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

Infertility

Direct effects

Transgenerational

Cancer

Breast

Prostate

Testis

Metabolic Syndrome

Obesity

Diabetes (Type I and II)

Insuline resistance

Hypertension

Dyslipidemia

Neurobehavioural deficits

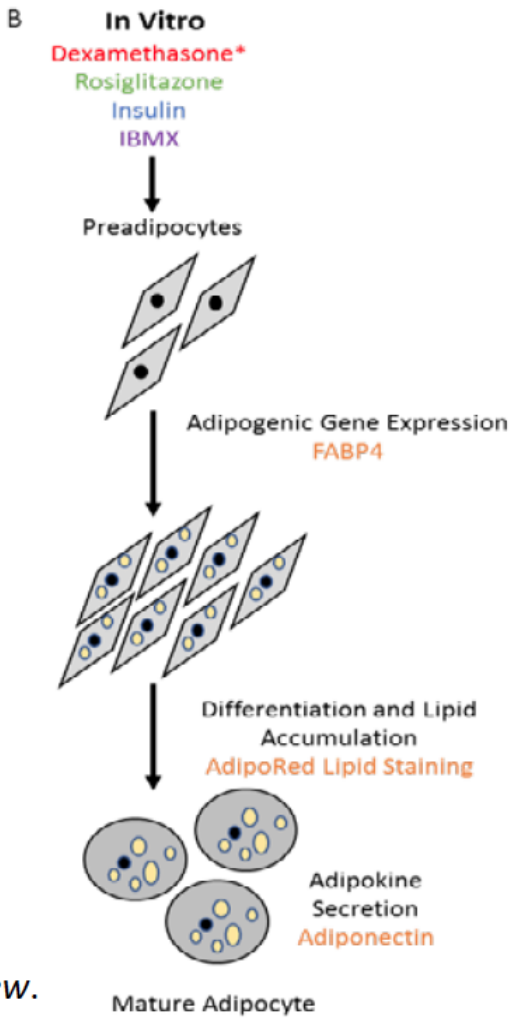
Neurodevelopment

Immunedisorders

Review by Decoster and van Larebeke Journal of Environmental and Public Health 2012, doi:10.1155/2012/713696

AOP-Driven Assay Development

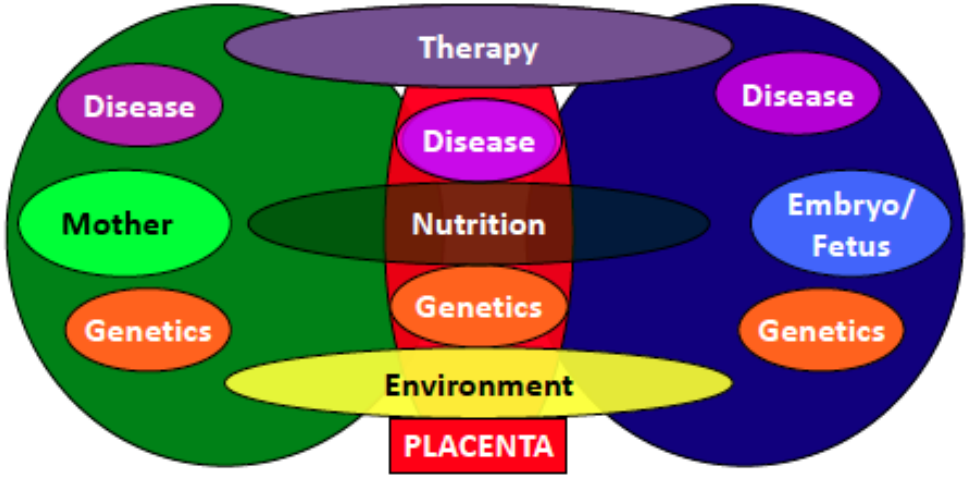
- Adipogenesis: differentiation of stem cells to mature adipocytes
- Concerted activation of several hormone signaling pathways
  - Well described in human, rodent, and invertebrates
- Glucocorticoid receptor activation is necessary for adipogenesis



Hartman et al., *In review*.

