Degradability of Pharmaceuticals in the Aquatic Environment

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Chemicals are part of modern life. They are part of all spheres of human life. They are used as pharmaceuticals, pesticides, detergents, fertilizers, dyes, pints, finish, preservatives, food additives and others. They contribute to our well being, high expectancy of life and economical prosperity. There is also a back side of this success story. If chemicals are not used in closed loops they can enter into the environment. Especially if they are used in everyday life and if they are constituents and ingredients of consumer products they are emitted into the environment by non point sources. After administration pharmaceutical substances are excreted by the patients into waste water. Outdated medicaments or reminders are sometimes disposed in drains in households, presumably 20-40 % in Germany. Therefore, pharmaceutical substances enter municipal sewage and sewage treatment plants. If they are not eliminated during sewage treatment they are emitted into surface water and can reach drinking water. This makes it difficult to hold them back efficiently.

A long half live in the environment results in a big temporal and spatial range. Therefore, for persistent chemicals, a risk assessment is not possible. With bigger scales involved uncertainty increases time and possible effects cannot be tested in lab trials. Persistency is therefore one of the most important criteria for the environmental assessment of chemicals. For persistent organic pollutants (POPs) the Stockholm convention (http://www.pops.int/documents/context/ convtext_en.pdf)

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came into force. Until now only 12 organo-halogen compounds the so called dirty dozen are regulated under this convention among them polychlorinated biphenyls (PCBs), a classical example of persistent pollutants. PCBs have been synthesized for the first time in 1877. In 1899 severe health problems (chloracne) associated with the handling of PCBs had been reported. Throughout the years the poisoning of rice oil by these compounds and neurotoxic effects as carcinogenicity has been described in detail. Despite this knowledge it took until 1999 to ban PCBs fully within the EU – 100 years after the first reports of its severe toxicity! This example demonstrates that it is not only the time scales of the chemicals itself and the environmental processes impacted by them but also the time scales of economical and political systems. Additionally, the use of persistent chemicals is often associated with high costs in the long run – at least for the general public.

In the Stockholm convention a half life of more than 50 days in water is set as a criterion for POPs. Recent research show that other chemicals that are less persistent and have higher polarity then the dirty dozen are distributed globally and can accumulate in humans. A statistical correlation between the persistency of chemicals and the prevalence of the presence of chemicals in the environment that can initiate cancer has been reported only recently.

The potential for chemicals to undergo biotransformation is an important aspect of assessing the environmental fate and risk of chemicals. Several different non-biotic processes can result in the removal of chemicals from sewage, surface waters, ground waters, drinking water processing, and soil. Biologically mediated processes (i.e. biotransformation) and non biotic processes can result in the full transformation or mineralization of chemicals in the aquatic environment. In rare cases chemicals are fully broken down to water, carbon dioxide and inorganic salts. Very often transformation is incomplete and unknown transformation products are formed.

Since the nineteen-eighties pharmaceuticals from different groups have been detected in the environment (e.g. Kümmerer 2004). Only few data is currently available concerning the biodegradability of antibiotic compounds in STPs and surface water. It has been found that most pharmaceuticals are not biodegraded fully in sewage treatment and in the environment. It has been found that in the case of pharmaceuticals total degradation does take place only rarely and the process is stopped before total mineralization. These intermediates (i.e. stable metabolites or so called transformation products) of (bio)transformation can be even more stable than the parent compounds. They often also differ in terms of toxicity and have a different potential for accumulation compared to the parent compound. This also holds true for drugs which are excreted as conjugates after they have been hydroxylated or transformed for instance into sulfates, glycosides and others. If at all, these products are usually less active than the parent compound. They can also be regained by microbial activity in the environment or in STPs.

