Environmental toxicants in Food & Breast milk & Adverse Health effects

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## Faculty Disclosure

<table>
<thead>
<tr>
<th>Commercial Interest</th>
<th>Nature of Relevant Financial Relationship (Include all those that apply)</th>
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<td>What was received</td>
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<td>• None</td>
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After participating in this presentation, learners should be better able to:

• Identify toxicants in foods and the associated potential health effects

• Understand the adverse health risks of certain otherwise healthy foods for young girls and pregnant women.

• Understand the impact of food toxicity on the highly exposed fetus
Content

• History persistent toxicants
• Exposure to toxicants across the world
• Adverse health effects
• HUMIS/NoMIC study
  – Correct exposure assessment, pre-and postnatal effects
  – Mixtures
• Sources
• Recommendations
History is short….

• 1950
  – Birds dead
  – Analysis dead birds
    • High concentration
      – Mercury
      – DDT
        • Toxic to many more organisms than intended to kill.

  – Analyses food
    • Egg, meat and fish
      – DDT and mercury
        • Become far more widely distributed
One Earth

- **Mid-1950s:**
  - Pilots
    - Discolored haze on the horizon
    - Identified as pollutants industrialized areas Europe
  - **Norway**
    - **Svalbard:** clean undisturbed environment?
      - Toxic organic compounds in polar bears
        - Unexpectedly high levels.
Persistent environmental pollutants POPS

Bioaccumulate
- Long half lives
- Fat-solubility
- Accumulate in fatty tissue

The baby, before birth and when breast-fed, consumes the most concentrated amount of POPs (PCBs, DDT, HCB and dioxins etc).
Biomagnifies in the food chain

- Highest concern humans and animals on the top of the food chain

- High concentration in fish, seal and seabirds (seabirdsegs)
- High concentrations in human milk
  - Humans on top of food web
  - Accumulate throughout the life time of the mother
  - High fat content of milk
- Reflects current AND earlier exposure
Time-trends:
Dioxin and PBDE in human milk

Borrowed with the courtesy of Gunilla Lindstrøm
More than 100 000 chemicals in use in EU today in high volumes

- Only a small fraction has been fully evaluated for potential adverse effects to human health

Endocrine disruption challenging
WHO-UN report

• The vast majority of chemicals in current commercial use have not been tested at all.
  • 800 chemicals are known or suspected of interfering with hormone receptors, hormone synthesis or hormone conversion
  • Only a small fraction of these chemicals have been investigated in tests capable of identifying overt endocrine effects
Recent UN/WHO report concludes:

- Synthetic chemicals have serious health implication and has become a “global threat”

- Proven or suspected behind many of the diseases we see increasing in the western world

  - Diseases of the endocrine system (diabetes, thyroid disease, obesity, infertility, and breast and prostate cancers)
POPs

- Fetotoxic
- Neurotoxic
- Immunotoxic
- Cancer promoters
- Hormonal effects

- Basic mechanisms
  - molecular level
- Health effects
  - secondary effects
    - long chain of disturbances.

- Complicated research
  - Analysis require expertise
  - PCB: 209 congeners
    - Toxicity
  - Sensitivity vary between species
  - Occur in mixtures
    - additive, synergistic or even antagonistic effects

Persistent organic pollutants

- Dioxins and Furans
- PCB
- PBDE/ Flame retardant
- Organopesticides (DDT, HCB ++)
- Perfluorinated compounds
- Others
Adverse effects some specific toxicants

- **DDT**: suspected or proven
  - Spontaneous abortions, preterm delivery, obesity, delayed puberty, length-growth, behavioral effects, liver cancer, reproduction, neurodevelopmental, adrenal gland

- **Mercury**:
  - Exposure during pregnancy developmental delays and brain damage
Priority

- Pooled analysis on data from multiple cohorts
  - Data files actually shared
- Power
- Standardized analysis
- Eliminates publication bias
- Improves control for unmeasured confounding

