

# From a Problem to a Business Opportunity

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## Design for Environmental Biodegradability



**Prof. Dr. Klaus Kümmerer**



**LEUPHANA**

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<http://www.leuphana.de/en/institutes/isec.html>



International Sustainable Chemistry  
Collaborative Centre

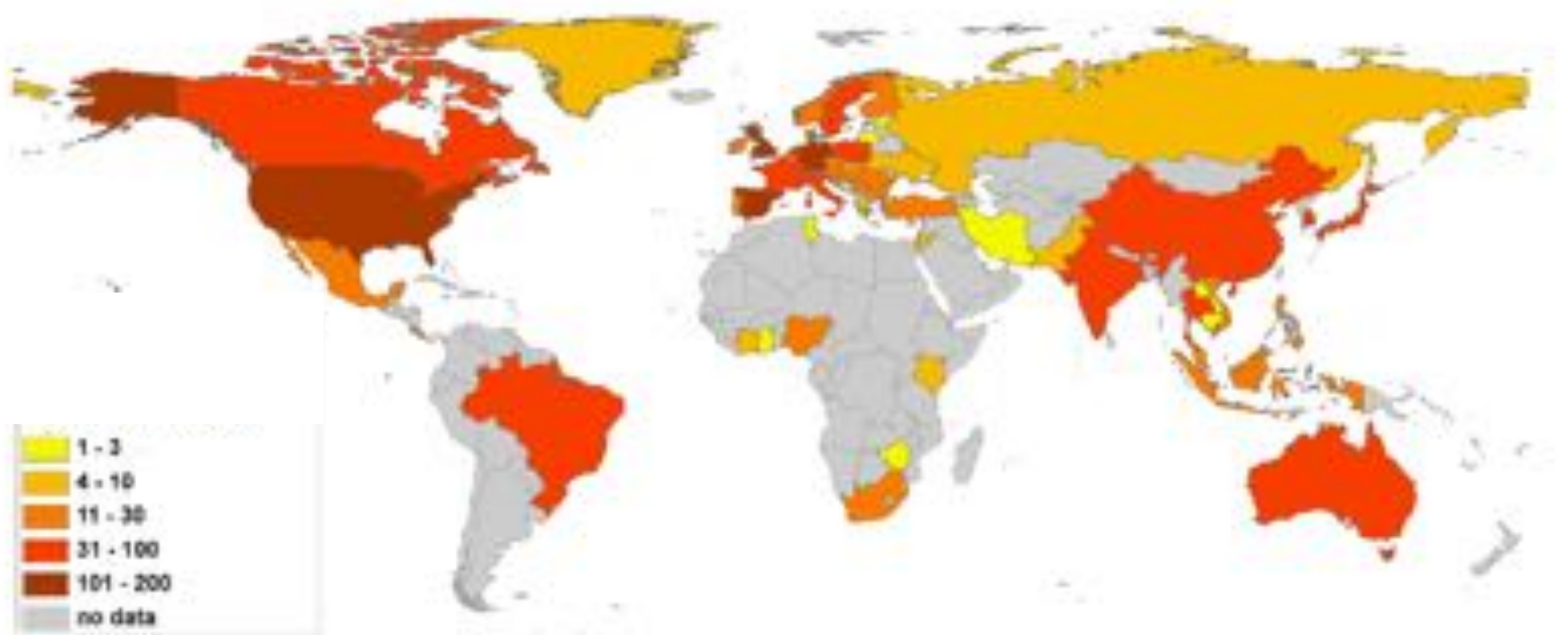
<http://isc3.org>


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1. Introduction
  2. Approach
  3. Examples
  4. Conclusions

# Increasingly End of Life Issues

(concentration, temporal and spatial scales, variety of micro pollutants)

