From a Problem to a Business Opportunity
Design for Environmental Biodegradability

Prof. Dr. Klaus Kümmerer

LEUPHANA
Institute of Sustainable and Environmental Chemistry
http://www.leuphana.de/en/institutes/isec.html

ISC3
International Sustainable Chemistry Collaborative Centre
http://isc3.org
1. Introduction
2. Approach
3. Examples
4. Conclusions
Increasingly End of Life Issues
(concentration, temporal and spatial scales, variety of micro pollutants)

Number of pharmaceuticals detected in surface water, ground water, tap water (number per country)

Tim aus der Beek, Frank-Andreas Weber, Axel Bergmann, Gregor Grüttner, Alexander Carius:
Pharmaceuticals in the environment: Global occurrence and potential cooperative action under the Strategic Approach to International Chemicals Management (SAICM), Umweltbundesamt, Texte Nr. 67/2016, Berlin, September 2016, 38
Metformin and Biotransformation Product Guanyl Urea

German Rivers Elbe, Weser and North Sea

Elimination of Micro-Pollutants in Advanced Waste Water Treatment

Ozonation

PACX/UF

Many Precursors - One Transformation Product
(formation of possibly unknown, toxic chemicals in advanced effluent treatment)

- **Methadon and other drugs with amine moieties**
  - Hanigan et al., ES&T, 2015

- **Membranes**

- **Dissolved organic matter**

**N-Nitrosodimethylamine**
- Highly heptaoxic
- Probably human carcinogen
- Threshold drinking water USA: 7 ng/L

**Ozonation**
- Incomplete Degradation
- Soil

**Chlorination**
- Potable Water

**Tolylfluanid**
- Schmidt und Brauch ES&T, 2007

**Water**
One Precursor – Many Transformation Products

UV-Photolysis of Ciprofloxacin
Detected Transformation Products (High Resolution LC-MS/MS)

Toxicity of CIP Photo Products
(Micro-Nucleus Test, Cell Toxicity)

Window of Genotoxicity

Garcia-Käufer, Haddad, Bergheim, Gminski, Gupta, Mathur, Kümmerer, Mersch-Sundermann (2012), ESPR, 19, 1719-1727
Not just many different parent compounds – also often numerous unknown transformation products per parent compound -
Too little knowledge, too many compounds for targeted treatment and end points for a risk assessment
Products of Incomplete Mineralization (mostly unknown!)

Parent Compound

Metabolites

Environmental Transformation Products
- biological
- non biological
  - (Hydrolysis, Oxidation, Reduction, Photolysis...)

Technical Transformation Products
- Synthesis, Water and effluent treatment, ...
  - (Hydrolysis, Oxidation, Rearrangement, Photolysis...)

Klaus Kümmerer
Dynamics of Compounds
Usage of Pharmaceuticals (Germany)

Data: Ebert et al., Umweltbundesamt (2014)
Short Comings of (Advanced) Effluent Treatment

- Advanced filtration technologies (reversed osmosis, membrane filtration, nano-filtration), and (photo)oxidation technologies are emerging.
- Even combinations fail to remove all contaminant
- Efficiency depends strongly on the type of compound.
- AOP: Reaction by-products may be toxic, mutagenic, genotoxic, …
- Costs?
- Storm water?
- Infiltration of the ground before STP?
Increasing Need of Water (Re)use

> 80% of the world’s wastewater released untreated

Increasing need of water (re)use (population growth, climate change)
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A smart person solves a problem.

A wise person avoids it.

Attributed to Albert Einstein
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Attributed to Albert Einstein

Measures at the source (users, molecules)

Kümmerer K., et al. Science of the Total Environment,
Less Usage-Feasible?

Usage of a Pharmaceutical

- Medical Doctors
- Authorities
- Pharmaceutical Companies
- Pharmacists
- Economists
- Scientists
- Scientists
- Scientists
- Politics & Politicians
- Health Insurances
Less Usage-Feasible!
Use Patterns (DDD per 1000 people per day)

Anti-diabetics

Anti-cholesterols
Less Usage-Feasible!
Use patterns (DDD per 1000 people)
Antibiotics 2011

Y-axis: DDDs per day per 1000 population
X-axis: Countries

Countries listed from left to right: Netherlands, Finland, Luxemburg, Belgium, Denmark, Greece, Italy, Spain, Portugal, UK, Croatia, Hungary, Germany, Austria, Switzerland, France, Romania, Bulgaria.
Less Usage-Feasible!
Use Patterns Veterinary Antibiotics (EU)
(mg/kg Biomass)

Grave et al., 2010
In the Patient
Less excretion

• Improved up take in the intestine and the target (drug delivery, drug targeting, resorption)

• Improved degradation of the non resorbed share in the intestine

• Watch out! Compounds of higher efficacy may result in lower amounts and environmental concentrations but not lower risk!
Compounds Still Needed and Excreted

- What Is the Problem?