- Some selected POPs
Risk of wheeze or bronchitis in high DDE versus low exposed group

Forest plot showing risk estimates for individual studies and the combined meta-analysis results for the highest versus the lowest DDE exposure and the occurrence of bronchitis or wheeze. 14% increase

Adjusted for gender, age of the child at the time of outcome assessment, duration of breastfeeding, gestational age, number of siblings of the child at the time of birth, maternal age, maternal body mass index, maternal smoking during pregnancy and during postnatal life of the child, maternal education, maternal allergy or asthma, and time of sample collection for POPs analysis.
PCB and birth weight

- 15 European cohorts, including 8000 children.

Although variation across cohorts, most show negative estimates

Total combined effect estimate: -150 g in birth weight

Govarts et al.
EHP
Perfluorinated compounds

- Single study from the Faroese
- 656 infants

- Prenatal effects
- For each doubling in prenatal exposure to PFOS 40% lower antibody responses at 5y

- Postnatal effects
- A 2-fold increase in PFOS and PFOA concentrations at age 5 years was associated with odds ratios between 2.4 and 4.2 for falling below a clinically protective level of 0.1 IU/mL for tetanus and diphtheria antibodies at age 7 y

- *Grandjean JAMA 2012*
HUMIS/ NoMic Study

- Cohort of 2600 mother-child pairs
  - Recruited 2002-2009
  - 200 ml milk in 2400
    - Pooled 8 samples
    - Approx. 1 month
  - Subset of 550
    - Infant fecal samples at 6 age-points up to 2
    - Recruited at hospital
    - Followed up at 10-12y
HUMIS-NoMIC

Pregnancy

1 & 4 days
1 & 4 months
6 months
1 year
2 years
10-12 years

Child

Fecal samples

Childs Hospital Journal

Medical Birth Registry

Mother

Pregnancy journals

200 ml Milk

QI

QII

QIII

QIV

2 years

Hair, spit, skin swabs

Clinical examination QV

Norwegian Patient Register linked in
- **PCBs:**
  - -28, 52, 74, 99, 101, 138, 153, 170, 180, 194, 8
  - **mono-ortho** PCBs 105, 114, 118, 123, 156, 157, 167, 189
- **BFRs:**
  - 28, 37, 47, 85, 99, 119, 153, 154, 181, 183
  - 209 & HBCD
- **Organopesticides:**
  - DDE, HCB, bHCH, oxychlordane
- **Perfluorated compounds**
  - PFOS, PFOA, PFHxS
- **Heavy metals:** Mercury, Lead, Arsenic and other heavy metals
- In subsets
  - **In 70 (15) samples:**
    - PCBs 31, 47, 66, 56, 87, 136, 110, 151, 149, 141, 137, 187, 183, 128, 199, 196, 209, and 209, DDT, α-HCH, γ-HCH, cis-chlordane, trans-nonachlor, mirex, 17 dioxins, and furans
- **Organotins**
- **Phtalates**
Geographical differences in marine food intake

- Cod/lean fishes
- Fish liver
- Pike, fresh water fish
- Crabs
Challenges perinatal assessment POPs

- **Exposure assessment**
  - Due to long half-lives single exposure assessments have been assumed to be accurate
  - However, major limitations to this assumption in pregnancy and lactation
    - Marked changes in blood lipid composition, maternal weight, glomerular filtration rate during pregnancy
    - Elimination by transfer to the child during breastfeeding

- Concentrations POPs vary in the period of pregnancy breastfeeding and for the infant while being breastfed and growing
Brominated flameretardants

The youngest are the highest exposed within a population-Norway 1998

• Cathrine Thomsen et al
Factors influencing levels of DDE in human milk

- Statistical significant factors shown
  - Smoking significant in crude but not adjusted model.
  - Siblings, sex, maternal education, number of years between last and current child not significant

