Prenatal exposure to EDCs and obesity: combining toxicology and epidemiology

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Obesity on the Rise

- Prevalence increasing in children, adolescents, adults worldwide
- Risk factors
  - Diet
  - Physical activity
  - Genetics
  - Exposure to chemicals?
OBesogenic Endocrine disrupting chemicals: Linking prenatal exposure to the development of obesity later in life

- European Commission FP7 funded research project
- Project duration: May 2009 – November 2013
- 7 research institutes throughout Europe (NL, BE, FR, SK, NO)
**OBELIX research question**

- Does exposure to endocrine disrupting chemicals (EDCs) early in life play a role in the development of obesity later in life?

  - Change in early growth?
  - Change in body weight at birth and in childhood?
  - Change in fat cell differentiation?
  - Mechanism: altered epigenetics?

  - Changes in hormone and lipid metabolism?

**Early exposure**

**EDCs?**

**Obesity later?**
EDCs studied in OBELIX are present in maternal diet

Van Leeuwen et al., 2009
OBELIX approach

Human Exposure and Health Assessment
Mother/child cohorts:
• Belgium
• The Netherlands
• Norway
• Slovakia

Laboratory studies
• In vivo mice
• In vitro cell culture
• Gene expression & methylation analysis (human&mice)

Risk Assessment
THE OBELIX & ENRIECO COHORTS

GREENLAND

FAROE ISLANDS

ICELAND

RUSSIA

BELORUSSIA

ICELAND

UNITED KINGDOM

NORWAY

SWEDEN

FINLAND

POLAND

GERMANY

UKRAINE

FRANCE
OBELIX-ENRIIECO cohorts: prenatal PCB 153 exposure in European children

Birth weight declined by 150g (95% CI 50-250 g) per 1µg/L increase in PCB 153 cord serum concentration

Perinatal exposure to EDCs and growth/BMI

<table>
<thead>
<tr>
<th>EXPOSURE</th>
<th>OUTCOME</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth</td>
<td>2 y</td>
</tr>
<tr>
<td></td>
<td>7 y</td>
</tr>
<tr>
<td>Growth 0-2 y</td>
<td>BMI 7 y</td>
</tr>
</tbody>
</table>

@PCB
*DDE
#HCB

#TEQs
PFOA
PFOS

PRENATATAL
POSTNATAL
(Verner et al, EHP, 2013)

Slide courtesy of Nina Iszatt, NIPH, Data under review at EHP

©negative association with growth 0-2 y *positive association with growth 0-2y
#positive association with BMI 7 y (preliminary)
Laboratory studies

• *In vivo* mice
• *In vitro*
• Epigenetic mechanisms

Prenatal exposure to synthetic estrogen (DES) (Newbold et al., 2007, *Repro.Tox*)
Experimental study design

<table>
<thead>
<tr>
<th>weeks</th>
<th>-6</th>
<th>-4</th>
<th>-3</th>
<th>0</th>
<th>3</th>
<th>21-53</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Premating</td>
<td>Mating</td>
<td>Gestation</td>
<td>Lactation</td>
<td>Offspring</td>
<td></td>
</tr>
</tbody>
</table>

Challenge: HF diet

(Maternal) dietary exposure

Mouse strain: C57BL/6J * FVB

- body weight
- fat pad weight
- histopathology
- food consumption
- spontaneous locomotor activity
- serum lipid and endocrine profile
- glucose tolerance test
- internal dose

Mother  

Father  

F1
Early life exposure to BPA affects adipocyte size in white and brown adipose tissue

control

BPA

Males

3000 µg/kg/day

van Esterik et al, 2014, Toxicology
<table>
<thead>
<tr>
<th>Chemical</th>
<th>Critical effect in animal studies</th>
<th>OBELIX BMDL</th>
<th>EFSA BMDL</th>
<th>OBELIX TDI</th>
<th>EFSA TDI</th>
<th>human exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td>BPA</td>
<td>↓ fat pad wt females μ/k/d</td>
<td>292</td>
<td>3300</td>
<td>0.28</td>
<td>5</td>
<td>0.2-1.1</td>
</tr>
<tr>
<td>PFOA</td>
<td>↓ fat pad wt females μ/k/d</td>
<td>46</td>
<td>300</td>
<td>0.23</td>
<td>1.5</td>
<td>0.002-0.006</td>
</tr>
<tr>
<td>TCDD</td>
<td>↑ fat pad wt females p/k/d</td>
<td>453</td>
<td>25</td>
<td>&gt;2</td>
<td>2</td>
<td>0.5-2</td>
</tr>
<tr>
<td></td>
<td>↓ fat pad males</td>
<td>130</td>
<td>25</td>
<td>&gt;2</td>
<td>2</td>
<td>0.5-2</td>
</tr>
<tr>
<td>PCB153</td>
<td>↑ glucagon females μ/k/d</td>
<td>1042*</td>
<td>1200*</td>
<td>86#</td>
<td>44-214#</td>
<td>0.010-0.045</td>
</tr>
<tr>
<td>DEHP</td>
<td>↑ FFA males μ/k/d</td>
<td>4390</td>
<td>5000</td>
<td>44</td>
<td>50</td>
<td>2.5-26</td>
</tr>
</tbody>
</table>

*critical body burden in μg/kg bw  #margin of BB
OBELIX summary

Perinatal exposure to some EDCs (DDE, dioxin-like chemicals) early in life is associated with increased growth and weight in children.

In laboratory studies, EDC exposure early in life changes lipid and hormone metabolism long after exposure has stopped. Effects on body weight (both increases and decreases) were found. In vitro studies show that EDCs stimulate the differentiation of fat cells.
OBELIX discussion

• Effects in animals show clear gender specificity
• Divergent effects of pre- and postnatal exposure in children
• Mechanisms: generated new hypotheses
  • changes in DNA methylation related to EDC exposure
• Interactions with other risk factors?
• Long term consequences of changes in growth and BMI early in life?
• Exposure to mixtures?
• Are current TDIs protective enough? Need to include metabolic disruption as a relevant endpoint of endocrine disruption
THANKS TO THE European Commission TEAM