Human milk biomonitoring

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> PPTOX 2007 Abstr. 56 <
Transfer of xenobiotics into breast milk

- **Diffusion processes**
- MW
- Lipophilicity
- Plasma Protein binding
- Ionisation (pKa)
  - weakly acidic : plasma > < milk : weakly alkaline
- **Carrier mediated**
  - Cation transporter (Cimetidine)
  - Anion transporter (Benzylpenicillin)

- **In favour**
- Low ( < 200)
- High
- Low
- Cationic

- ??????
Hypothesis of the molecular sive of the mammary gland

• For essential compounds appearing significantly in breast milk GI absorption (bioavailability) will be adequate

• similarly:

• non-essential compounds (Xenobiotics) appearing in breast milk will most likely be bioavailable by GI adsorption in the infant
Limitations of human milk data

- Different protocols (pooled, individual)
- Incomplete reporting
- Not representative
- Different timing of sampling
- Focus on few substances (POPs)
- Limited data on partitioning, carry-over
PCB 153 in mothers milk [µg/g lipid]
POPs in human milk in SH (μg/g lipid)
Food contamination (SH-DDS)

- **S-PCB**: 1997 = 9.0, 2004 = 6.0
- **S-DDT**: 1997 = 7.0, 2004 = 5.0
- **HCB**: 1997 = 2.0, 2004 = 1.0

**Units**: μg/kg food lipid (MW)
(2) Estimated cumulated dose
(Cssfat [ng/g fat])

- $\text{Cssfat} = \text{DI} * t^{\frac{1}{2}} [\text{days}] * (1/\ln2) / Vd$

- $\text{DI} = \text{daily intake}$
- $t^{\frac{1}{2}} = \text{half-life}$
- $Vd = \text{Volume of distribution}$

- from Rowland und Tozer (1980)
## Biaccumulation and estimated $t^{1/2}$

<table>
<thead>
<tr>
<th></th>
<th>Σ-PCB</th>
<th>Σ-DDT</th>
<th>HCB</th>
<th>TEQ</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Daily intake (DI)</strong> [ng/kg KG/d]</td>
<td>12</td>
<td>8</td>
<td>1,5</td>
<td>1 pg</td>
</tr>
<tr>
<td><strong>Body burden</strong> [μg/kg milk fat]</td>
<td>274</td>
<td>164</td>
<td>32</td>
<td>26 pg</td>
</tr>
<tr>
<td><strong>Half-life $t^{1/2}$ [years]</strong></td>
<td>6.9</td>
<td>6.2</td>
<td>6.5</td>
<td>7.5</td>
</tr>
</tbody>
</table>
## Calculated half-life of PCB

<table>
<thead>
<tr>
<th>PCB-congener</th>
<th>$t_{1/2}$ (y)</th>
</tr>
</thead>
<tbody>
<tr>
<td>28</td>
<td>0.55</td>
</tr>
<tr>
<td>52</td>
<td>0.38</td>
</tr>
<tr>
<td>101</td>
<td>1.5</td>
</tr>
<tr>
<td>118</td>
<td>2.8</td>
</tr>
<tr>
<td>138</td>
<td>5.0</td>
</tr>
<tr>
<td>153</td>
<td>6.8</td>
</tr>
<tr>
<td>180</td>
<td>7.5</td>
</tr>
</tbody>
</table>
Meironyte, Noren, Bergmann: JTEH 1999
Musk fragrances in human milk (US)

- Musk xylene
- Musk ketone
- **HHCB** (Galaxolide)
- AHTN (Tonalide)
- HHCB-lactone
- PhIP

- 2 – 150 [ng/g lipid]
- 2 - 238
- **5 – 917** (220 mean)
- 4 -144
- 10 -88
- 23 pg/ml

- Reiner et al, EST 2007
Wittsiepe et al.; Chemosphere 2007
B/M ratio (lipid base)

- PBDE
- PCB 180
- PCB 153
- PCB 118
- TEQ
- OCDD
- HpCDD
- TCDD

Bar chart showing the B/M ratio for different compounds, with OcDD having the highest ratio and TEQ having the lowest.
Body burden (model) and breastfeeding

Kerger et al., Chemosphere 2007
PCB-B and history of breastfeeding
(German KIGGS, n=1060)
PFOS S/M partition

from Kärrman et al., EHP 2006
PFOS

- Serum : 10 – 50 ng/ml
- Milk : 0.1 – 0.5 ng/ml
- M/S ratio: 0.01
- Dose:
  PFC Exposure ~ 200 ng/day
  ~ 40 ng/kg b.w.
  TDI ~ 100 ng/kg b.w.

Kärrman et al., EHP 2006
# Biomonitoring of Phthalates

<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>MEHP</td>
<td>4</td>
<td>-</td>
<td>9.5 - 13</td>
</tr>
<tr>
<td>MEHHP</td>
<td>-</td>
<td>17</td>
<td>?</td>
</tr>
<tr>
<td>MEOHP</td>
<td>-</td>
<td>16</td>
<td>?</td>
</tr>
</tbody>
</table>
Phthalate-metabolites and toxicity

- **Metabolite IX (MEHHP), > I >> VI (MEOHP) ≈ V > DEHP ≈ MEHP = 2-EH >> 2-EHA**

- Secondary metabolites:
- IX = mono-(2-ethyl-5-hydroxyhexyl) phthalate
- VI = mono-(2-ethyl-5-oxohexyl) phthalate

Bisphenol A

- Human milk = 0.1 - 0.7 [ng/g]
- Colostrum = 3.4 (mean)
- Serum = 0 - 2.2 [ng/ml]

» from: Otaka; Ikesuki; Kuroto-Niwa; Sajiki
Study proposal

- Development of breast cancer?
- Sensitization with Bisphenol A
- Induction by carcinogen PhIP
Risk- assessment for postnatal contaminants

- Dose concept (% TDI, MOS)
- Single compounds? Tox. End-points ?
- PBPK and AUC concept (bioavailability)
- Biomonitoring infant (RfC)
- Benefits of BM!: masking negative effects?
- Cohort ? : breast fed – bottle fed
- Vulnerable group ? : preterm babies !!
American Academy of Pediatrics (AAP)

- Exclusive breastfeeding for approximately the first six months
- and support for breastfeeding as long as mutually desired by mother and child.

» Pediatrics 2005
Conclusions

- Sentinel: constant vigilance to monitor trends and to detect new xenobiotics!
- Harmonize study protocols
- Investigate partition (develop model)
- Integrated risk-assessment
- „Breastfeeding or not?“ is not the question!
- Goal: low pre- & postnatal exposures