If the parent compounds are degraded only partially resulting transformation products with high stability under environmental conditions will remain in the environment too. They can also be toxic against humans and environmental organisms. In this case the situation may be worse as we have usually much less knowledge on the stable transformation products and their fate and effects in the environment than on the parent compounds. Furthermore, if the input rate is higher than the rate of degradation or mineralization of chemicals they will nevertheless be present at constant levels in the environment. This can be called persistency of second order or pseudo persistency.

Kümmerer 2004: Pharmaceuticals in the Environment, 2nd Ed., Springer, Heidelberg New York Tokyo, 2004, 3rd Ed. In praparation

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10th Japanese-German Workshop on Water Technology
Berlin, October 9th-10th 2006

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Detection of Pharmaceuticals in the Environment

Reports from:
A, AUS, BRA, CDN, CH, D, DK, GB, F, I, J, NL, S, USA, ...

- in hospital effluent, waste **water**, rivers, ground water, drinking water in the **ng/L-μg/L range**
- from **all therapeutical groups** as far as studied up to now (also: diagnostics, disinfectants e.g. QACs)
- **in soil**: antibiotics, growth promoters (up to 300 μg/kg, higher in manure)
- continuous emission into the environment:

pseudo persistence!

..., Färber et al. 2002, Kolpin et al. 2002, Sacher et al. 2001, Kümmerer et al. 2001, Hamscher et al. 2002, Zuccato et al. 2001, Hirsch et al. 1999, Ternes 1998ff, Kümmerer et al. 1996, 1997 Heberer 1996ff ,...

Elimination of Pharmaceuticals in Sewage Treatment Plants

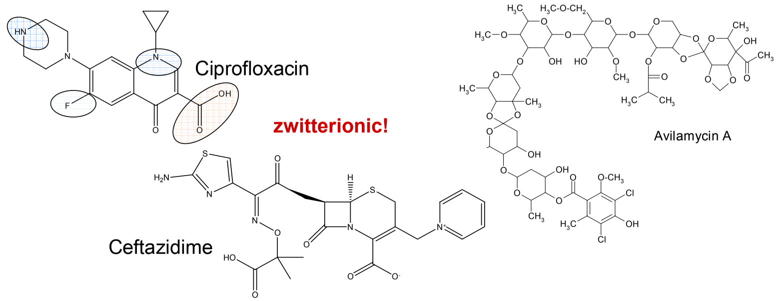
- Antibiotics: 0 -100%
- Zytostatics: 0 -100%
- Hormones: 20 - 80%
- Statines 0 - 50%
- Pain killers 0 - 50%
- Antidepressents 0 - 50%
- Disinfectants: 0 -100%
- Diagnostics(x-ray, MRI): 0 - 20%

...., Golet et al. 2002, Färber et al. 2002, Kolpin et al. 2002, Sacher et al. 2001, Kümmerer et al. 2001, Zuccato et al. 2001, Hirsch et al. 1999, Ternes 1998ff, Heberer 1996ff, Richardson und Bowron 1985, ...

What Does Elimination Mean?

Pharmaceuticals are Special!

"Designed" for bioactivity and stability, complex molecules with several, often different functional groups!



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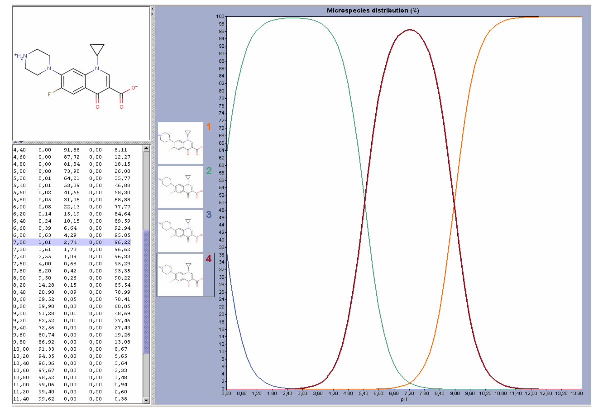
Ciprofloxacin as Zwitterion (pH 6.5-8.0)



