Endocrine Disrupting Chemicals & Their Health Effects

Laura N. Vandenberg

University of Massachusetts – Amherst (USA)
The 1940’s led to a hunt for synthetic hormones

Estradiol

DES

BPA
Diethylstilbestrol (DES)

- **birth control**
- **treatment of menopause symptoms**
- to stop lactation
- Prevent spontaneous miscarriage
The tragedy of diethylstilbestrol

Given to between 2 and 10 million pregnant women in the US between the years of 1948 and 1971.

Clear cell adenocarcinoma of the vagina is detected in exposed daughters

Banned in the US in 1971, but continued to be used in other countries until the 1980s.
What are Endocrine Disrupting Chemicals (EDCs)?

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

1. Endocrine cells release hormone.
2. The hormone enters the blood and is carried throughout the body.
3. The hormone leaves the capillaries and diffuses to all tissues through the extracellular fluid.
4. The hormone affects cells bearing receptors to which the hormone can bind.
5. The hormone cannot affect cells that only bear receptors to which the hormone cannot bind.
Suspected EDCs

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

Sources of exposure
The UNEP/WHO report (2012)

(1) Data from controlled laboratory studies confirm that chemicals can contribute to endocrine disorders. Many of these diseases have been observed in humans and wildlife populations.

(2) Wildlife populations are affected by EDC exposures with negative effects specifically observed on growth and reproductive endpoints.

(3) The methods that are widely used to identify and evaluate the safety of EDCs examine only limited endpoints, missing a large fraction of the known spectrum of endocrine disrupting effects.
Today, I hope to impress upon you that:

One. EDCs are a threat to human and environmental health, even when exposures are “low”

Two. Hazards/Risks are not borne evenly across populations

Three. The ways we are testing chemicals for safety are insufficient to protect public health
1. EDCs are a threat to human and environmental health, even when exposures are ‘low’

Disrupted sexual differentiation of frogs exposed to herbicides

Abnormal behaviors in rodents and children exposed to chemicals in plastics

Obesity in rodents exposed to chemicals in consumer goods

Breast cancer associated with exposure to legacy pesticides
When talking about environmental chemicals, what are low doses?

“LOW DOSES” FOR EDCs:

• BELOW AN OVERTLY TOXIC DOSE (KNOWN FROM PRIOR STUDIES)

• IN THE RANGE OF HUMAN EXPOSURES

• REPLICATE HUMAN SERUM LEVELS
Atrazine & male sexual differentiation, a fascinating example
Sexual differentiation in amphibians

On W chromosome, DM-W gene $\rightarrow$ aromatase expression
Atrazine: alters sexual differentiation after exposures to 1 ppb

Hayes et al. 2010
BPA alters brain development & behavior in rodents

Rubin et al. Endocrinology 2006
BPA and children’s behaviors

Prenatal exposures
- ↑ anxiety
- ↑ depression
- ↑ aggression
- ↑ hyperactivity

Childhood exposures
- ↑ anxiety
- ↑ conduct problems
- ↑ hyperactivity
- ↑ inattention
- ↑ depression

Obesity
Obesity

1. Increased adipogenic commitment
   - BADGE
   - Firemaster 550
   - Fludioxonil
   - Quinoxyfen
   - Tributyltin
   - Triflumizole

2. Increased adipocyte differentiation
   - Acetamiprid
   - BADGE
   - BDE-47
   - BPA
   - DES
   - Dioxin
   - Forchlorfenuron
   - Flusilazole
   - PCB-77
   - Pymetrozine
   - Quinoxyfen
   - Spirodiclofen
   - Triphenyltin
   - Triflumizole

3. Increased adipocyte proliferation (in vivo)
   - BPA
   - DES
   - Nicotine
   - PCB-77
   - Tributyltin

4. Increased lipid uptake (in vivo)
   - BPA
   - Nicotine
   - PCB-77
   - Tributyltin
EDCs and obesity in humans

Veiga-Lopez et al., Trends in Endocrinology & Metabolism (2018)
EDCs: Mammary Gland Development, Function & Breast Cancer

- Bisphenols
- Phthalates
- PFAS
- Dioxins & industrial chemicals
- Development
- PFAS
- DES
- DDT / DDE
- Bisphenols
- PFAS
- DES
- DDT / DDE
- Bisphenols
- Dioxins
- Cancer
- Phytoestrogens

Brody et al. Environ Health Perspect., 2011
Mammary Gland Development, Function & Breast Cancer

Many, many more examples...
2. Hazards / Risks are not borne evenly across populations

