Global concern!
Content

- What is an endocrine disruptor?
- Why do we concern about such exposure?
- What are we doing in the Swedish SELMA study?
  - Reproduction and sexual development
In order to understand endocrine disrupting chemicals it might be good to learn what we know about our natural endocrine system
Our natural hormones are of the greatest importance for a healthy development during the entire life span from the moment of conception until death.
Hormones are receptor specific

- Secreting cell
- Blood vessel
- Target cell I
  - Response I
- Target cell II
  - Response II
- Not a target cell
  - No receptor
  - Wrong receptor

Pufendorf Indoor
Hormones acts at very low concentrations
Hormones are life stage dependent.

Example of estrogen exposure

- Developmental programming (irreversible)
- Reversible effects
Endocrine Disrupting Chemicals (EDCs)

Binding

Adverse health effect

Figure 1. Chemical structures of estradiol and endocrine disrupters with estrogen activity.
Four reasons for emerging public health concern for EDC-exposure

Low doses/non-monotonic

Early life is important

The ubiquity of exposure

The wide range of health effects
The low dose controversy exemplified by bisphenol A
The low dose controversy exemplified by bisphenol A

Cell proliferation (% BrdU positive)

Range of serum concentrations commonly observed in people

BPA dose

0 0 0.1 0.023 1.0 0.23 10 2.3 100 23 nM ppb

"Apparent NOAEL"

Myer et al., 2008
The dose-response paradigm

Phillippus Aureolus Theophrastus Bombastus von Hohenheim Paracelsus

1493-1541
Fetal life is important due to development and programming effects.
Early life is important

Sigmund Freud (1856-1939)
Early childhood experiences impacts behavior later on in life

David Barker (1938-2013)
The fetal period is important for chronic diseases later on in life, e.g., hypertonia, diabetes, cardiovascular diseases...
Birth weight
Birth weight and the risks for non-fatal cardiovascular disease

Birth weight and the risks for non-fatal cardiovascular disease

Hypertonia
Cardiovascular diseases
Diabetes
Overweight

Low birth weight

Body weight

Birth  Wean  Adult

Macrosomia
Median
IUGR
Low birth weight & Centile crossing

- Macrosomia
- IUGR***
- Median
- IUGR
Mechanisms of developmental programming
(Ross & Desai 2013)

Fetal nutrition, stress, environmental toxins

Binding

Endocrine Disruptor

Hormone

Receptor

Response

Adverse health effect
Cleaning & Personal care products

Sources for EDCs are everywhere...

Dietary, cook wares and packages
Developmental neurotoxicology

phthalates, bisphenol a, glycol ethers, perfluorinated chemicals, flame retardants, etc.

Hormonal cancer

Reproductive health

Metabolic syndrom incl. diabetes

Immunological effects

Beginning a lifetime of vulnerability. A recent study that in...
Regulatory decision and research on EDCs have to be based on principles of endocrinology!

Vandenberg et al., 2013, Reproductive Toxicology
Research for a healthier future
Swedish Environmental Longitudinal, Mother and child, Asthma and allergy study
# Asthma and allergy

- Eczema
- Asthma
- Rhinitis
- IgE

## Metabolic outcomes

- Inflammation markers
- Growth since birth
- BMI

## Reproduction and sexual development

- AGD
- Puberty onset
- Play behavior

## Neurodevelopmental and behavioral outcomes

- Cognitive outcomes
- Speech and language
- Motor outcomes
- Executive functions & behavior

## Health outcomes

### Asthma and allergy

<table>
<thead>
<tr>
<th>Age</th>
<th>Conception</th>
<th>Birth</th>
<th>1y</th>
<th>2y</th>
<th>3y</th>
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</table>

## Exposure data

### Biobanked samples

- Serum/Urine
  - Mother: n=2,356
  - Child: n=1,516
- Urine: Child: n=900

### Questionnaires

- Q1, Q2, Q3, Q4, Q5, Q6, Q7, Q8

### Data from public child health care

- X: Available

## Analyzed biomarkers

- EDC exposure*
- Thyroid hormones
- Vitamin D
- Cord blood**

## Genetics & Epigenetics (e.g., placenta related miRNA, etc.)

- Prenatal
- Cord Serum/Urine
- Blood
- Urine
- Etc.

## Data from public child health care

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- EDC exposure*
- Thyroid hormones
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<table>
<thead>
<tr>
<th>Group</th>
<th>Parent compound</th>
<th>Metabolite</th>
<th>n&gt;LOD</th>
<th>GM (95% CI) (ng/mL)</th>
<th>95% (ng/mL)</th>
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<td>(urine)</td>
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<td>5.24 (5.17 - 5.32)</td>
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</table>

**Perfluorinated compounds (serum)**

- **PFCs**
  - PFNA
  - PFDA
  - PFUnDA
  - PFDoDA
  - PFHxS
  - PFHxS
  - PFDA
  - PFOS

100% of 2,356 pregnant women are exposed, data from the SELMA study.
Human reproduction
Chemicals with endocrine disrupting properties "Xenoestrogens"
Natural sexual hormones

Estrogen
Testosterone

Chemicals with endocrine disrupting properties
“Xenoestrogens”

Sexual development & fertility

AGD measures in male infants

196 boys in SELMA at 21 months of age
Prenatal Phthalate Exposures and Anogenital Distance in Swedish Boys

Carl-Gustaf Bornehag, Fredrik Carlstedt, Bo AG. Jönsson, Christian H. Lindh, Tina K. Jensen, Anna Bodin, Carin Jonsson, Staffan Janson, and Shanna H. Swan

http://dx.doi.org/10.1289/ehp.1408163

Received: 22 January 2014
Accepted: 10 October 2014
Advance Publication: 29 October 2014
1\textsuperscript{st} trimester DiNP exposure increase the risk for shorter AGD in 196 SELMA boys (21m)

Phthalate metabolites in quartiles

- MEP
- MBP
- MBzP
- DEHPsum
- DiNPsum
Natural sexual hormones

Estrogen
Testosterone

Chemicals with endocrine disrupting properties
“Xenoestrogens”

Sexual development & fertility

AGD measures in male infants

A shorter AGD
Incomplete masculinization
Chemicals with endocrine disrupting properties

“Xenoestrogens”

Natural sexual hormones
Estrogen
Testosterone

Sexual development & fertility

A shorter AGD

Newborn boys
Genital malformations

Adult men
Fertile problems
Examples of indoor related sources for DiNP
Replacement of phthalates in PVC

DEHP

DiNP

DINCH

Non-phthalate
1\textsuperscript{st} trimester urinary levels in 2,355 SELMA mothers
The four most used phthalates in Sweden 2012 (>1,000 ton/year)

- DPHP
- DEHP
- DIDP
- DiNP
Thank you!

Bornehag et al., 2004
Nilsson et al., 2005
Sundell et al., 2005
Bornehag et al., 2005
Larsson et al., 2009
Larsson et al., 2010
Choi et al., 2010
Guo et al., 2012
Carlstedt et al., 2013
von Kobyletzki et al., 2013
Kochback Bölling et al., 2013
Shu et al., 2014
Bornehag et al., 2014
Unenge Hallerbäck et al., *manuscript*
Von Kobyletzki et al., *manuscript*
Bohman et al., *manuscript*
Larsson et al., *manuscript*
Choi et al., *manuscript*
Shu et al., *manuscript*
Shu et al., *manuscript*