Synthetic EDCs at the present human exposure ARE NO RISK for human health
What are EDCs’

• **2013 Berlaymont Declaration**
  – defines EDC
  – Makes NO distinction between synthetic and *natural EDCs*
  – Does NOT define any ‟*acceptance level*“

• ‟*Natural EDCs*“ include
  – sugar (glucose, saccharose, fructose)
  – Isoflavones from plants e.g. soy (genistein, daidzein
  – Bisphenol F from yellow mustard

• ‟*Acceptance levels*“: how much exposure is socio-economically tolerated that will still produce a very low but accepted incidence of health effect in humans (e.g. food contaminants (aflatoxins) & cancer: 1 addtl. Tumor in 1 Mio inhabitants)
List of human diseases „associated“ with exposure to EDCs

<table>
<thead>
<tr>
<th>Infertility</th>
<th>Cancer</th>
<th>Metabolic Syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Direct effects</td>
<td>Breast</td>
<td>Obesity</td>
</tr>
<tr>
<td>Transgenerational</td>
<td>Prostate</td>
<td>Diabetes (Type I and II)</td>
</tr>
<tr>
<td></td>
<td>Testis</td>
<td>Insulin resistance</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hypertension</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dyslipidemia</td>
</tr>
</tbody>
</table>

**Neurobehavioural deficits**

**Neurodevelopment**

**Immunedisorders**

AOP-Driven Assay Development

• Adipogenesis: differentiation of stem cells to mature adipocytes

• Concerted activation of several hormone signaling pathways
  • Well described in human, rodent, and invertebrates

• Glucocorticoid receptor activation is necessary for adipogenesis

Hartman et al., In review.

From R. Clewell et al March 15 2018, Annual Meeting of the Society of Toxicology
Direct and Indirect Actions on the Conceptus

From R. Miller et al March 15 2018, Annual Meeting of the Society of Toxicology
Daidzein, genistein BPA, DDE, are GR Agonists, but how potent are they?

Estradiol, estrone etc. regulate the GR and vice versa, so E-levels in utero matter

are foetuses exposed in utero to sufficient levels of Daidzein, genistein, BPA etc to program the baby for later onset of obesity and diabetes type II?
What is the situation during pregnancy

- Endogenous hormone levels vary dramatically during pregnancy

**Circulating Hormones during Pregnancy**

<table>
<thead>
<tr>
<th>Hormone (ng/mL)</th>
<th>Non-pregnant</th>
<th>3rd Trimester</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chorionic Gonadotropin</td>
<td>&lt;0.05 mU/mL</td>
<td>100,000 mU/mL (Peak 1st Trimester)</td>
</tr>
<tr>
<td>Progesterone</td>
<td>10</td>
<td>130 – 150</td>
</tr>
<tr>
<td>Estradiol</td>
<td>0.4</td>
<td>40</td>
</tr>
<tr>
<td>Estriol</td>
<td>0.05</td>
<td>12 – 20</td>
</tr>
<tr>
<td>Testosterone</td>
<td>0.002</td>
<td>0.004</td>
</tr>
<tr>
<td>Cortisol</td>
<td>72.5</td>
<td>181 – 290</td>
</tr>
<tr>
<td>Placental Lactogen</td>
<td>0</td>
<td>5000-15000</td>
</tr>
</tbody>
</table>


- Serum concentrations of estrone, estradiol and estriol were 1.61-85.1 nM, 9.09-69.7 nM, and 1.5-36.3 nM, respectively
- Daidzein and genistein levels were **10-100 fold lower** than endogenous estrogen levels
- **BPA levels were 100’000 fold lower** than endogenous estrogen levels
Comparison of BPA and BPF intake

