Benign by Design
Session 6: Sustainability from the beginning – the pharmaceutical example

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Emerging Contaminants

- Myriads of parent compounds
- Multiplied by even more transformation products (in even lower concentration)
- Multiplied by numerous environmental matrices, locations and points in time
- Multiplied by numerous tests with even more endpoints and parameters

Risk assessment impossible!
A smart person solves a problem.

A wise person avoids it.

Attributed to Albert Einstein
The Problem

Persistence!
### Biodegradability of Pharmaceuticals in the Aquatic Environment (in %)

<table>
<thead>
<tr>
<th>API</th>
<th>OECD 301 D</th>
<th>OECD 301 F</th>
<th>OECD 302 B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valproic acid</td>
<td>72</td>
<td>78</td>
<td></td>
</tr>
<tr>
<td>Mesalazin</td>
<td>&gt; 90</td>
<td>&gt; 90</td>
<td></td>
</tr>
<tr>
<td>Acetylsalicylic acid</td>
<td>81</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Penicillin V</td>
<td></td>
<td>&gt; 90</td>
<td>&gt; 90</td>
</tr>
<tr>
<td>Piracetam</td>
<td>&gt; 90</td>
<td>&gt; 90</td>
<td></td>
</tr>
<tr>
<td>Hydroxamic acid</td>
<td>50</td>
<td>90</td>
<td></td>
</tr>
</tbody>
</table>

*Kümmerer and co-workers, unpublished*
### Impact on Biodegradability in the Aquatic Environment
### Rules of Thumb

<table>
<thead>
<tr>
<th>Favorable</th>
<th>Less Favorable</th>
</tr>
</thead>
<tbody>
<tr>
<td>![Favorable Structure 1]</td>
<td>![Less Favorable Structure 1]</td>
</tr>
<tr>
<td>![Favorable Structure 2]</td>
<td>![Less Favorable Structure 2]</td>
</tr>
<tr>
<td>![Favorable Structure 3]</td>
<td>![Less Favorable Structure 3]</td>
</tr>
<tr>
<td>![Favorable Structure 4]</td>
<td>![Less Favorable Structure 4]</td>
</tr>
<tr>
<td>![Favorable Structure 5]</td>
<td>![Less Favorable Structure 5]</td>
</tr>
</tbody>
</table>

- Kümmerer K (2007) Green Chem. 9, 899
De Novo Synthesis
(1) Targeted Structure Variation

Goal: Improved Efficacy and biodegradability in the environment

- Improved by variation of the sugar?
- Improved by variation of substituents at the furan ring?
- Improved by variation of the aromatic ring?

### Improved Active Pharmaceutical Ingredient

<table>
<thead>
<tr>
<th>Structure ID</th>
<th>Log Kow</th>
<th>Effect threshold (rel. units)</th>
<th>Biodegradation [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>GSF</td>
<td>-2.1</td>
<td>1</td>
<td>19</td>
</tr>
<tr>
<td>2211_2 (Glu, Cyclohex)</td>
<td>-1.8</td>
<td>&gt; 1</td>
<td>37</td>
</tr>
<tr>
<td>2211_3 (Gal, Cyclohex)</td>
<td>-1.8</td>
<td>&gt; 1</td>
<td>37</td>
</tr>
<tr>
<td>2211_4 (Glu-Br)</td>
<td>-0.5</td>
<td>&gt; 1</td>
<td>14</td>
</tr>
<tr>
<td>2211_5 (Glu-F)</td>
<td>-0.9</td>
<td>&gt; 1</td>
<td>14</td>
</tr>
<tr>
<td>2211_6 (Glu-Cl)</td>
<td>-0.7</td>
<td>&gt; 1</td>
<td>14</td>
</tr>
<tr>
<td>2211_7 (Glu-I)</td>
<td>-0.5</td>
<td>&gt; 1</td>
<td>14</td>
</tr>
<tr>
<td>2211_8</td>
<td>-2.0</td>
<td>&lt;0.01</td>
<td>54</td>
</tr>
<tr>
<td>2211_9 (Desoxyglu)</td>
<td>-1.5</td>
<td>&gt; 1</td>
<td>31</td>
</tr>
</tbody>
</table>

![Chemical Structures](images)

Frei et al., patent pending

Re-Design

β-blocker: Metoprolol

Photodegradation

Metoprolol

Biodegradation

Closed Bottle Test [CBT, OECD 301D]
Manometric Respirometry Test [MRT, OECD 301F]

Drug Like
Biodegradable
Photo TPs

‘Green’ derivatives of β-blocker
Better biodegradable and possess non-inferior or improved pharmacological properties

Rastogi T, Leder C, Kümmerer K (2014), Chemosphere, 111, 493–499,
Rastogi T, Leder C, Kümmerer K (2015), ES&T, in press, doi/10.1021/acs.est.5b03051
**Biologische Abbaubarkeit**

**Tensid LAS**

**TPS:**
nicht biol. abbaubar

**Tensidverordnung 1962**

**LAS:**
leicht biologisch abbaubar
Gezielte Verbesserung
Komplexbildner EDTA vs. S,S-EDDS

Dixon N. 2004 (http://www.euconferences.com/chemicalsmanagement04 /day2presentations.htm)
Carrots

- New business case
- Prolonged patent life-time
- Fast track authorization
- Precautionary principle (subset of arguments)
- Important contribution to CSR
- Increased reputation
... and Sticks

- EMA: Revision of EMEA guideline (EU Parliament)?
- Legislation (e.g. EU Water Framework Directive)
- U.S. Senate Hearing
- The greener consumer

Benign by Design

Also for

• Chemicals
• Materials
• Complex products
• Substance flows
• Material flows