA)
- Stroke (PCBs)

**Brain/Nervous System**
- Alzheimer's disease (Lead)
- Parkinson’s disease (Pesticides)
- ADHD/learning disabilities (PCBs, Lead, Ethanol, Organochlorine, Pesticides)
EDCs: Should We Be Concerned?

- The high incidence and the increasing trends of many endocrine-related disorders in humans;
- Observations of endocrine-related effects in wildlife populations;
- The identification of chemicals with endocrine-disrupting properties linked to disease outcomes in laboratory and human studies;
- Increased numbers of chemicals with endocrine-disrupting properties (beyond E, A, T) along with new sites of action;
- Increased body burden of EDCs across the globe;
- Lack of knowledge of sources of EDCs;
- Inadequate testing.

There are no longer any pristine areas in the world devoid of environmental contamination!
Implications of Principles of Endocrinology for EDC Toxicity Testing and Human Health

• High dose effects are likely to be nonspecific.
• Need wide dose responses covering “low dose” concentrations.
• High dose effects don’t predict low dose effects.
• Can’t extrapolate from high dose studies to what will happen at lower untested doses.
• Must test developmental exposures and assess effects across lifespan.
• Must test mixtures.
• Need improved testing protocols to take account these characteristics of EDCs.
The Good News….

Focus on:

• Prevention of Disease
  – Focus on pregnancy, early childhood and puberty as sensitive periods
  – Reduced exposures to environmental agents during development

• Development of biomarkers to indicate developmental exposures

• Improved toxicity testing

• Green chemistry…improved next generation chemicals
Not the End... but the end of the beginning

Bemidji Statement:

“We have the sacred right and obligation to ensure that our decision-making is guided by consideration of the welfare and well being of the seventh generation to come.”

Thank you...