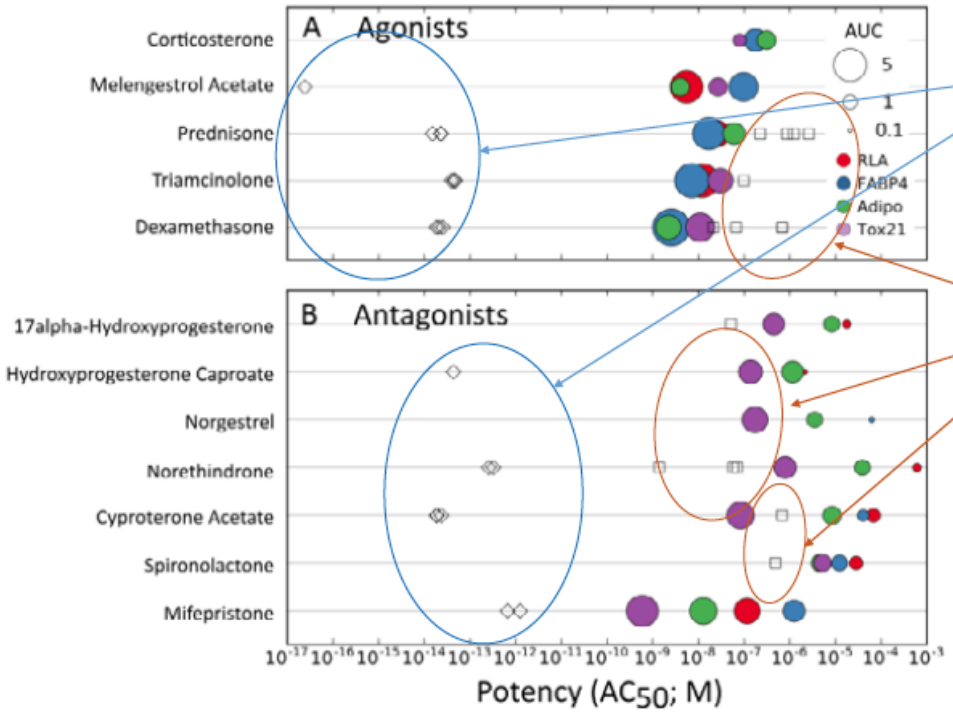
From R. Clewell et al March 15 2018, Annual Meeting of the Society of Toxicology

Direct and Indirect Actions on the Conceptus



From R. Miller et al March 15 2018, Annual Meeting of the Society of Toxicology

MoE and Therapeutic Index for GR-Active Compounds



MoE for environmental exposures >> 10,000 for most compounds (estimated exposures from ExpoCast)

Mifepristone: ~ 300 – 10,000 depending on assay

In vitro assays predict therapeutic index

Hartman et al., *In review*

From R. Clewell et al March 15 2018, Annual Meeting of the Society of Toxicology

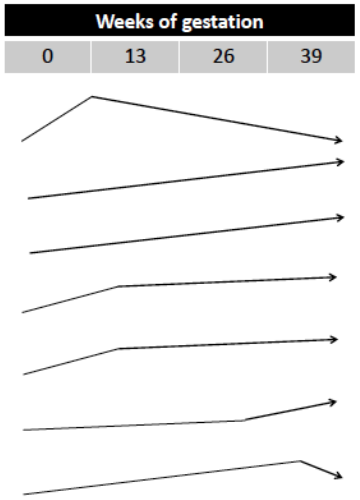
- Daidzein, genistein BPA, DDE,are GR **Agonists, but how potent are they?**
- Estradiol, estrone etc. regulate the GR and vice versa, so E-levels in utero matter
- **are foetuses exposed in utero to sufficient levels of Daizein, genistein, BPA etc to program the baby for later onset of obesity and diabetes type II?**

What is the situation during pregancy

- Endogenous hormone levels vary dramatically during pregnancy

Circulating Hormones during Pregnancy

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



Creasy and Resnick, 2009; Freemark, *Horm Res*, 2006

Teeguarden et al March 2018: Comparative Estrogenicity of Endogenous, Environmental, and Dietary Estrogens in Pregnant Women I: Serum Levels, Variability, and the Basis for Urinary Biomonitoring of Serum Estrogenicity

- 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 1 Daily uptake of bisphenol A and bisphenol F

