Chemical mixtures: challenges for research and risk assessment?
Cumulative risk assessment of 4 phthalates

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Introduction

Setting the scene

• **Not a new concept** – but very challenging to address – both theoretically and practically wrt testing and regulation

• **Chemical cocktails affect our health and environment**
  - recognized e.g. for endocrine disruptors, mutagens, narcotic acting substances, environment, metals, pesticides
  - introduced in regulation for C&L (known chemicals, intentional mixtures), PPPR and MRLs (intentional mixtures, effect based grouping), BPR, testing current framework (REACH phthalates)

• However, no instruments to address mixtures and combination effects systematically across EU legislation from multiple sources

• From generic and theoretical RA of single chemicals to assessment and management of real world exposure to multiple chemicals
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Scope and reasoning

• The aim of the restriction (scope) is to protect humans from exposure from 4 phthalates (DEHP, DBB, BBP and DIBP) by either inhalation or direct contact (skin + mucous membranes)

• The 4 phthalates are all classified as Reprotoxic Cat 1B and act via an anti-androgenic mode of action

• Previous work on cumulative exposure of 2-year olds and surveys on consumer products showed:
  • single articles can contain high concentration of single phthalates
  • Dose addition can lead to an unacceptable risk
  • Combined exposure from articles need to be assessed
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Information on exposure

• Exposure groups:
  – 2-year-olds, 6/7-year-olds, adults

• Exposure routes: oral, dermal, inhalation

• Exposure sources:
  – Food – literature review
  – Indoor environment – literature review, simulations
  – Consumer products – calculated based on migration data
  – Not everything is included, e.g. exposure from medical devices, medicine

Literature: Link between exposure from indoor env. and number of household articles containing phthalates
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Exposure sources and assumptions

**Consumer products:**
Shoes, bags, shower curtains, oil cloths & dinner mats, swimming equipment, swimming pools, balance balls, training balls, erasers, sex toys
- Only a selected number of relevant articles

**Exposure assumptions for the 3 age groups***:
- Weight
- Exposure duration (min/d)
- Exposed surface area (cm²)


All assumptions explicitly stated, choices can always be discussed – a key challenge
Method – RCRs and combined exposure

Concept of dose addition – modified hazard index

\[
\text{DNEL} = \frac{(N/L)\text{OAEL}}{\text{Assessment Factor}}
\]

All 4 phthalates are anti-androgens, DNEL based on anti-androgenic effects

For consumer products, indoor environment and food, individual risk characterisation ratios (RCR) are calculated:

\[
\text{RCR}_{\text{consumer product, DEHP}} = \frac{\text{Exposure}_{\text{consumer product, DEHP}}}{\text{DNEL} \times \text{DEHP}}, \text{ RCR} > 1: \text{uncontrolled risk}
\]

- Total RCR (DBP) = Total exposure DBP (consumer products, indoor env, food)/DNEL (DBP)

- Total RCR (anti-androgenic) = RCR (DBP) + RCR (DEHP) + RCR (DIBP) + RCR (BBP)
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Risk characterisation assumptions

Exposure expected to differ between and within age groups

- RCR calculated for median exposure estimates
- for values from literature – average of median values found
- for migration values – exposure times indicate median and worst case scenarios
- RCR for realistic worst case scenario (95th percentiles or max)
# The phthalate restriction dossier

## Cumulative risk characterisation

<table>
<thead>
<tr>
<th></th>
<th>Age</th>
<th>RCR based on median range, realistic scenario</th>
<th>RCR for realistic worst case scenario (95&lt;sup&gt;th&lt;/sup&gt; percentiles)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RCR indoor environment (air and dust)</strong></td>
<td>2-year old</td>
<td>0.14</td>
<td>0.78</td>
</tr>
<tr>
<td></td>
<td>6/7-year old</td>
<td>0.05</td>
<td>0.31</td>
</tr>
<tr>
<td></td>
<td>Adult</td>
<td>0.02</td>
<td>0.11</td>
</tr>
</tbody>
</table>

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<thead>
<tr>
<th></th>
<th>Age</th>
<th>RCR based on median range, realistic scenario</th>
<th>RCR based on realistic worst case scenario (97.5 percentiles)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RCR food</strong></td>
<td>2-years old</td>
<td>0.44*</td>
<td>0.44</td>
</tr>
<tr>
<td></td>
<td>6/7-years old</td>
<td>0.30*</td>
<td>0.30</td>
</tr>
<tr>
<td></td>
<td>Adults</td>
<td>0.13*</td>
<td>0.13</td>
</tr>
</tbody>
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</tr>
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<tr>
<td><strong>RCR articles</strong></td>
<td>2-year old</td>
<td>0.05</td>
<td>0.14</td>
</tr>
<tr>
<td></td>
<td>6/7-year old</td>
<td>0.53</td>
<td>5.64</td>
</tr>
<tr>
<td></td>
<td>Adult</td>
<td>0.04</td>
<td>0.90</td>
</tr>
</tbody>
</table>
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Biomonitoring

- Peer reviewed biomonitoring data – urinary samples
- Most recent data from 2007 (exposure from food uncertainty factor)
- High exposure to 1 phthalate → high exposure to the other phthalates
- The truth is in the tails – relevant to look at the 95th percentiles as well
- Difficulties to estimate exposure based on urinary excretion
- “Reference value” for calculated exposures
- New data from EU in 2013?

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<th>RCR for realistic worst case scenario (95th percentiles)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RCR biomonitoring</td>
<td>Child 0.43 0.39</td>
<td>1.59 1.23</td>
</tr>
<tr>
<td></td>
<td>Adult</td>
<td></td>
</tr>
</tbody>
</table>
Immediate risk in realistic worst case scenario

Calculated results supported by biomonitoring results

4 anti-androgenic substances – the work does not cover all exposure pathways and all anti-androgenic substances

There is an immediate need to reduce exposure to these 4 phthalates and endocrine disrupting chemicals (anti-androgens) in general
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RAC opinion

- RAC decision based primarily on biomonitoring results
- Available data from 2007 do not indicate current risk
- Current and future regulatory requirements will further reduce risk
- D-A first tier RA, incl uncertainties and conservativeness

DK does not agree:

- Exposure from imported articles not considered
- No documentation for decline of exposure in the near future
- DEHP use in Asia >50% of all plasticisers (much less in Europe) – not taken into account in the RAC opinion
- The effect of the authorisation process is unknown – especially considering the RAC opinion

When is enough enough? Infinite refinement possibilities
Challenges
Examining options

Overall aim is to reduce the chemicals pressure
- D-A is limited to known mixtures
- Risk assessment paradigm assumes thresholds
- Reversed burden of proof – risk properly documented in registrations?

Approach the risk of combination effects horizontally across sectors
- Establish knowledge on actual exposures, drivers for toxicity or is the truth also in the tails?
- Until knowledge gap is filled:
  - focus on priority mixtures?
  - develop a horizontal pragmatic approach?
Challenges
Examining options

Are there straight-forward solutions?

From same Mode of Action to Common Adverse Outcome Pathways (same endpoint)?

Precautionary approach if 0.1<RQ<1?

- requires a standpoint on read-across, exposure assessment and grouping

- extra (M)AF? Experiences from LV-cases to be drawn upon (drinking water)?

Use read-across and grouping in registrations directly?

What are our options – from a legal point of view?
Thank you