Effects of EDCs on Reproduction: Reducing Scientific Uncertainties

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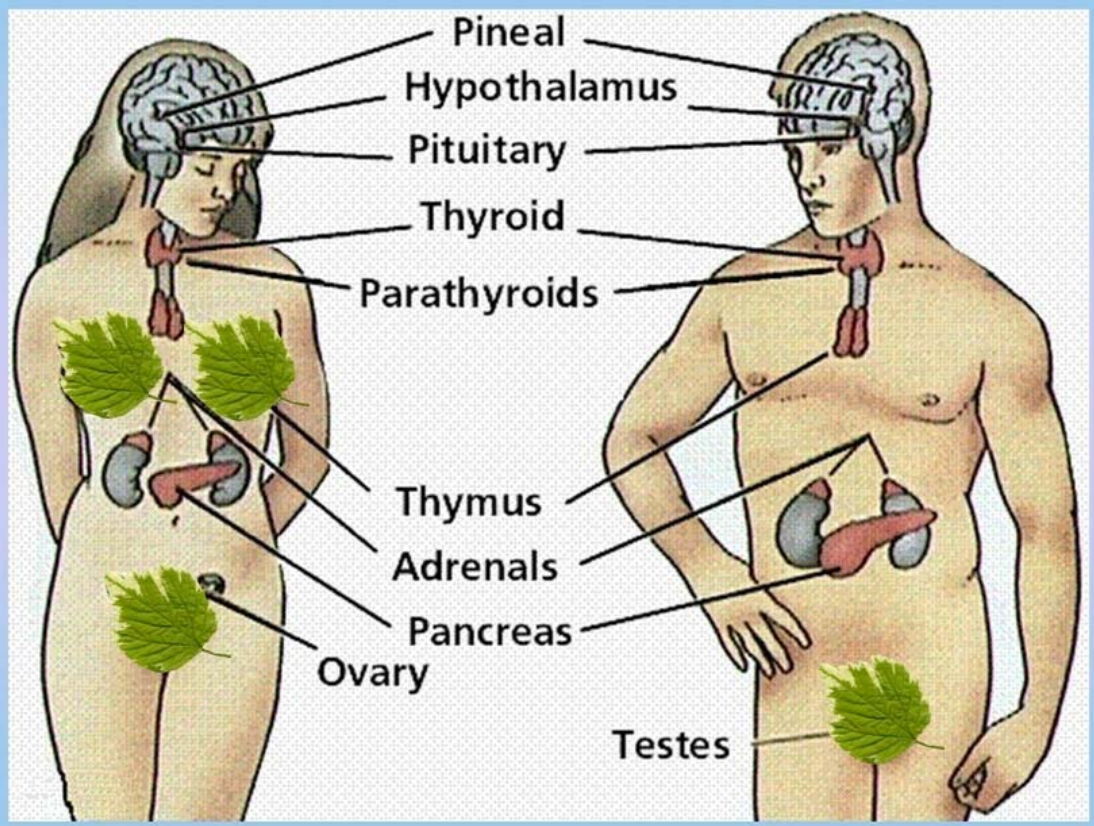
Endocrine System



- Metabolism
- Digestion
- Reproduction
- Stress
- Physiological Homeostasis

Endocrine System

- A complex network of coordinated regulatory changes
- Functions to maintain a homeostatic balance through hormonal feedback loops
- Presents a variety of targets for EDCs
  - Receptor mediated mechanisms
  - Hormone synthesis and clearance
  - Hormone storage and release
  - Hormone transport

Endocrine Disruptor

- An exogenous substance or mixture that alters the function(s) of the endocrine system and consequently causes adverse health effects in an intact organism, or its progeny, or (sub)populations.

(IPCS, 2002)

Effects of EDCs on Reproduction: Lines of Evidence

- Endocrine disruption in laboratory based toxicology studies
- Adverse effects observed in wildlife, fish and ecosystems
- Increased incidence of endocrine-related human diseases

Experimental Evidence:
Laboratory Based Toxicology Studies

- EDCs, by a variety of mechanisms, can have adverse effects on the reproductive system.
- Exposure during reproductive development and various life stages can produce different adverse effects.

Experimental Evidence: Laboratory Based Toxicology Studies

- Effects on the developing reproductive tract following in utero and/or lactational exposure
  - Phenotype in exposed offspring: Malformations, masculinization/feminization, reduced fertility, latent effects
  - Estrogens (DES, methoxychlor, ethynyl estradiol)
  - Anti-androgens (vinclozolin, p,p' DDE, phthalates, prochloraz)
  - Steroid synthesis inhibitors (prochloraz, fenarimol, ketoconazole, dibromoacetic acid)
  - Ah Receptor Agonists (Dioxin, PCBs)
  - CNS (Atrazine)
  - Androgens (Trenbolone)

Experimental Evidence: Laboratory Based Toxicology Studies

- Effects of EDCs on reproduction following exposure during adulthood
  - Female (Disruption of cyclicity, ovulation and/or pregnancy, early reproductive senescence, mammary tumors)
    - Atrazine, Thiram (CNS mode of action, LH surge)
    - Nonylphenol, ethynyl estradiol, methoxychlor (ER)
  - Male (Disruption of spermatogenesis, reduced testosterone, Leydig cell hyperplasia, infertility)
    - Vinclozolin, PBDE-71,methoxychlor (AR)
    - Ketoconazole, prochloraz (steroid inhibitor)