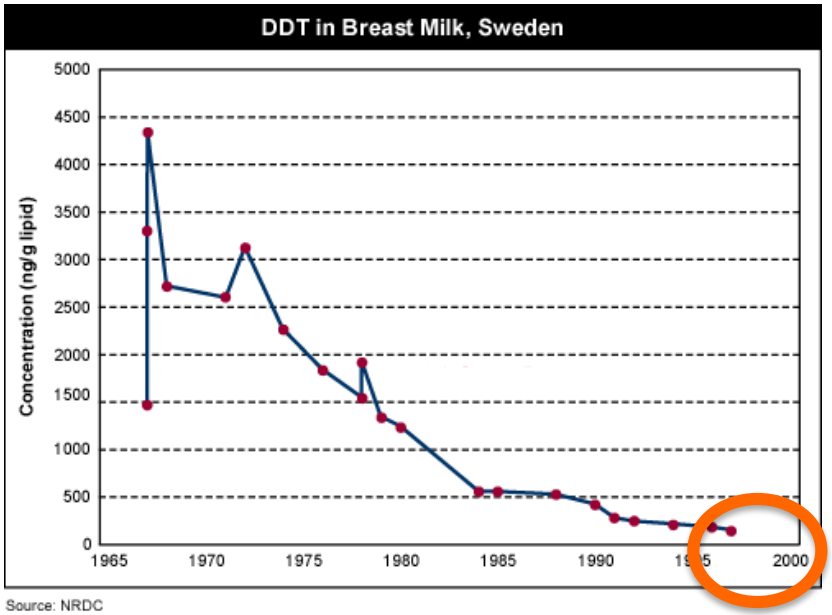
	Daily consumption of mustard (g)	Content of BP-F (µg)	Daily BP-F intake of a 60 kg person (µg/kg/day)
BP-F			
Average consumer	1–2	8.4–16.7	0.14–0.28
High but relatively frequent	20	167	2.8
Extreme but not impossible	80	668	11.1
Recently estimated BP-A dietary intake by EFSA (EFSA Journal 2015)			
BP-A			
Infants and toddlers			Up to 0.875 µg/kg bw per day
Women of childbearing age and men of the similar age			Up to 0.388 µg/kg bw per day
Highest aggregated exposure for adolescents			1.449 µg/kg bw per day

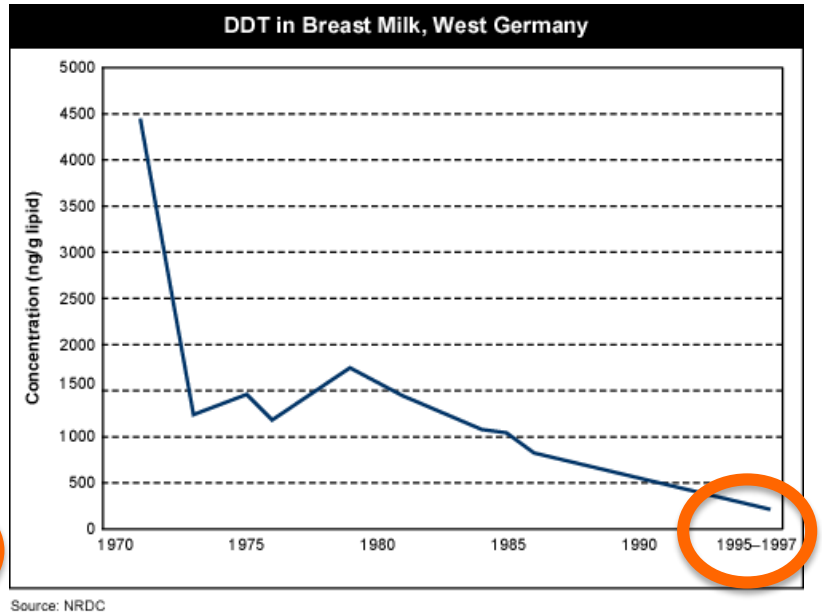
From Dietrich and Hengstler, 2016, ***Arch. Toxicol.***, 90(2), 489-491