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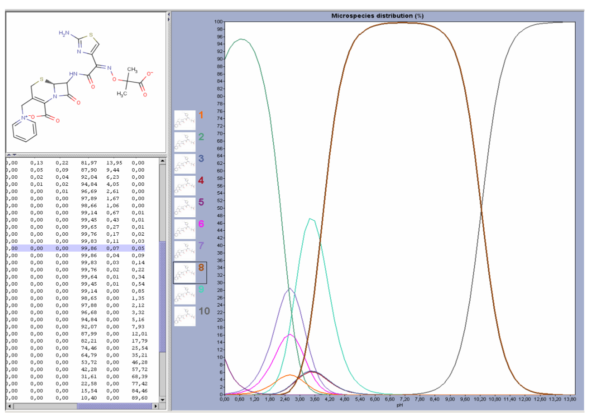
Ceftazidime Species as Function of pH



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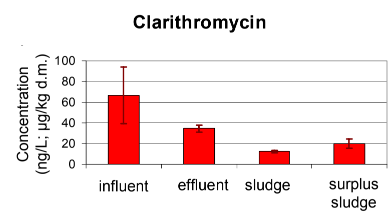
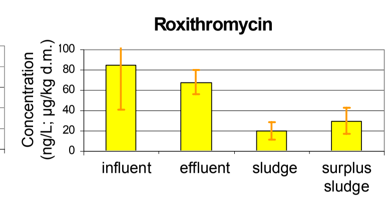
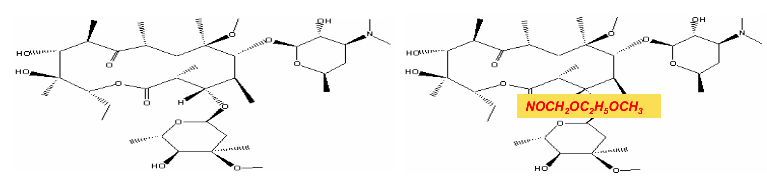
Elimination of Antibiotics in a STP: Impact of Structure







Alexy, Sacher, Wenz, Kümmerer, submitted

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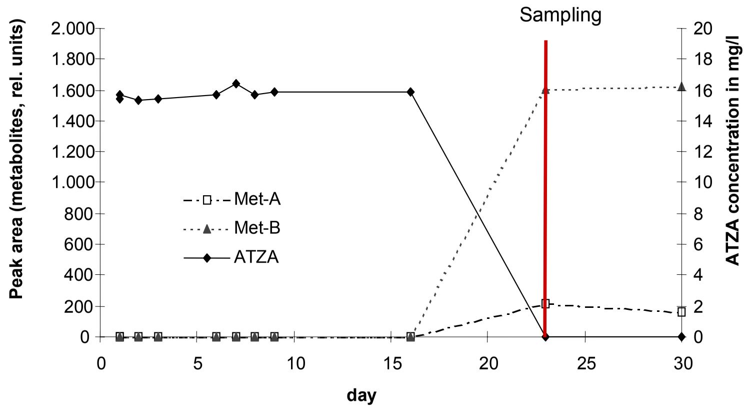
Elimination of ATZA in the Zahn-Wellens Test (OECD 302B)



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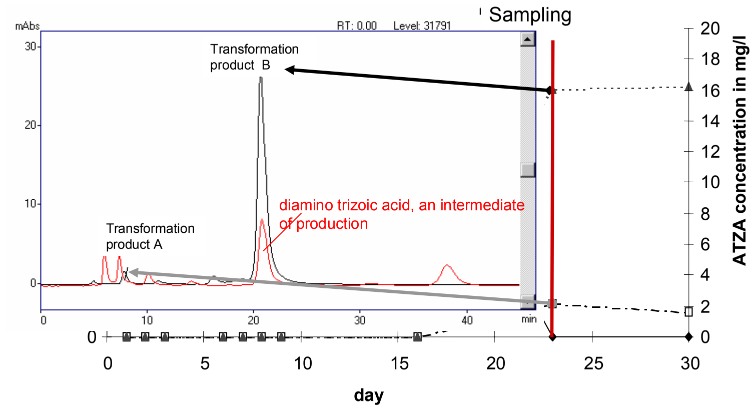

