Endocrine Disrupter Chemicals: the right to know

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Concern started
EDC-2: The Endocrine Society’s Second Scientific Statement on Endocrine-Disrupting Chemicals


*Endocrine Reviews* 36:E1–E150, 2015
Outline

1. 25 years since the first reports on EDCs
2. Developmental Origins of Health and Disease (DOHaD)
3. Metabolism disrupter chemicals (MDCs)
4. Environmental Health - curriculum HCPs
5. New generations and health
Definitions of EDCs

“…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.” (ICPS, 2012)

“… an exogenous chemical, or mixture of chemicals, that interferes with any aspect of hormone action” (Endocrine Society)

estrogen, androgen and thyroid hormone
Characteristics of **hormones**: implications during development

- levels, receptors, physiological responses change intensely across the life cycle

- appropriate levels hormones during early development – fetus and infant

- disorders of sexual development e.g. abnormal androgen or estrogen levels
Characteristics of **EDC**: implications for developmental exposures

- EDCs can mimic or antagonize hormonal systems and change the developmental pathway
- Timing of exposure, nature of the EDC, and its levels, an adverse outcome may be evident at birth, or later in life
- Result from changes in gene expression
  - Altered protein levels etc
  - Tissue more susceptible disease and dysfunction across lifespan

Developmental Origins of Health and Disease (**DOHaD**)
RISKS RELATED TO WINDOWS OF EXPOSURE

Early prenatal week 1-16

Central nervous system (3wks - 20 years)
Ear (4-20 wks)
Kidneys (4-40 wks)
Heart (3-8)
Limbs (4-8w)
Skeleton (1-12w)

Late prenatal week 17-40

Immune system (8-40 wks)
Lungs (3-40 wks; alveoli birth-10yrs)
Reproductive system (7-40wks; maturation in puberty)

Postnatal Birth -25 years

Week 1-16
Week 17-40
Birth – 25 years
Diethylstilbestrol (DES)

- First orally active synthetic estrogen 1938
- Since 1947 prescribed to prevent abortion
- 1970 first case clear cell vaginal cancer
- 1971 more cases, FDA withdrew DES
- Not effective, in fact worse
First Report of endocrine disruption in humans
Reproductive health changes reported in men

Evidence for decreasing quality of semen during past 50 years

Elisabeth Carlsen, Aleksander Giwercman, Niels Keiding, Niels E Skakkebæk

BMJ. 1992 Sep 12; 305(6854): 609–613

Scientific reaction to the news of declining sperm-counts was mixed.
Reproductive health changes reported in men

Possible *carcinoma-in-situ* of the testis.
Skakkebaek NE. Lancet. 1972

Germ cell neoplasia *in situ* (GCNIS): testicular pre-invasive germ cell malignancy Berney et al., Histopathology 2016

“Whistleblower” for EDC and MRH
Testicular Dysgenesis Syndrome

Environmental factors incl. endocrine disrupters

Disturbed Sertoli cell function → Impaired germ cell differentiation → REDUCED SEMEN QUALITY

Androgen insufficiency → HYPOSPADIAS

Decreased INS13 expression → CRYPTORCHIDISM

Genetic defects e.g. 45,X/46, XY, point mutations

TESTICULAR DYSGENESIS

Skakkebaek et al., 2001
MRH abnormalities DES sons

- hypoplastic testis
- epididymal cysts
- cryptorchidism
- hypospadias

Giusti et al., Ann Intern Med 1995
Hypospadias in grandsons
multigenerational national cohort study

• Grandmother received DES
• Mother exposed *in utero*
• Third-generation hypospadias grandsons

Kalfa et al., Fertility and Sterility, 2011
Mechanism permanent reprogramming tissue development after chemical exposures

- likely epigenetic mechanisms
  - DNA methylation
  - post-translational modifications of histones
  - noncoding RNA
- alter enzymes and gene expression
- tissue permanently functionally changed
- results in increased sensitivity to disease
Decline sperm count??
24 years later

- Japan and European Union persistently low total fertility rates (TFR) below replacement level (2.1 child per woman)
- male reproductive problems: testicular cancer, DSD, cryptorchidism, hypospadias, low T levels, poor semen quality, changed sex ratio, more ART
- several adult MRH problems arise *in utero* as signs of TDS and exposures
- environmental exposures arising from modern lifestyle most NB
- epigenetic mechanisms - impact several generations post-exposure

Skakkebaek et al. Physiological Reviews 2016
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Endocrine Reviews 36:E1–E150, 2015
EDC-2 on EDCs

STRONG EVIDENCE OF ENDOCRINE DISRUPTION

1. obesity and diabetes
2. female reproduction
3. male reproduction
4. hormone-sensitive cancers in females
5. prostate
6. thyroid
7. neurodevelopment and neuroendocrine systems

Andrea C Gore et al., 2015
EDC-2 on EDCs

CHEMICALS WITH INFORMATION AVAILABLE

• Bisphenol A
• Phthalates
• Pesticides
• Persistent organic pollutants such as DDT, PCBs, PBDEs, and dioxins

Andrea C Gore et al., 2015
Quantify EDC disease burden and costs

• For EDCs, laboratory evidence is supplemented by varying levels of epidemiologic evidence
  • each condition is clearly multifactorial

• Absent estimates of the burden of disease and disability potentially produced by EDC exposures, high costs of alternatives are likely to outweigh concerns about the health consequences of using EDCs.