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

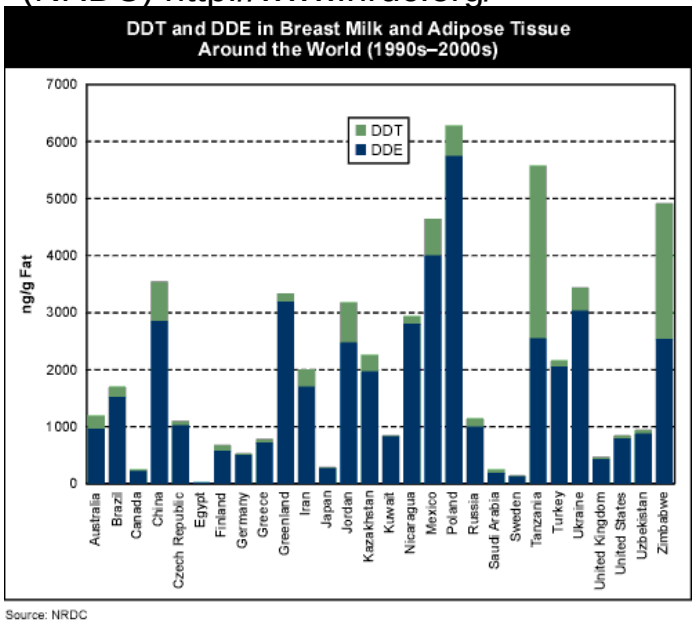
The NTP Research Report on the CLARITY–BPA Core Study with rats February 2018 shows:
„BPA produced minimal effects that were distinguishable from background in this study, particularly below 25‘000 µg/kg bw day.“

Trends in DDT/DDE concentrations in human Breast Milk and Adipose Tissue





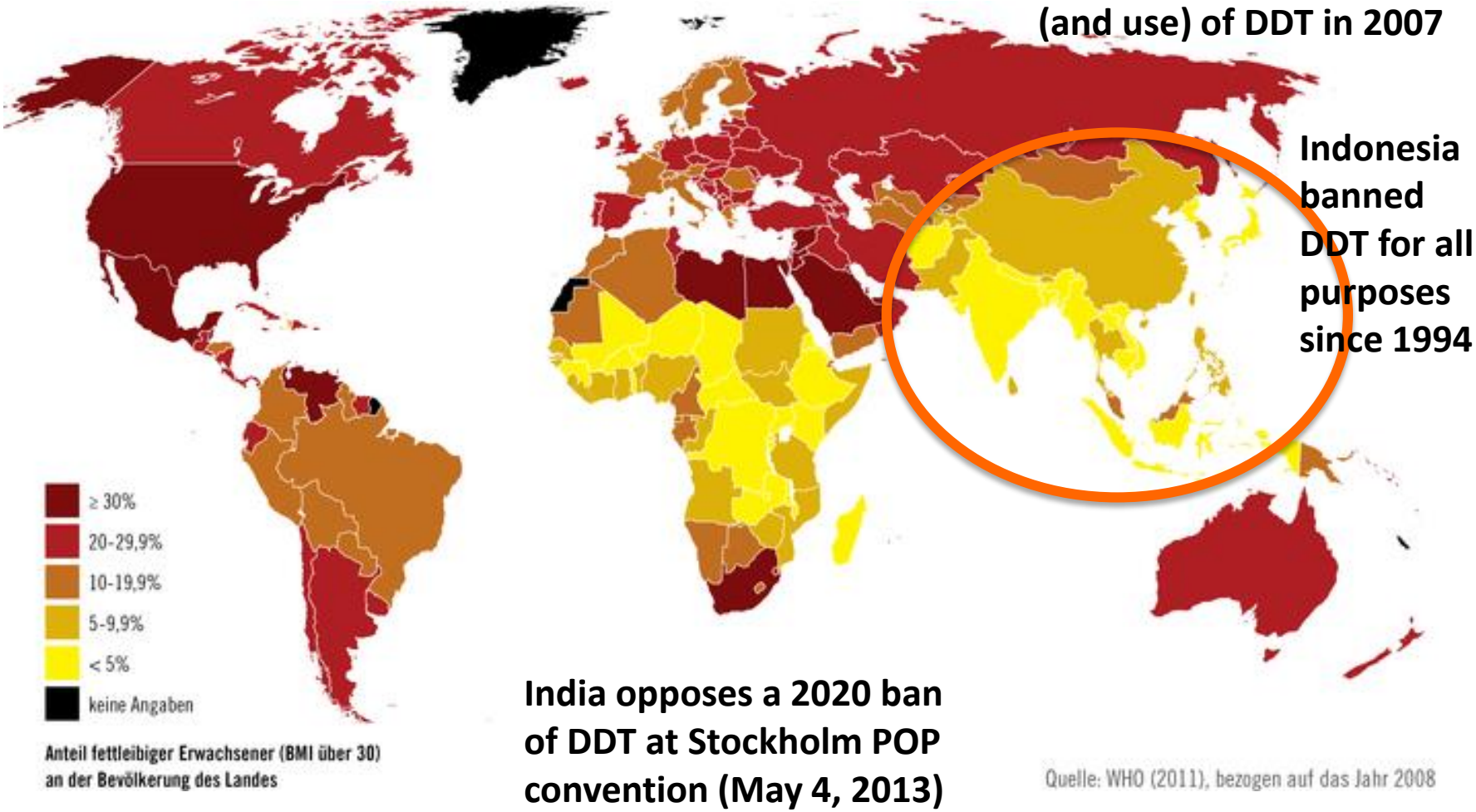
Natural Resources Defense Council (NRDC) http://www.nrdc.org/