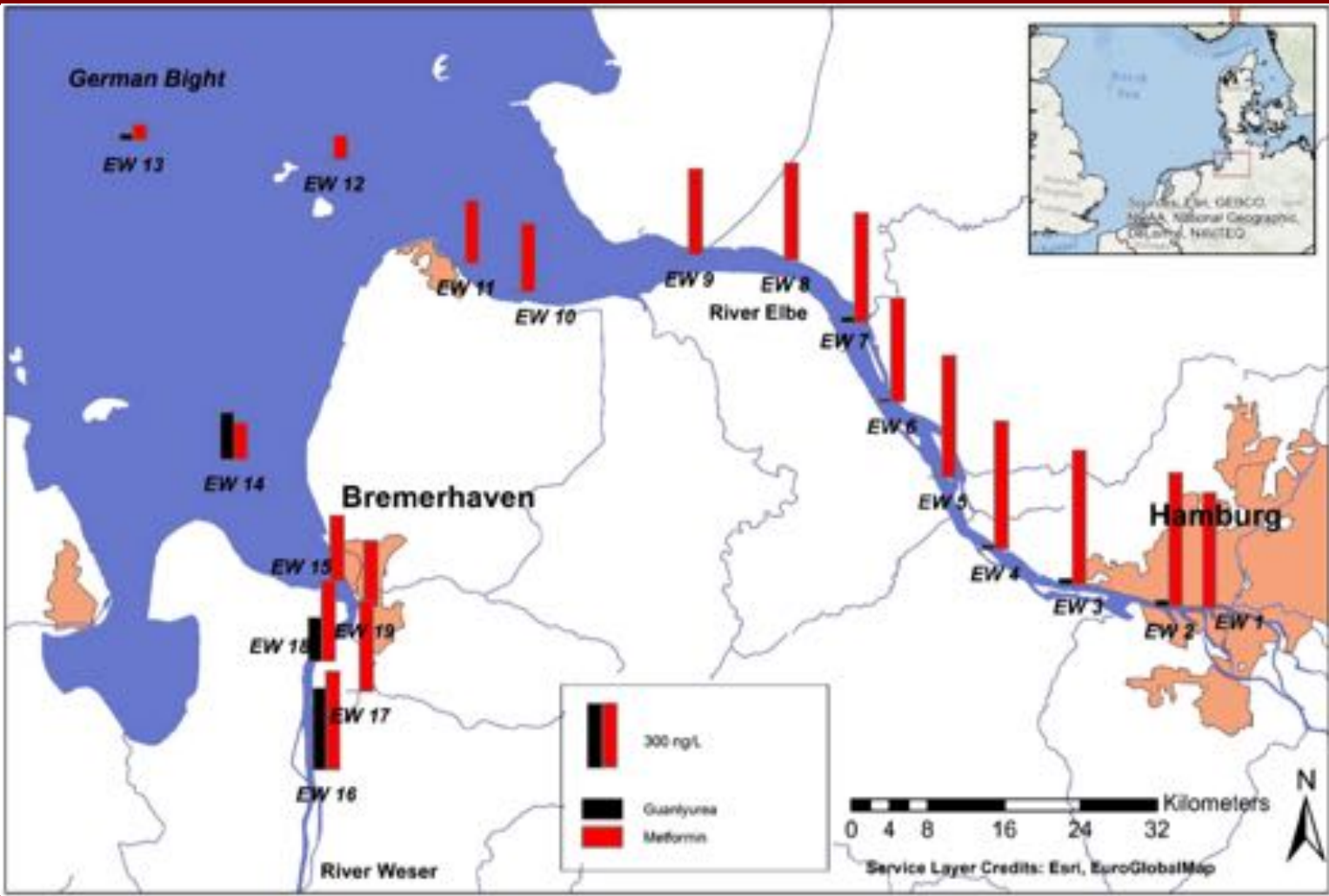
Number of pharmaceuticals detected in **surface water, ground water, tap water (number per country)**



 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

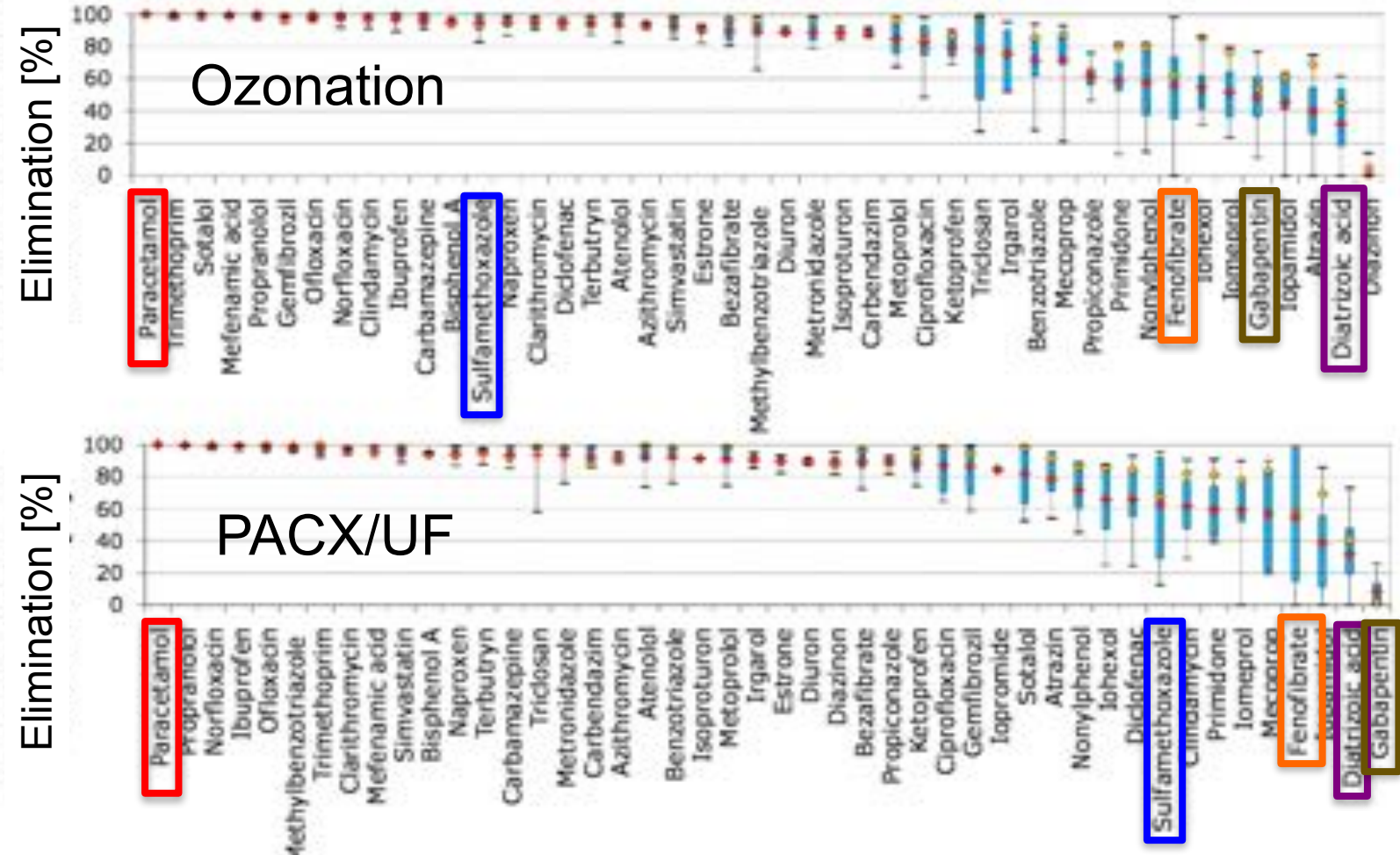
# Metformin and Biotransformation Product Guanyl Urea