- 38% explained variance prior to input of dietary variables

- Largely the same variables that predicted other POPs

- Data from a linear regression model, the estimated change shown as percentage change of median levels. Unpublished data
• Exposure in postnatal period not constant (BB)
  – One single estimate at any time point will misclassify
  – Critical windows within this period
Exposure in early childhood

- Simulated toxicokinetic profiles in children breastfed for 4 months.
- Duration of breastfeeding determines postnatal exposure
  - In babies not breastfed: total exposure during infancy small
- Misclassification of exposure

Verner MA et al. EHP 2013
- Levels 5 x higher breastfed for more than 4 months
- Median breastfeeding 4 months
Table 2.6. List of known and suspected environmental obesogens (A=Animal study, C=Cell culture study, H=Human study). Janesick & Blumberg (2011) provide more detailed information about obesogens.

<table>
<thead>
<tr>
<th>Chemical</th>
<th>Commercial use</th>
<th>Relevant EDC action</th>
<th>Obesogenic activity</th>
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<tbody>
<tr>
<td>Tributyltin</td>
<td>Pesticide, wood preservation</td>
<td>Binds PPARγ</td>
<td>Changes identity of adipose precursors, increases triglycerides in adipose tissue (A)</td>
</tr>
<tr>
<td>Phthalates</td>
<td>Plasticizer</td>
<td>Binds PPARγ</td>
<td>Induce adipocyte differentiation (C), men’s waist size (H)</td>
</tr>
<tr>
<td>PFOA</td>
<td>Non-stick coatings</td>
<td>Weakly activates PPARγ</td>
<td>Induce adipocyte differentiation (C)</td>
</tr>
<tr>
<td>Flavanone</td>
<td>Natural plant products used as flavourings</td>
<td>Binds PPARγ</td>
<td>Induce adipocyte differentiation (C)</td>
</tr>
<tr>
<td>PCBs</td>
<td>Electronics</td>
<td>Binds AhR in adipocytes</td>
<td>CB-77 promotes adipocyte differentiation, obesity (C,A)</td>
</tr>
<tr>
<td>Bisphenol A</td>
<td>Plastics</td>
<td>Binds ER, ERRγ</td>
<td>Induces adipogenesis (C), obesity (A)</td>
</tr>
<tr>
<td>Hexachlorobenzene</td>
<td>Fungicide</td>
<td>Alters TH signaling</td>
<td>Gestational exposure levels influence BMI (H)</td>
</tr>
<tr>
<td>Bisphenol A diglycid ether</td>
<td>Epoxy resins</td>
<td>Unknown</td>
<td>Induces adipogenesis (C)</td>
</tr>
<tr>
<td>PBDEs</td>
<td>Fire retardants</td>
<td>Reduces thyroid function</td>
<td>Stimulate fat production (C)</td>
</tr>
<tr>
<td>Diethylstilbestrol</td>
<td>Pharmaceutical estrogen</td>
<td>Binds ER</td>
<td>Perinatal exposures cause obesity (A), BMI in young children (H)</td>
</tr>
<tr>
<td>Genistein</td>
<td>Natural component in soy</td>
<td>Binds ER</td>
<td>Perinatal exposures cause obesity (A).</td>
</tr>
<tr>
<td>Perfluorooalkyl sulfonate</td>
<td>Non-stick coatings</td>
<td>Binds ER</td>
<td>Perinatal exposures cause obesity, alter insulin &amp; leptin levels (A).</td>
</tr>
<tr>
<td>Nicotine</td>
<td>Found in tobacco products</td>
<td></td>
<td>Alters development of pancreas &amp; adipose tissue, increases adipose cell size (A).</td>
</tr>
<tr>
<td>DDE</td>
<td>DDT metabolite</td>
<td>Binds ER</td>
<td>Concentrations in mothers associated with weight and BMI in female offspring (H)</td>
</tr>
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</table>