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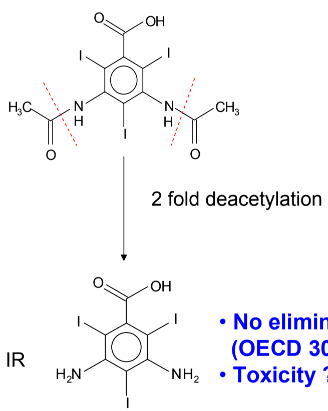
Significance of Metabolites and Transformation Products?

Amidotrizoic acid (ATZA)



Diaminotrizioc acid
(metabolite B)
Confirmed by MS, 1-H-NMR, IR

- **No elimination in STP (OECD 303A)**
- **Toxicity ?**

A. Haiß, K. Kümmerer, Chemosphere, 62 (2006) 294–302

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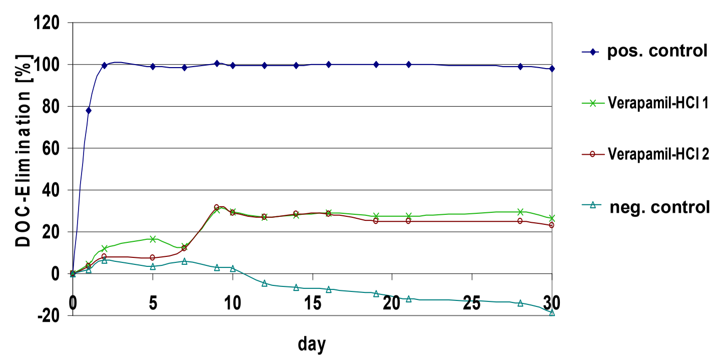
DOC-Elimination of Verapamil-HCl in the ZWT



Trautwein & Kümmerer, submitted

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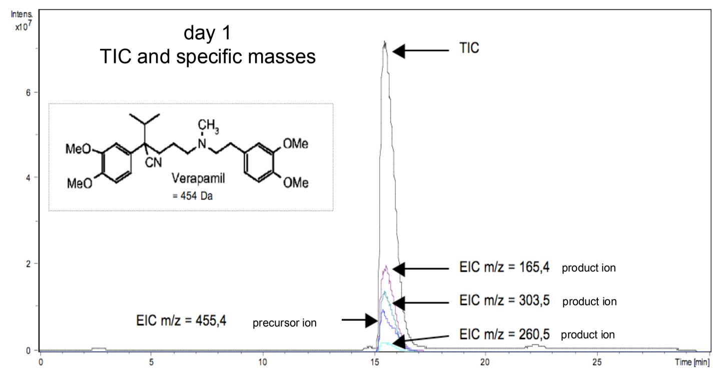
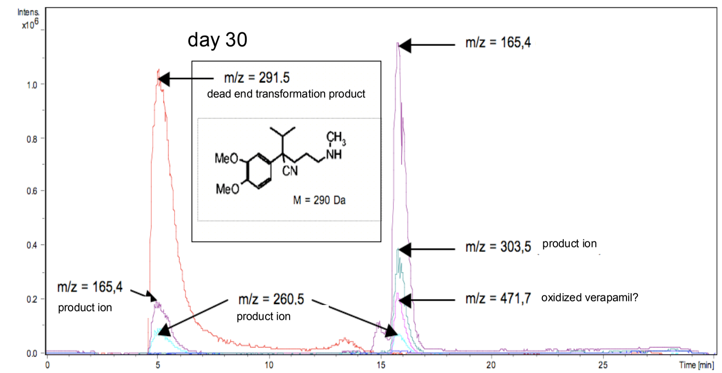
Primary Elimination of Verapamil in the ZWT (LC-MS/MS)