German Rivers Elbe, Weser and North Sea



Trautwein  
C, Berset J-  
D, Wolschke  
H, Kümmerer  
K, Environ Int  
(2014) 70,  
303-212

# Elimination of Micro-Pollutants in Advanced Waste Water Treatment

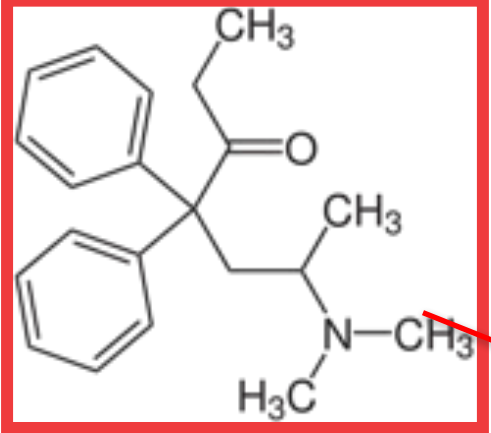


📖 Margot et al. 2013, Sci. Total Environ. 2013, 461-462, 480-498



# Many Precursors - One Transformation Product

(formation of possibly unknown, toxic chemicals in advanced effluent treatment)



**Methadon and other drugs with amine moieties**

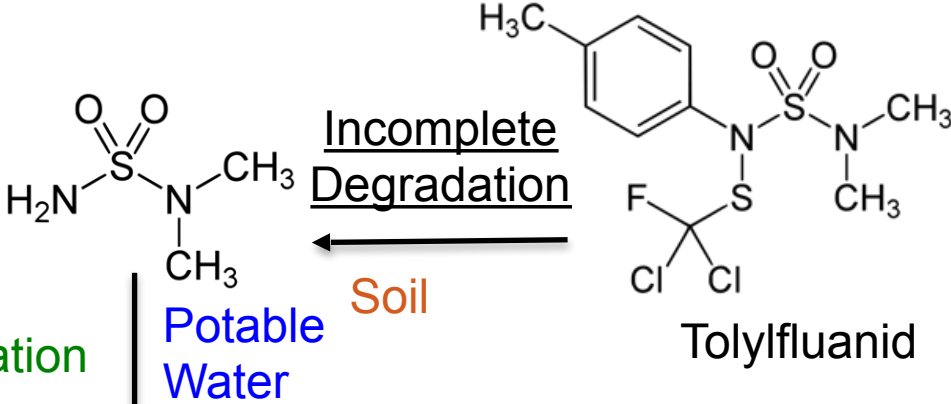
Hanigan et al., ES&T, 2015

**Membranes**

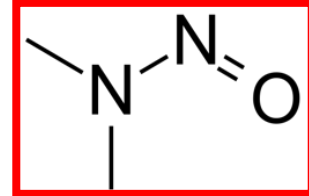
Erisan et al. (2015) ES&T Lett. 2, 66-69