Hazard assessment

Exposure assessment

Dose response
Lessons from the Dutch Famine

- Survival
- Health
- Stroke
- Diabetes
- Cancer
Our developmental stage and physiology predicts if/how we will be affected by EDCs

<table>
<thead>
<tr>
<th>Week 1-16</th>
<th>Week 17-40</th>
<th>Birth – 25 years</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Early Prenatal</strong></td>
<td><strong>Mid-Prenatal</strong></td>
<td><strong>Late Prenatal</strong></td>
</tr>
<tr>
<td><strong>Central nervous system (3wks - 20 years)</strong></td>
<td><strong>Ear (4-20 wks)</strong></td>
<td><strong>Kidneys (4-40 wks)</strong></td>
</tr>
<tr>
<td><strong>Limbs (4-8wks)</strong></td>
<td><strong>Immune system (8-40 wks; competence &amp; memory birth-10yrs)</strong></td>
<td><strong>Skeleton (1-12 wks)</strong></td>
</tr>
<tr>
<td><strong>Reproductive system (7-40wks; maturation in puberty)</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Central nervous system** (3wks - 20 years)

**Ear** (4-20 wks)

**Kidneys** (4-40 wks)

**Heart** (3-8)

**Limbs** (4-8wks)

**Immune system** (8-40 wks; competence & memory birth-10yrs)

**Skeleton** (1-12 wks)

**Lungs** (3-40 wks; alveoli birth-10yrs)

**Reproductive system** (7-40wks; maturation in puberty)
“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
Exposures to EDCs vary widely across populations

Hazard assessment

Exposure assessment

Dose response
3. The ways we are testing chemicals for safety are insufficient to protect public health

- IDENTIFY LD50, MTD, LOAEL, NOAEL
- CALCULATE RFD (NOAEL/10, 100 OR 1,000)
- COMPARE THE RFD TO HUMAN EXPOSURE LEVELS
An illustration: perchlorate

NHANES 95th percentile: 0.234 µg/kg/day

<table>
<thead>
<tr>
<th></th>
<th>NOAEL</th>
<th>RfD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.007 mg/kg/day</td>
<td>0.0007 mg/kg/day (0.7 µg/kg/day)</td>
</tr>
</tbody>
</table>
An illustration: perchlorate

MATERNAL PERCHLORATE IN TOP 10%

OFFSPRING IQ IN LOWEST 10% AT AGE 3
Another illustration: Diisononyl Phthalate (DINP)

Human exposure range

Testing range in rats

AGD

NOAEL

Nipple retention

Testing range in rats

1

10

100

1,000

10,000

100,000

900,000

300,000

100,000

10,000

10

1

Another illustration: Diisononyl Phthalate (DINP)
So, what are we doing wrong?

Conflicts
- Most of the data used in regulatory decision-making were generated by groups with vested interests, and academic studies are ignored because of the regulatory framework
- The regulatory structure can prevent new data from being collected

Endpoints
- We might be good at evaluating toxicity, but these outcomes aren’t relevant to human diseases
- We can’t even agree on what is “adverse”

Doses
- EDCs, like hormones, have effects at low doses but these are rarely included in toxicity testing. Even if they are, the endpoints aren’t sensitive enough to detect adverse outcomes
- Effects observed at low doses are ignored if they aren’t observed at high doses
So, what are we doing wrong?

**Conflicts**
- Most of the data used in regulatory decision-making were generated by groups with vested interests, and academic studies are ignored because of the regulatory framework
- The regulatory structure can prevent new data from being collected

**Endpoints**
- We might be good at evaluating toxicity, but these outcomes aren’t relevant to human diseases
- We can’t even agree on what is “adverse”

**Doses**
- EDCs, like hormones, have effects at low doses but these are rarely included in toxicity testing. Even if they are, the endpoints aren’t sensitive enough to detect adverse outcomes
- Effects observed at low doses are ignored if they aren’t observed at high doses
What is an adverse outcome?

A change in:

- Biochemistry
- Physiology
- Growth
- Lifespan
- Development
- Behavior
- Response to stress
Standard Assays to evaluate Hazard
Conditions that are treated by the pharmaceutical industry are not considered “hazards” when induced by chemicals...
How we address uncertainties matters: experimental design in low dose studies
Incorporating more doses and more endpoints: revealing effects of BPA

- Prins et al. BCPT 2018; Vandenberg et al. Nat Reviews Endo 2019
So, what are we doing wrong?