Persistence
Avoiding Environmental Persistence

Chemical

Fast and complete mineralization in the environment

No Exposition

No Effect

No Risk
Putting benign by design into practice—novel concepts for green and sustainable pharmacy: Designing green drug derivatives by non-targeted synthesis and screening for biodegradability

Christoph Leder, Tushar Rastogi, Klaus Kümmerer *
Stability i.e. Reactivity (!) is a Function of ...

- Diversity of metabolic enzymes, e.g. bacteria: narrow spectrum in humans, broad spectrum in the environment
- pH (municipal sewage 7-9; stomach < 2)
- Redox potential: gut anaerobic, environment often aerobic
- Light: access, spectrum, and intensity; photolysis type I & II (e.g. by presence of humic substances)
- Temperature
- Concentration
- Humidity
- ...

Kümmerer K., Green Chem. 9, 899
Rational Drug Design - Revisited

- High oral absorption
- Effective and efficient
- Receptor specific
- Reduced/no unwanted side-effects
- metabolized to harmless metabolites
- ...

- High degree of mineralization after introduction into the environment
What Would that do to the Drug Discovery Process?

• Starting from (already known?) lead structure
• Optimization as usual (e.g. by chemoinformatics)
• **New:** including after use life at early stage
  – Challenging
  – Paradigm shift
  – Fascinating problem (not toxic/environmentally biodegradable)
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“Non Systematic” Re-Design

Non biodegradable drug 🌟 Photodegradation 🌟 Propranolol 🌟 Biodegradation 🌟 Closed Bottle Test [CBT, OECD 301D] 🌟 Manometric Respirometry Test [MRT, OECD 301F]

Identification of Biodegradable Photo Products 🌟 high resolution LC-MS² analysis 🌟 Orbi-Trap

Pharmaceutical Assessment: Activity, Toxicity

4-Hydroxypropranolol

Rastogi T, Leder C, Kümmerer K (2015) Environmental Science and Technology, 49, 11756–11763 (Propranolol; editors choice, open access)
Pharmacological Activity of 4-Hydroxypropranolol

*In Vitro* Analysis

Mean receptor activity

Regression
95% Confidence Band
95% Prediction Band

**EC$_{50}$**: 0.32 ± 0.06 µM

Propranolol:
**EC$_{50}$**: 0.83 ± 0.019 µM
Re-Design and De-Novo Design Examples

Anti-Cancer Drugs: patent


β- Blockers:


Antibiotics: Two patent applications pending

Ionic liquids:
Carrots

- Prolonged patent life-time
- Fast track authorization
- Precautionary principle (subset of arguments)
- Important contribution to CSR
- Increased reputation
- Vision: „next generation“ is greener!
Incentives

New compound

New business opportunity
Carrots

Opportunity/business case

VS.

falling behind
... and Sticks

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

New product for birth control under investigation

Composition:
- natural, degradable estrogens
- and a biodegradable progesterone
Arguments and Counter Arguments

**Ethics:** Not to deny anyone from a new pharmaceutical, however, how many are not developed for economical reasons (antibiotics, malaria, AIDS, lepra, children …)

**Costs:** Drug development is very expensive, however, quite a big share of costs is related to marketing (> 2/3?)

**Shortage of new compounds:** further regulation (environment) will result in less compounds, however,

(1) already more than one compound on the market for most groups (e.g. sartanes)
(2) new regulations result in the longer run in new and better compounds (see e.g. increased toxicological requirements after Contergan case) - new innovation space
Instead of a Summary

New ideas are not successful because the people sticking to the old ideas are convinced but because they will die out and the next generation is raised with the new ideas.

Max Planck
1. (Advanced) Effluent treatment cannot cope with the challenge
2. Re-Design can result in active but environmentally biodegradable pharmaceuticals
3. Environmental biodegradability can be included in de-novo design
4. Benign by Design is a new business opportunity!