**Dissolved organic matter**

Marti et al. (2015) Water Res. 72, 262-270



Schmidt und Brauch ES&T, 2007



**N-Nitrosodimethylamine**

Highly heptaoxic

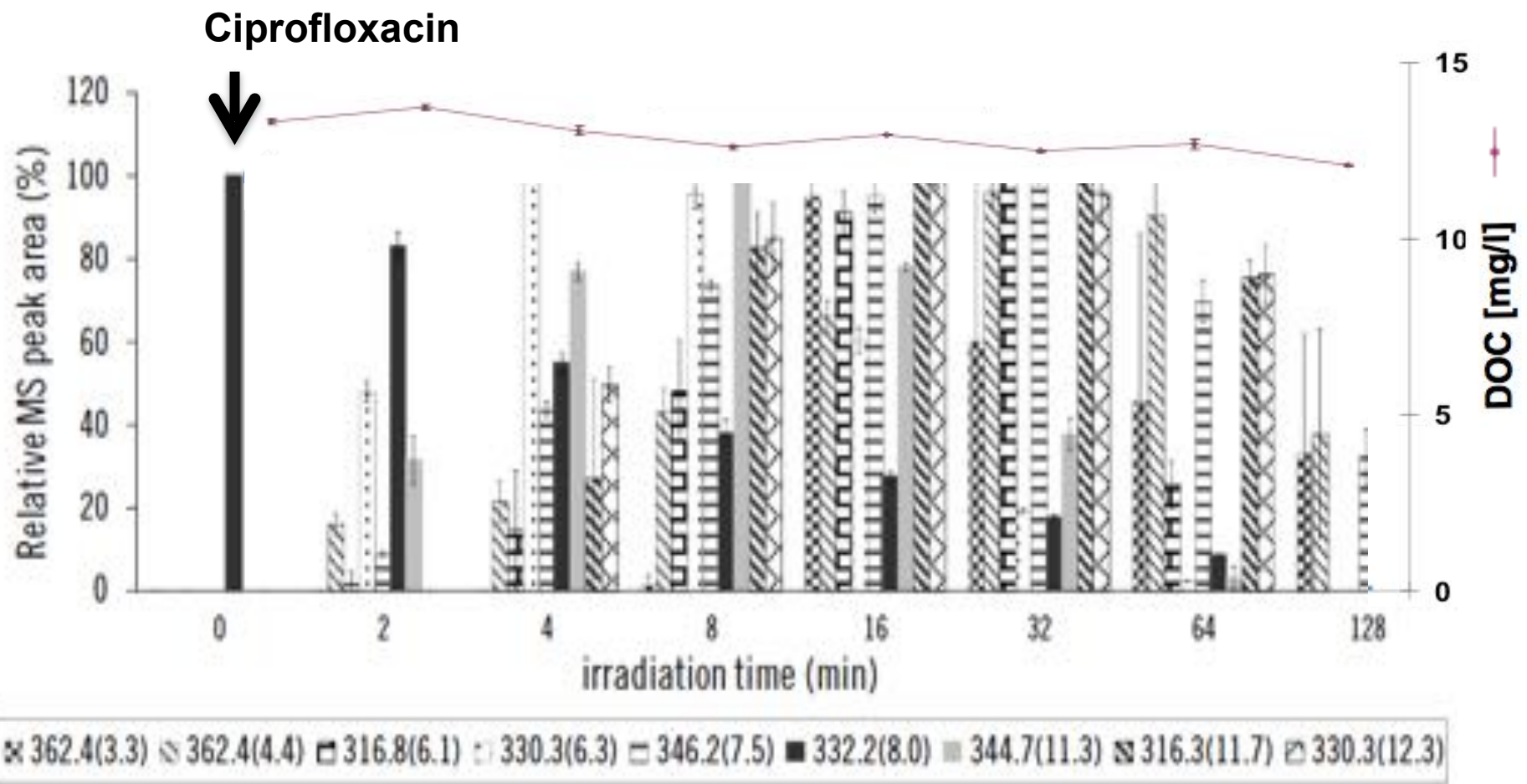
Probably human carcinogen

Threshold drinking water USA: 7 ng/L

# One Precursor – Many Transformation Products

## UV-Photolysis of Ciprofloxacin

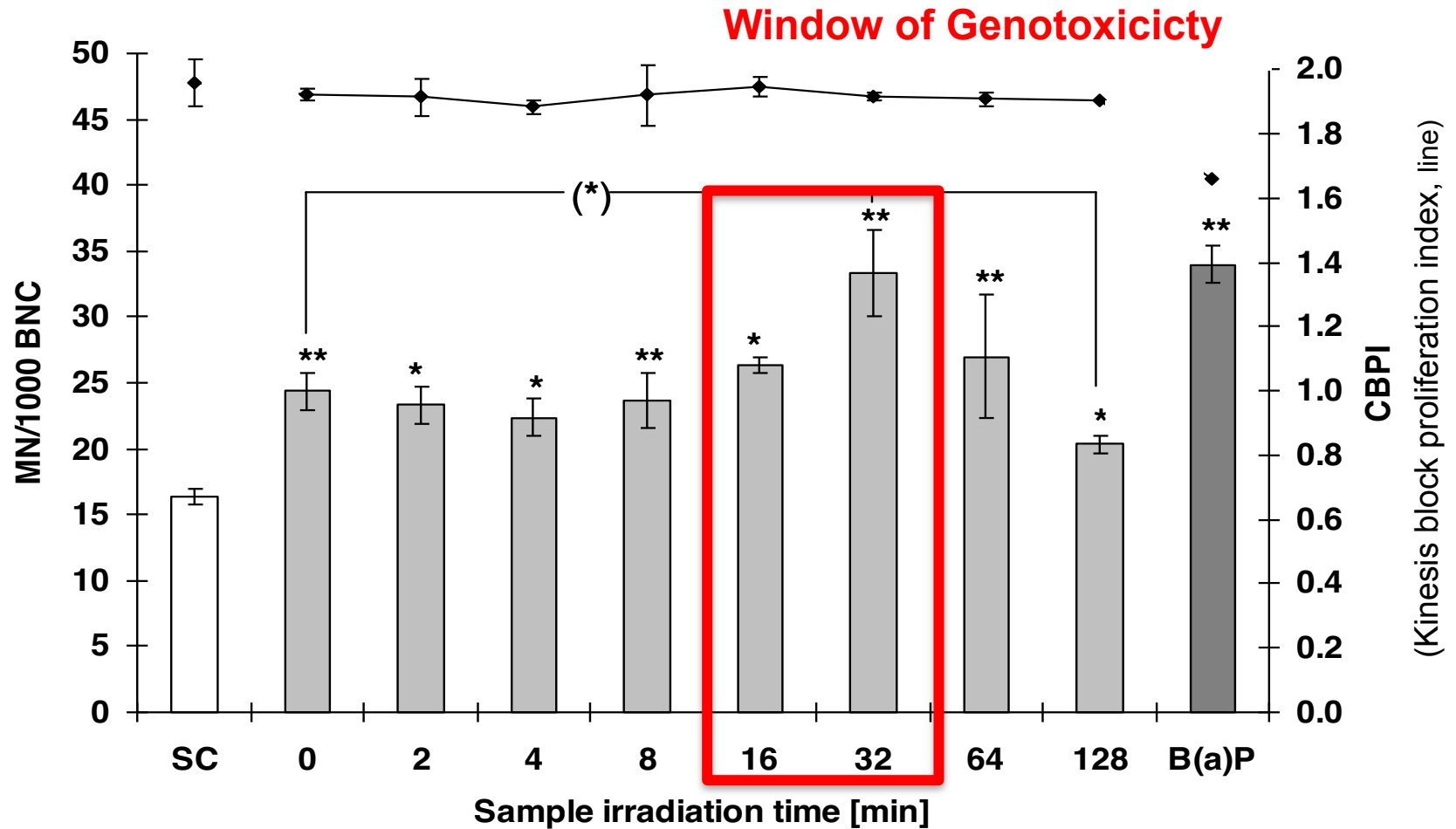
Detected Transformation Products (High Resolution LC-MS/MS)



Haddad T. and Kümmerer K. (2015), Chemosphere 115, 40-46

# Toxicity of CIP Photo Products

(Micro-Nucleus Test, Cell Toxicity)



Garcia-Käufer, Haddad, Bergheim, Gminski, Gupta, Mathur, Kümmerer, Mersch-Sundermann (2012), ESPR, 19, 1719-1727