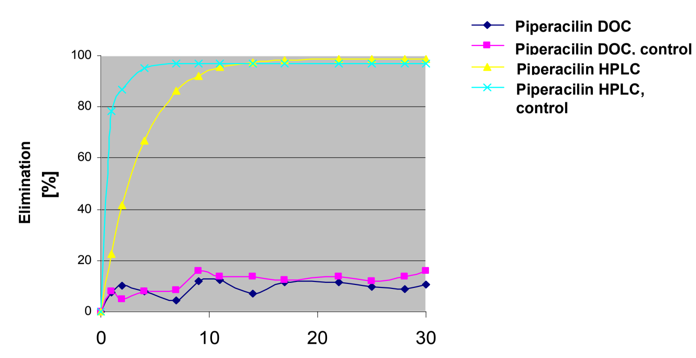
Trautwein & Kümmerer, in preparation

Elimination of Verapamil in the ZWT (LC-MS/MS)



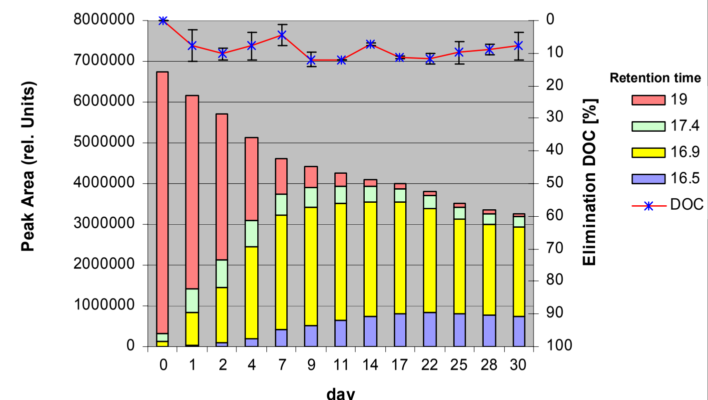
Trautwein & Kümmerer, submitted

Elimination of Piperacilin: DOC vs. HPLC-UV/Vis



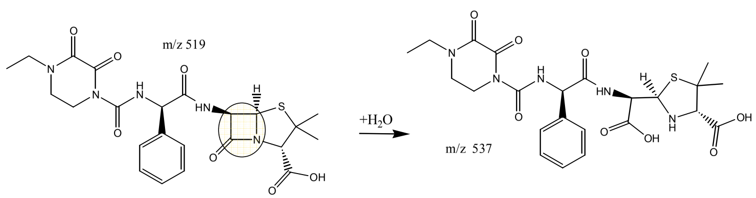
Kümmerer et al., submitted

Transformation Products of Piperacilin (HPLC-UV/Vis)