Impact:
Laboratory Based Toxicology Studies

- Confirmation of endocrine disruption resulting from exposure to a wide array of chemicals
- Identification of modes of action
- U.S. EPA's Endocrine Disruptor Screening Program
  - Tier I Screening Battery (incorporates MOA for estrogen, androgen and thyroid hormone systems, HPG) (http://www.epa.gov/scipoly/oscpendo/assayvalidation/consider.htm)

Reported Wildlife Effects

Studies in environments with high levels of persistent organic pollutants

- The Baltic Sea: (DDE, PCBs). Immune and reproductive impairment in marine mammals; Lowered reproductive capacity in birds; Low survival rate of salmon. (MOA unclear)
- The Great Lakes: (TCDD, PCBs). Poor reproduction in fish (salmon, lake trout) and birds (gulls, terns, cormorants, bald eagles). (EDC MOA unclear).

Reported Wildlife Effects

Studies in environments with accidental spills:

- **Lake Apopka, FL**. (dicofol) Population decline in alligators, evidence gonadal and developmental abnormalities with altered sex steroid level. Supporting lab data. (EDC MOA unclear)
- **Sewage Treatment Plant, England**. (Estrogenic compounds). Increases in vitellogenin production and intersex in fish. Caging of naïve fish near source and lab studies support association. (EDC MOA strong).
- **Concentrated Animal Feed Lots (CAFOs) Effluent**. (Androgens, trenbolone). Altered steroid levels in fish. Lab studies masculinized fish and female rat offspring. EDC MOA strong.

Possible Human Health Effects

- Human male reproductive disorders.
  - Declining sperm counts. (Temporal and geographical differences).
  - Association between sperm quality and occurrence of malformations (undescended testes, hypospadias) and testicular cancer. (Testicular dysgenesis syndrome)
  - Changes in fertility rates

Cause-and-effect relationships weak

MOAs unclear

Possible Human Health Effects

- Human female reproductive disorders.
  - Infertility and spontaneous abortions
  - Shortened lactation
  - Endometriosis
  - Precocious puberty
  - Breast cancer
  - Polycytic ovary syndrome

Cause-and-effect relationships equivocal

MOAs unclear

Conclusions: Lines of Evidence

- "Although it is clear that certain environmental chemicals can interfere with normal hormonal processes, there is weak evidence that human health has been adversely affected by exposure to EDCs. However, there is sufficient evidence to conclude that adverse ED effects have occurred in some wildlife species. Laboratory studies support these conclusions."

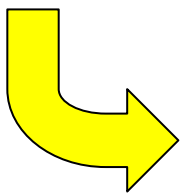
  IPCS (Global Assesment, 2002)

RESEARCH & DEVELOPMENT

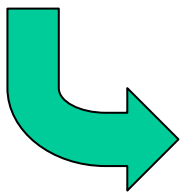
Building a scientific foundation for sound environmental

Criteria For Causality

Statement of Hypothesis
- Outcome of concern
- Exposure of Concern



Assessment Factors
- Temporality
- Strength of association
- Consistency
- Biological Plausibility
- Recovery



Overall Strength of Evidence
- For the outcome
- For the hypothesis
- For an EDC mechanism

Impact

Criteria for Assessing EDCs

Stressor → Adverse Outcome

Stressor → EDC Mechanism

Temporality, Strength of Association, Consistency, Biological Plausibility, Recovery

- Endometriosis (W,M)
- Breast Cancer (W,W)
- Neurobehavioral Development (M,M)
- Early Puberty
- Male Reproductive Health malformations, semen quality (W,W), cancer]
- Altered Immune Function (M,W)
- Shortened Lactation

- Imposex (S,S)
- GLEMEDS (S,W)
- Egg Shell Thinning (S,M)
- Lake Ontario Trout (S,W)
- Apopka Alligators (S,W)
- Vitellogenin in UK (S,S)
- Bleached Kraft Mill Effluent (S,S)
- Limb Malformations in Frogs (W,W)

Hypothesis/EDC Mechanism

Biological Plausibility of EDC Action

Reducing Uncertainties

Exposure-Outcome Relationships

- Latency
- Persistent vs. non-persistent contaminants
- Fate and transport
- Isolated case versus global response

Comparative toxicology

- Degree of homology between species

Dose-response relationships

- Shape, low dose effects, timing of exposure

Biological Plausibility of EDCs Action

Reducing Uncertainties

Chemical diversity

- Structure and potency

Multiple mechanisms of action

- Receptor, co-factors and co-repressors
- Dissimilar modes with similar phenotypes
- Polymorphisms

Cumulative exposures and effects

Summary

- Although no strong exposure-outcome relationship for human reproductive effects, laboratory based tox. studies and observation of adverse effects in wildlife in high exposure areas warrant attention.
- Hill Criteria provides framework for objective evaluation of EDC data.
- Research needed to address scientific uncertainties.

STAR Grant Presentations

- *Persistent Organic Pollutants and Endometriosis Risk*, Dr. Victoria Holt, Fred Hutchinson Cancer Research Center
- *Study of Phthalates in Pregnant Women and Children*, Dr. Shanna Swan, U. Missouri
- *Latent Effects of Gestational Exposure to Heptachlor*, Dr. Dean Baker, UC-Irvine