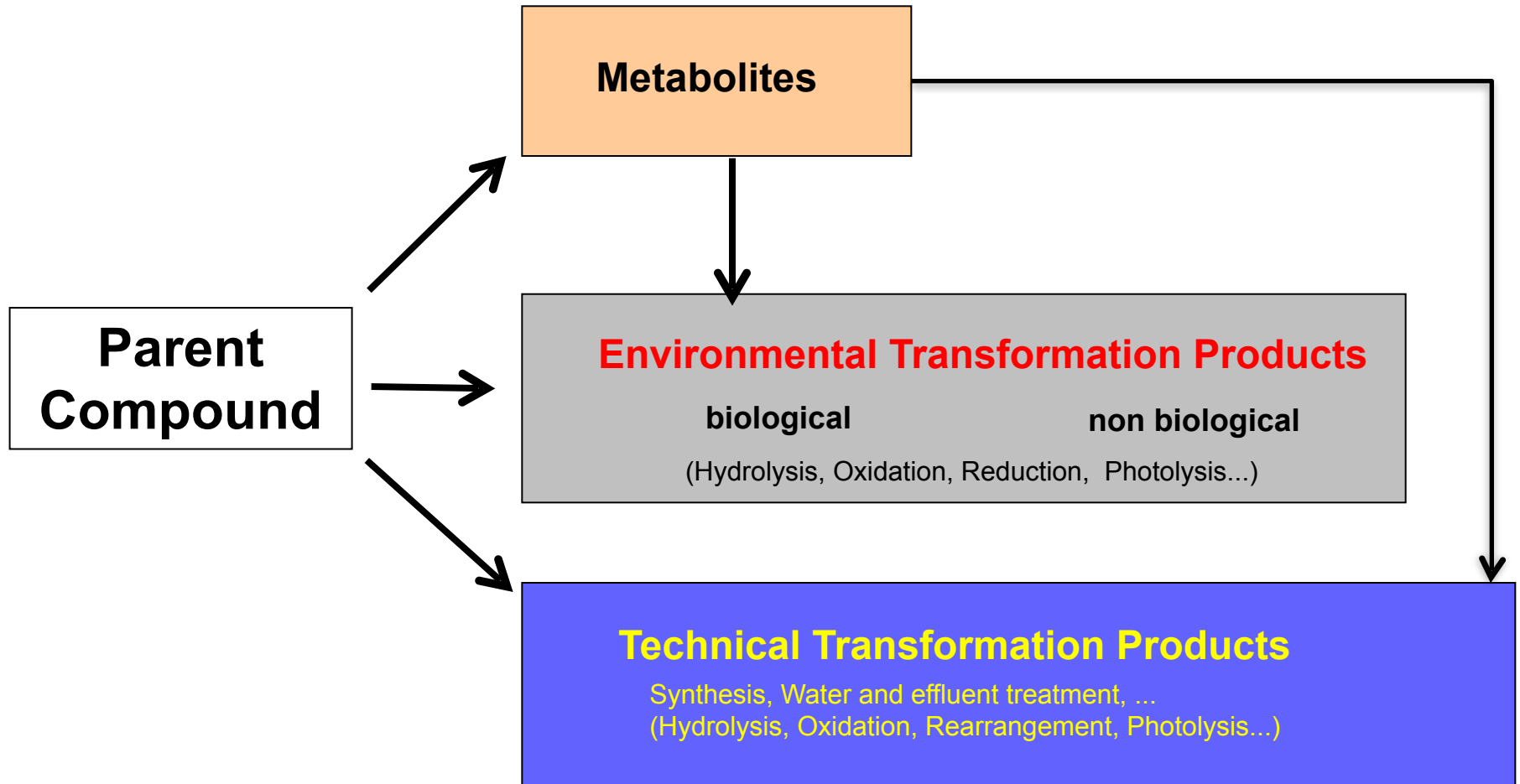
# Limits of (Advanced) Effluent Treatment

**Not just many different parent compounds – also often numerous unknown transformation products per parent compound**

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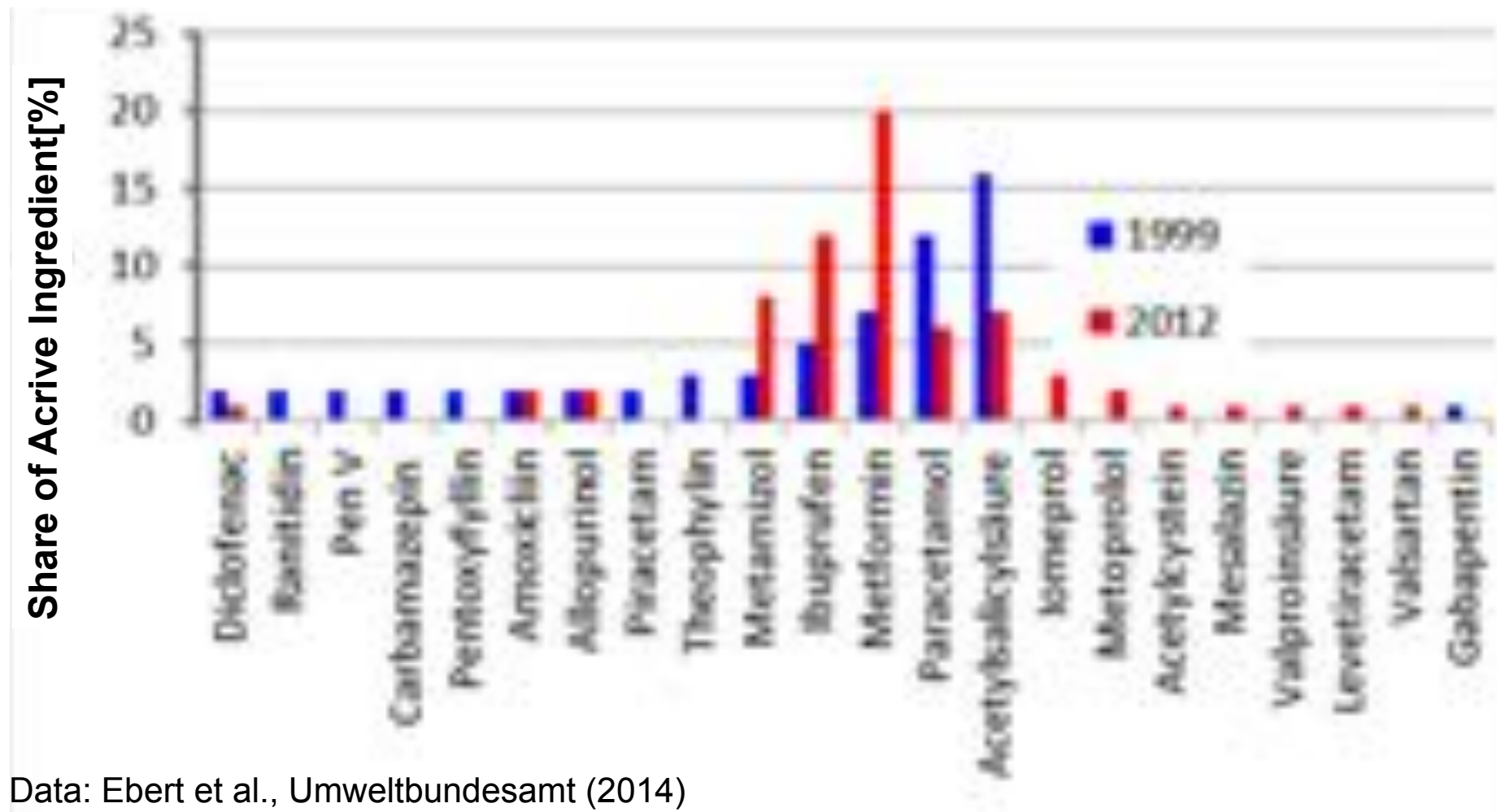
**Too little knowledge, too many compounds for targeted treatment and end points for a risk assessment**