Kümmerer et al., submitted

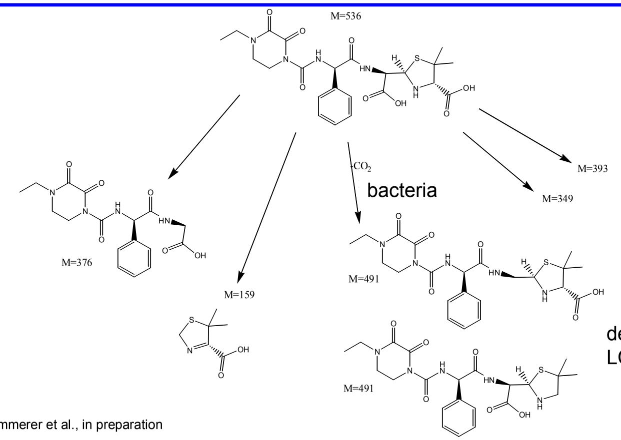
Hydrolysis of Piperacilin LC-MS/MS



confirmed by LC-MS/MS

Kümmerer et al., submitted

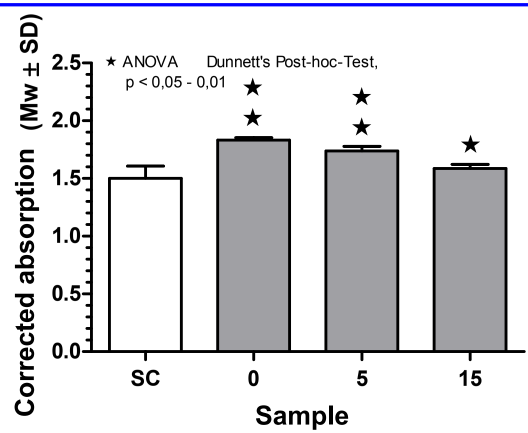
Decarboxylation of Piperacilin LC-MS/MS



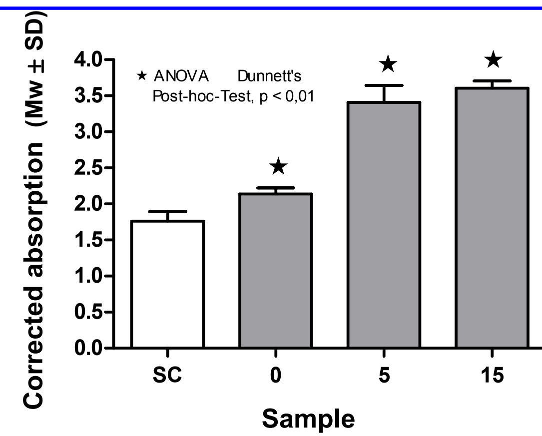
detected by LC-MS/MS

Kümmerer et al., in preparation

Decreasing Estrogenic Activity by Advanced Oxidation



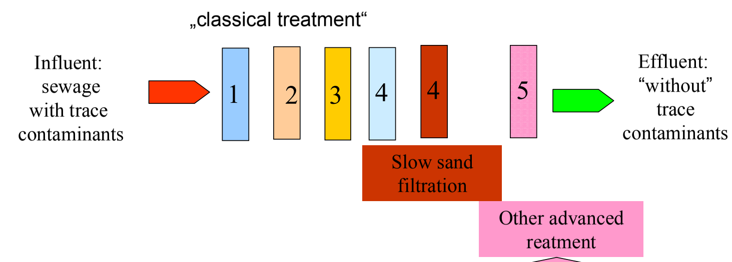
Increasing Androgenic Activity by Advanced Oxidation



Elimination?

Which compound to what degree!

Advanced Effluent Treatment - the Solution?



- Adsorption (coal)
- Membrane (bio-, membrane filtration, ultra-filtration, …)
- Advanced Oxidation (ozone, fenton-, photo-, …)
- Slow sand filtration

Advanced Effluent Treatment (1)

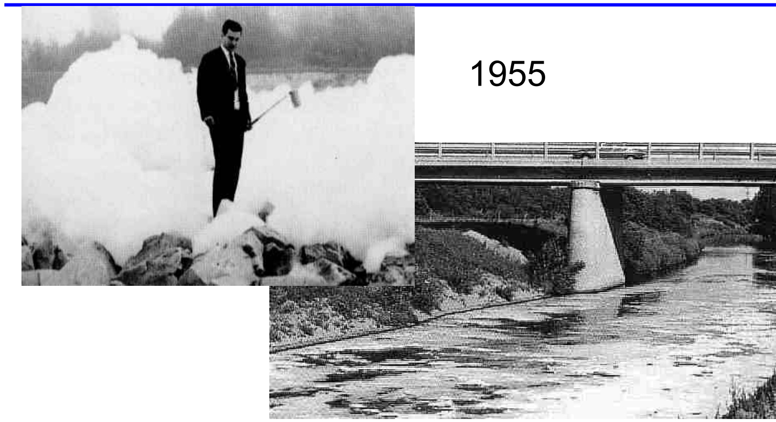
- Advanced filtration technologies (reversed osmosis, membrane filtration, nanofiltration), and (photo)oxidation technologies are emerging.
- Efficiency may depend strongly on the type of compound.
- Antibiotics: Resistance and bio-membrane (enrichment, residence time)
- Costs?
- Storm water?
- Infiltration of the ground before STP?
- Reaction by-products?