Intra-individual variations and time trends **1991–2001** in human serum levels of PCB, **DDE** and HCB (Hagmar et al., Chemosphere 64 (2006) 1507–1513; doi.org/10.1016/j.chemosphere.2005.12.054):

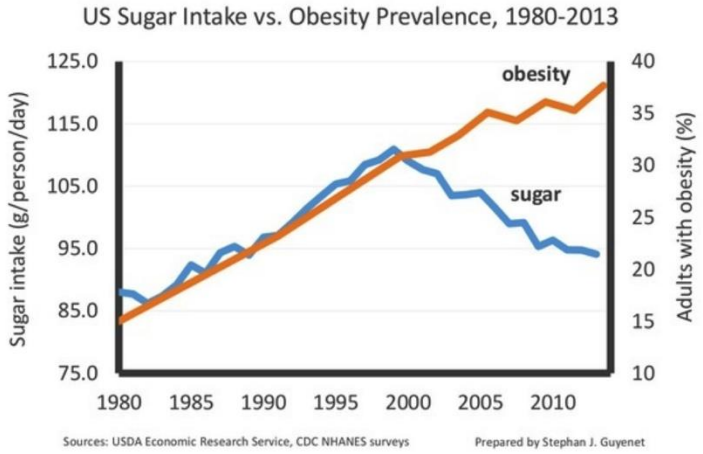
Results: *The **average decrease of p,p‘-DDE between 1991 and 2001 was 55%**, and could serum levels could only be weakly associated with a relative increase of BMI (β = 1.0, 95% CI 2.3, 0.2, p = 0.09), explaining only 5% of the variation.*“ **Conclusions:** „*The results support a continuing decrease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