# Products of Incomplete Mineralization (mostly unknown!)



# Dynamics of Compounds

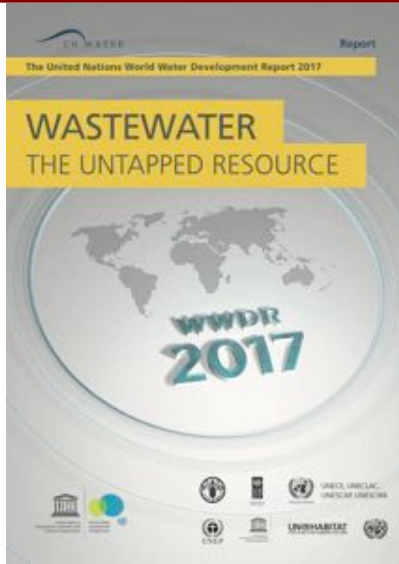
## Usage of Pharmaceuticals (Germany)



# Shortcomings 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 aconatminant
- 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)**



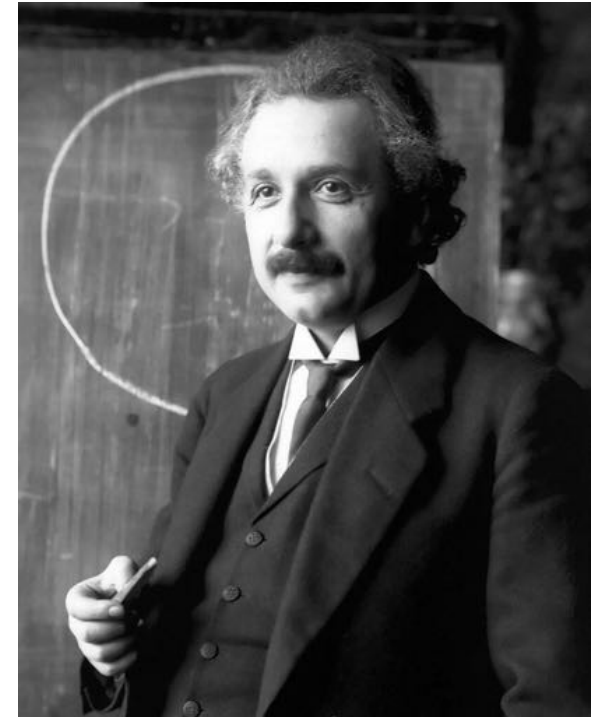


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**A smart person solves a  
problem.**