Advanced Effluent Treatment (2)

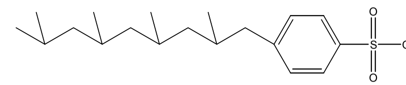
- Effective for new compounds?
- Not possible in less developed countries
- Not compatible with green chemistry.

Not Biodegradable TPS ...

1955



Improving Biodegradability: Surfactants

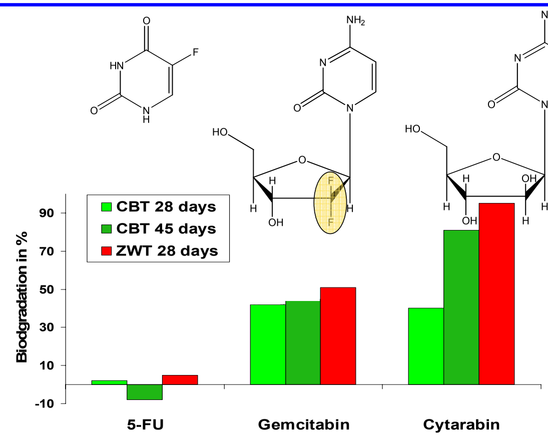


TPS: not biodegradable

New legislation for surfactants 1962

LAS: readily biodegradable

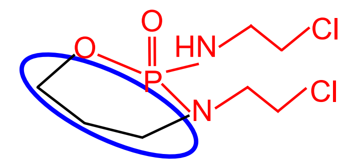
Different Biodegradability of Structurally Related Cytotoxics



Kümmerer & Ahmad, Acta Hydrochim. Hydrobiol., 25, 166-172 1997

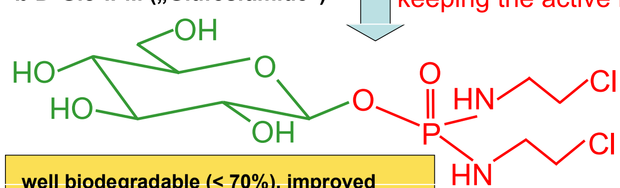
Improving Biodegradability: The Cytotoxics Ifosfamide and Glufosfamide

Ifosfamide:
not biodegradable (0%)



ß-D-Glc-IPM („Glufosfamide“)

keeping the active moiety



well biodegradable (< 70%), improved resorption in the gut; clinical trial phase III

Kümmerer et al. Chemosphere, 40, 767 (2000)

Long Term Risk Management: Green Chemistry & Pharmacy

New compounds are effective, efficient, and readily degradable in the environment

identification (sub)structures essential for
- **efficacy**
- **(bio)degradability**

Kümmerer, Green Chemistry, submitted; www.start-project.de

Economical and Other Aspects

- **… within a generation chemicals should be produced and applied that do not have any impact on the environment. (EU Parliament and EU-Commission 2002)**
- **In the middle and in the long run there will be an increase of innovation and economical advantages for healthy and environmental friendly products. (German Advisory Board for Environment 2003)**
- **Big Green Chemistry initiative by the U.S. Environmental Protection Agency**
- See also: Daughton C. G. (2003): Cradle-to-Cradle Stewardship of Drugs for Minimizing Their Environmental Disposition While Promoting Human Health. I. Rationale for and Avenues toward a Green Pharmacy. Environ. Health Perspect. 111, 757

Thank you!