The mechanisms by which most of these chemicals affect weight gain are largely unclear. Tributyltin, one of the few chemicals studied in detail, activates the combined peroxisome proliferator-activated receptor gamma (PPARγ)/ retinoid-X-receptor (RXR) pathway, the main pathway for fat cell differentiation (Janesick & Blumberg, 2011) and thereby stimulates fat cell differentiation in vitro and increases adipose tissue in vivo in mice. Similarly, chemicals with estrogenic activity like DES, genistein and BPA appear to act via estrogen receptors on fat cells, and cells of the brain and other tissues to regulate adipose tissue and food intake (Janesick & Blumberg, 2011).
Many on the list are found in human milk
- Organotins the exception on the list
- Nicotin only if exposed to environmental smoking
The positive effect of DDE on rapid growth is tied to the prenatal period.

Important to distinguish between pre- and postnatal exposure.

Results shown for IQR, and corresponds to weighting 250g more (50th percentile).

*Nina Iszatt EHP 2014*
• 24 different toxicants: PCBs, BDEs, HCB, DDT, DDE +
• Infant toddler check list
• Only DDT identified out of all studied
• A significant worsening in behavior at 12 months in offspring of mothers with high levels
Breastfeeding

• Breastmilk:
  – Optimal nutrition for the baby
  – Immunological crosstalk mother-child
  – Oligosaccharides important for gut microbiota composition

• Benefits of breast-feeding is believed to outweigh risks from POPs in mother's milk

• Exceptions:
  – Women unusually high POPs
  – For long duration of breastfeeding there is a tradeoff between benefits and exposure to POPs

• Most important: reduce levels in girls/women in reproductive age!
Sources
Sources

• POPs such as PCBs, DDT, HCB and Dioxins:
  – PCB: Electrical circuits/transformers, isolated window, building materials, airborne if proximity to contaminated sites
  – HCB: unintended biproduct chlorinated pesticide processes
  – Dioxins: unintended combustion products, fires

• Brominated flame retardants
  – Electronical equipment, furniture

• Perfluorinated compounds
  – Teflon, waterproof clothing (gortex), wax
  – Non-stick food packing
Sources

- POPs such as PCBs, DDT, HCB and Dioxins:
  - Fatty food, especially marine products

- Brominated flame retardants
  - Marine products, but also dust

- Perfluorinated compounds
  - Marine products, dust, water
  - Food choices (wrapping, teflon)
Contaminant pattern varies across marine products

- Lean fish: Mercury
- Fatty fish: POPs
- Shift in feed: farmed salmon fed more soy beans and less marine fats and the content of PCBs and other POPs have decreased while pesticides has increased
- Large and old fish
- Locally fished
Fish intake during pregnancy

- Omega-3 fatty acids promote brain development
- Source of Iodine
- Healthy proteins

- The 2010 Dietary Guidelines for Americans recommend 8 to 12 ounces — two average meals of seafood a week for pregnant women
- Avoid locally fished marine products
- Avoid fish known high content mercury
Pregnant women who ate fish >3 times /week

- Offspring higher BMI values at 2, 4 and 6 years of age

Fish consumption of >1 &< 3 not associated with increased risk of childhood overweight or obesity
When pregnant

• Avoid fish with high levels of mercury
  – Shark, swordfish, king mackerel, tuna and tilefish (sushi).

• Avoid old and large fish (large trouts, halibut, pike)

• Avoid locally fished products
  – Follow local fish and wildlife advisories strictly
Fish intake before pregnancy
In general

- Cooking reduces POPs in fish
- Avoid food-items from countries with less strict regulations, before childbearing and while pregnant
- Wash fruits and vegetables
- Follow fish and wildlife advisories
- The bigger and older the fish the worse (pike, halibut versus cod from open sea)
- Wild salmon will have more omega 3
After participating in this presentation, clinicians should be better able to:

- Apply specific concepts regarding the adverse health impact of environmental toxicants in food and breast milk when making dietary recommendations for young girls and pregnant women.
Acknowledgements

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