<table>
<thead>
<tr>
<th></th>
<th>Daily consumption of mustard (g)</th>
<th>Content of BP-F (µg)</th>
<th>Daily BP-F intake of a 60 kg person (µg/kg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BP-F</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average consumer</td>
<td>1–2</td>
<td>8.4–16.7</td>
<td>0.14–0.28</td>
</tr>
<tr>
<td>High but relatively frequent</td>
<td>20</td>
<td>167</td>
<td>2.8</td>
</tr>
<tr>
<td>Extreme but not impossible</td>
<td>80</td>
<td>668</td>
<td>11.1</td>
</tr>
</tbody>
</table>

Recently estimated BP-A dietary intake by EFSA (EFSA Journal 2015)

<table>
<thead>
<tr>
<th>BP-A</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Infants and toddlers</td>
<td>Up to 0.875 µg/kg bw per day</td>
<td></td>
</tr>
<tr>
<td>Women of childbearing age and men of the similar age</td>
<td>Up to 0.388 µg/kg bw per day</td>
<td></td>
</tr>
<tr>
<td>Highest aggregated exposure for adolescents</td>
<td>1.449 µg/kg bw per day</td>
<td></td>
</tr>
</tbody>
</table>

From Dietrich and Hengstler, 2016, *Arch. Toxicol.*, 90(2), 489-491

**Intake of naturally occurring BPF from yellow mustard is similar if not greater than daily BPA exposure**

The NTP Research Report on the CLARITY–BPA Core Study with rats February 2018 shows: „*BPA produced minimal effects that were distinguishable from background in this study, particularly below 25’000 µg/kg bw day.***“

Results: The average decrease of p,p′-DDE between 1991 and 2001 was 55%, and could serum levels could only be weakly associated with a relative increase of BMI ($\beta = 1.0$, 95% CI 2.3, 0.2, $p = 0.09$), explaining only 5% of the variation.” Conclusions: “The results support a continuing decrease in human body burdens of PCBs, DDE and HCB during the 1990s.”
World-Obesity Figures 2008

China stopped production (and use) of DDT in 2007

Indonesia banned DDT for all purposes since 1994

India opposes a 2020 ban of DDT at Stockholm POP convention (May 4, 2013)

http://www.chem.unep.ch/ddt/DDTProfiles/
Human Exposure to Chemicals Food and Human EDC associated diseases?


Obesity and Energy Intake in the US, 1961-2009


CDC NHES and NHANES 1960-2008 USDA ERS loss-adjusted food disappearance

Prof. Dan Dietrich 11
Human Cost Burden of Exposure to Endocrine Disrupting Chemicals: A Critical Review

- Trasande et al published seven papers in 2015 and 2016 estimating costs attributable to exposure to EDCs in U.S. and EU

€191 billion per year in EU

$340 billion per year in U.S

- European Commission, academics, and science journalists express skepticism about validity of estimates

Background
Conclusions regarding human cost burden due to EDC mediated health effects

• Current exposure levels of EDCs e.g. BPA and DDE are \textit{too low} to have any effect on the foetus or the developing child.

• Current exposures to \textit{isoflavones} could have an \textit{added-on endocrine effect}.

• Current exposures to known EDCs such as SUGAR \textit{Will definitelly have an adverse health effect}.

• Caloric intake \textit{Will definitelly have an adverse health effect}.

• Our review of the Trasande et al human cost burden analyses uncovered \textit{substantial flaws in approach taken and conclusions drawn and therefore are highly speculative and should not be considered} in weight of evidence approach.
Conclusions with regard to EDC mediated health effects

• EDCs follow a concentration response principle, with a threshold.

• With the exception of natural EDCs (Sugar, isoflavones, BPF), prominent human diseases, e.g. prevalence of T2D, are impossible to associate or causally relate or to synthetic EDC exposure based on the actual low concentrations found in exposed persons

• Any regulation of EDCs should embrace in language and foreseen procedure:
  – „causality“ and NOT „plausability“ of the hazards determined in the *in vivo, in vitro* and *in silico* test systems used
  – Must consider potency of the compounds in question
  – Must consider true human exposure (several age groups)
  – Must consider the „more likely explanations“ in a human disease, before an association of an EDC (or any other mechanism) with the specific disease is considered
Thank you for your attention!