• Expert panels quantified EDC disease burden and COST OF INACTION
The objective was to quantify a range of health and economic costs that can be reasonably attributed to EDC exposures in the European Union (EU).
EDC exposures EU likely contribute substantially to disease and dysfunction across the life course with costs in the hundreds of billions of Euros per year. These estimates represent only those EDCs with the highest probability of causation; a broader analysis would have produced greater estimates of burden of disease and costs.
Pesticides used in agriculture and homes

$\text{€} = \text{R}\text{17.86}$

- 13 million lost IQ points in each EU country $\rightarrow \text{€124B}$ lost earning potential
  
  $\rightarrow 59,300$ born each year with intellectual disability = additional $\text{€21.4B}$

- 1,555 obese 10 year olds = $\text{€24.6M}$

- 28,200 50–64 year olds with diabetes = $\text{€835M}$

Bellanger et al, Legler et al J Clin Endo Metab epub Mar 5 2015
Phthalates used in food wraps, cosmetics, shampoos, vinyl flooring

- 24,800 additional deaths 55 – 64 year old men = €7.96B lost economic productivity

- 618,000 additional assisted reproductive technology procedures costing €4.71B

- 53,900 50-64 year old women obese = €15.6B

- 20,500 50-64 year old women diabetic = €607M

Hauser et al, Legler et al  J Clin Endo Metab epub Mar 5 2015
Flame retardants used in electronics, furniture, mattresses

- 873,000 lost IQ points $\rightarrow €8.4B$ lost earning potential
- $\rightarrow 3,290$ intellectually disabled children = additional €1.9B
- 6,830 new cases of testicular cancer = €850M
- 4,615 boys born with undescended testis = €130M

Bellanger et al, Hauser et al J Clin Endo Metab epub Mar 5 2015
25 Years of Endocrine Disruption Research: Past Lessons and Future Directions

A Celebration of the People and the Science

September 18-20, 2016

Agenda

National Institutes of Health • U.S. Department of Health and Human Services
Metabolism Disrupter Chemicals

• obesity and metabolic syndrome diseases global epidemic

• environmental obesogen model proposes that chemical exposure during critical developmental stages influences subsequent adipogenesis, lipid balance and obesity.

• Tributyltin (TBT) is a high-affinity agonistic ligand for the retinoid X receptor (RXR) and peroxisome proliferator activated receptor gamma (PPARγ).

• RXR-PPARγ signaling is a key component in adipogenesis and the function of adipocytes; activation of this heterodimer increases adipose mass in rodents and humans

Bruce Blumberg, 2011
the findings numerous animal and epidemiological studies consistent with the hypothesis that environmental pollutants could contribute to the global obesity epidemic
Way forward

• **critical life stages**: perturbations of hormones can increase probability of disease or dysfunction later in life

• fuller understanding of endocrine principles by which EDCs act:
  – including non-monotonic dose-responses
  – low-dose effects
  – developmental vulnerability

• **healthcare providers to translate the science of endocrine disruption to improve public health**

Andrea C Gore et al., 2015
The Right to Know
Universal Access to Healthcare

• training curricula to include EDCs
• information on self protection and limitation of exposure
• labelling clear
• We must read labels!
• high index of suspicion
• printed and digital media
DDT Exposure *in Utero* and Breast Cancer

- **Outcome:** Daughters’ breast cancer 52 years F2

- **Results:** Maternal *o,p’*-DDT predicted daughters’ breast cancer (OR 4th vs first 3.7, 95% confidence interval 1.5–9.0).

- **Conclusions:** prospective human study linked DDT exposure *in utero* to risk of breast cancer in daughters

Cohn et al., J Clin Endocrinol Metab 2015; 100: 2865-2872
DDT Exposure *in Utero* and Breast Cancer

- DDT is still used in specific areas (e.g., Africa) for malaria vector control.

- Human populations have been and continue to be exposed to high levels of DDT (and thus to DDE), making potential transgenerational effects a real concern.

Cohn et al., J Clin Endocrinol Metab 2015; 100: 2865-2872
Challenge in Africa: 2012

Infectious killers

1. HIV/AIDS
2. Malaria
3. TB
4. acute respiratory infections
5. diarrhoeal disease
6. vaccine-preventable diseases

Brundtland, 2002; Boutayeb, 2006

malnutrition common contributor

~2020 NCD (ie. DM, HT) cause 7/10 deaths
Africa’s shifting burden of disease

• Diabetes
• Obesity and Lifestyle-related diseases
Knowing is not enough; we must apply.

Willing is not enough; we must do.

Johann Wolfgang von Goethe
The health of the next generations is in our hands!