World-Obesity Figures 2008

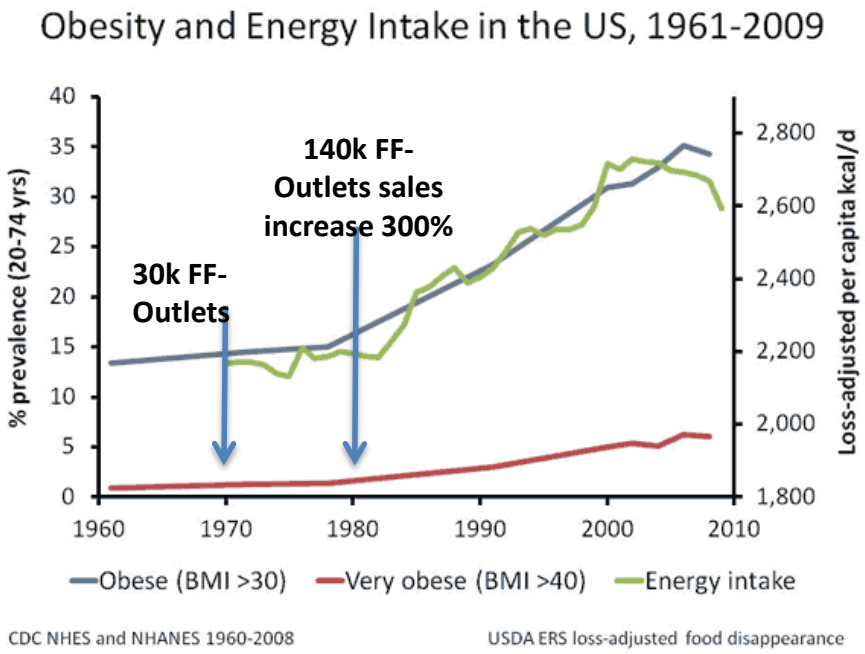


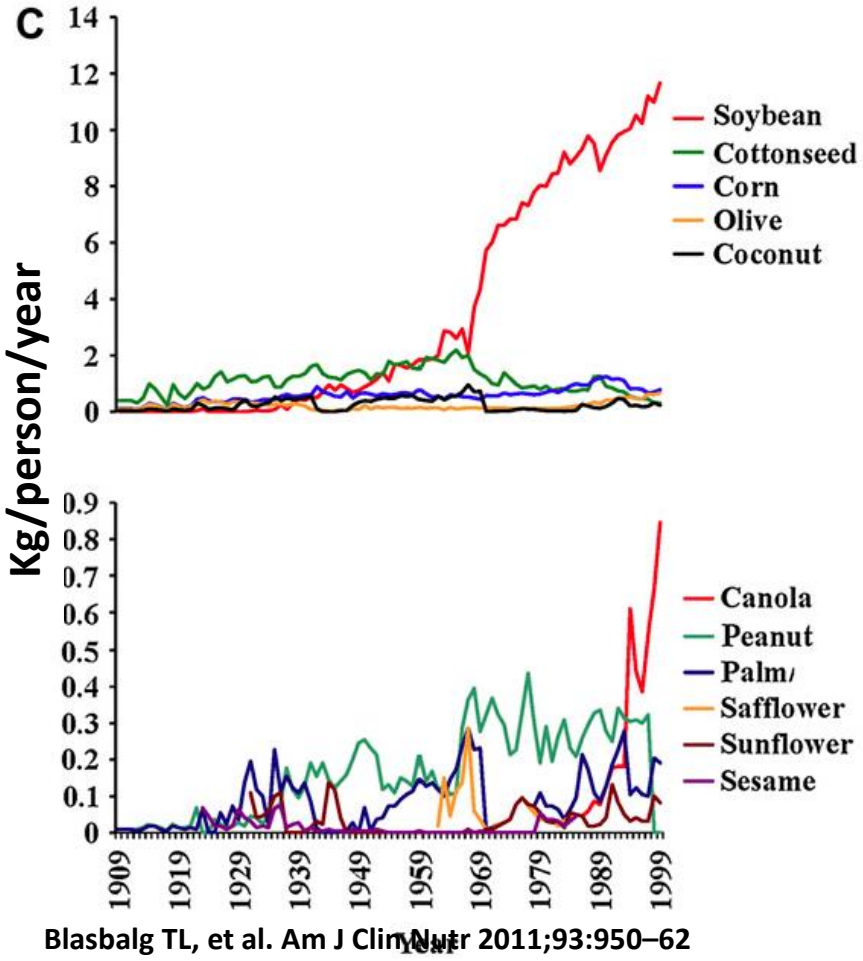
http://www.chem.unep.ch/ddt/DDTProfiles/

Human Exposure to Chemicals Food and Human EDC associated diseases?



Johnson RJ, et al. Am J Clin Nutr 2007;86:899–906





Blasbalg TL, et al. Am J Clin Nutr 2011;93:950–62

Human Cost Burden of Exposure to Endocrine Disrupting Chemicals: A Critical Review

Bond, G.G. and Dietrich D.R. (2017) Arch. Toxicol., doi: 10.1007/s00204-017-1985-y

Background

- 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

Conclusions regarding human cost burden due to EDC mediated health effects

- Current exposure levels of EDCs e.g. BPA and DDE are **too low** to have any effect on the foetus or the developing child

- Current exposures to **isoflavones** could have an **added-on endocrine effect**

- Current exposures to known EDCs such as **SUGAR Will definetly have an adverse health effect**

- **Caloric intake Will definetly have an adverse health effect**

- Our review of the Trasande et al human cost burden analyses uncovered **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!