Conflicts
- Most of the data used in regulatory decision-making was generated by groups with vested interests, and academic studies are ignored because of the regulatory framework
- The regulatory structure can prevent new data from being collected

Endpoints
- We might be good at evaluating toxicity, but these outcomes aren’t relevant to human diseases
- We can’t even agree on what is “adverse”

Doses
- EDCs, like hormones, have effects at low doses but these are rarely included in toxicity testing. Even if they are, the endpoints aren’t sensitive enough to detect adverse outcomes
- Effects observed at low doses are ignored if they aren’t observed at high doses
The expectation is that “the dose makes the poison”
Yet non-monotonic curves are common in medicine, pharmacology & endocrinology

Houshmand et al. 2009
Why this matters: ATI/RFD “safe” doses are calculated from NOAELs with an assumption of linearity.
Examples in the context of the NOAEL and RFD

Angle et al. 2013
Examples in the context of the NOAEL, RFD and human exposures

Do et al. 2013
Examples in the context of the RFD and human exposures

Vandenberg et al. 2013
Dozens of epidemiology studies reveal non-monotonic responses (presumably all below the RfD).

Lee et al. 2014
“But we’ve all been exposed and we’re all fine!”

Hormone associated diseases/disorders on the rise:

- Breast cancer
- Sperm count
- Genital defects
- Prostate cancer
- Obesity
- Diabetes
- Testicular cancer
- Asthma
- ADHD & autism
- Asthma
Are we fine?

Over recent decades there has been:

- significant increase in **reproductive problems** in some regions of the world, suggesting a strong role for unidentified environmental factors in disease etiology
- increase in **endocrine cancers**
- significant decrease in **human fertility** rates
- increase in use of assisted reproductive services
- Increases in **neurobehavioral disorders**
- increasing number of chemicals to which all humans in industrialized areas are exposed

Top: Tanner, Anderson & Must
Bottom: Levine et al., Hum Reprod Update. (2017)
Are we fine?

Over recent decades there has been:

- significant increase in **reproductive problems** in some regions of the world, suggesting a strong role for unidentified environmental factors in disease etiology
- increase in **endocrine cancers**
- significant decrease in **human fertility** rates
- increase in use of assisted reproductive services
- Increases in **neurobehavioral disorders**
- increasing number of chemicals to which all humans in industrialized areas are exposed

Top: Richiardi et al., Cancer Epidem. Biomark. (2004);
Bottom: based on data from http://data.euro.who.int/hfadb/
Are we fine?

Over recent decades there has been:

- significant increase in reproductive problems in some regions of the world, suggesting a strong role for unidentified environmental factors in disease etiology
- increase in endocrine cancers
- significant decrease in human fertility rates
- increase in use of assisted reproductive services
- Increases in neurobehavioral disorders
- increasing number of chemicals to which all humans in industrialized areas are exposed

Are we fine?

Over recent decades there has been:

- significant increase in **reproductive problems** in some regions of the world, suggesting a strong role for unidentified environmental factors in disease etiology
- increase in **endocrine cancers**
- significant decrease in **human fertility** rates
- increase in use of assisted reproductive services
- Increases in **neurobehavioral disorders**
- increasing number of chemicals to which all humans in industrialized areas are exposed

Top: Sun et al., PLoS One (2014);
Middle & bottom: Dabelea, Diabetes Care (2018)
There is a strong case that EDCs affect human health

• Even though exposures are typically low, many dozens of EDCs are associated with adverse health outcomes in human populations

• Increasing numbers of prospective (and occasionally retrospective) cohort studies support a causal relationship between EDC exposures and diseases

• Secular trends indicate that many endocrine-mediated diseases are increasing in prevalence (even though life expectancy has also increased)

• Animal studies have been very helpful in understanding the mechanisms by which EDCs induce adverse health outcomes
Yet, there is hope: relatively small changes can make a difference.
Mary Catanese          Lauren Hurley          Archana Gopal
Corinne Hill          Michelle Levine          Sarah Sapouckey
Charlotte LaPlante    Rebecca Goldberg         D’Andre Quinerly
Durga Kolla           Brian Martin           Deb Pimentel
Aastha Pokharel       Shawn Hallett          Anupama Singh
Mary Morcos           Michael Lemieux          Lauren Masse
Danny McSweeney        Alison Bowler           Meg Bernier
Klara Matouskova          

Support from National Institute of Environmental Health Sciences, National Cancer Institute, Paul G Allen Family Foundation, Cornell Douglas Foundation, Great Neck Breast Cancer Coalition