**A wise person avoids it.**

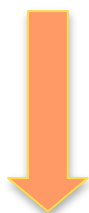
Attributed to Albert Einstein



**A smart person solves a problem.**

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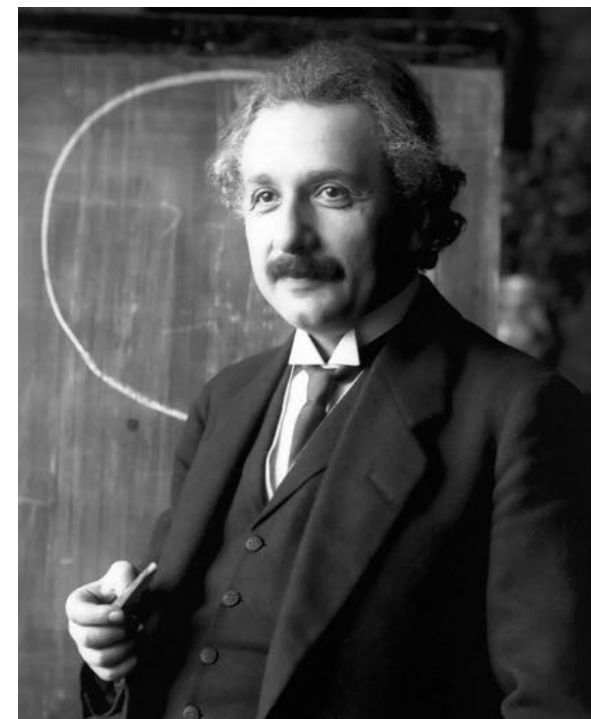
Attributed to Albert Einstein



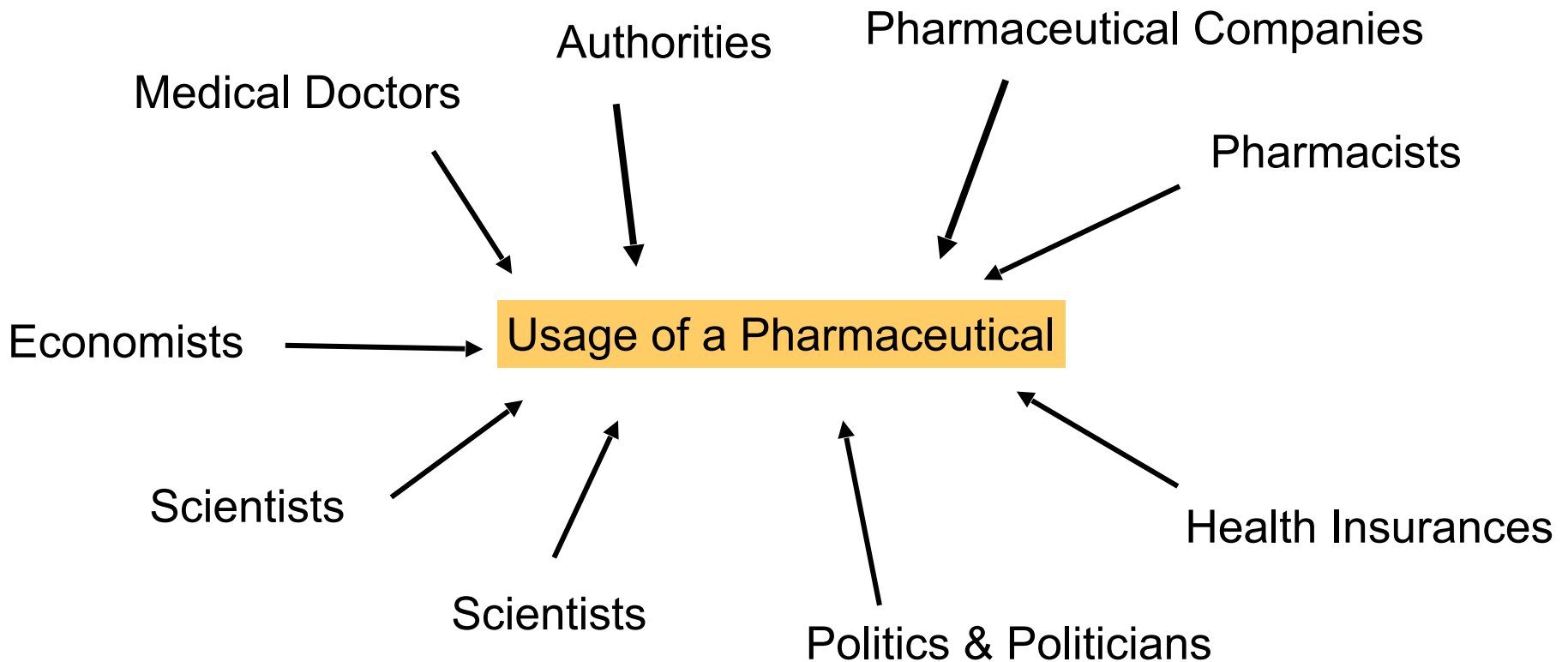
**Measures at the source (users, molecules)**

Kümmerer K., et al. Science 361 (6399), 222-224 (2018)

Kümmerer K., et al. Science of the Total Environment,



# Less Usage-Feasible?



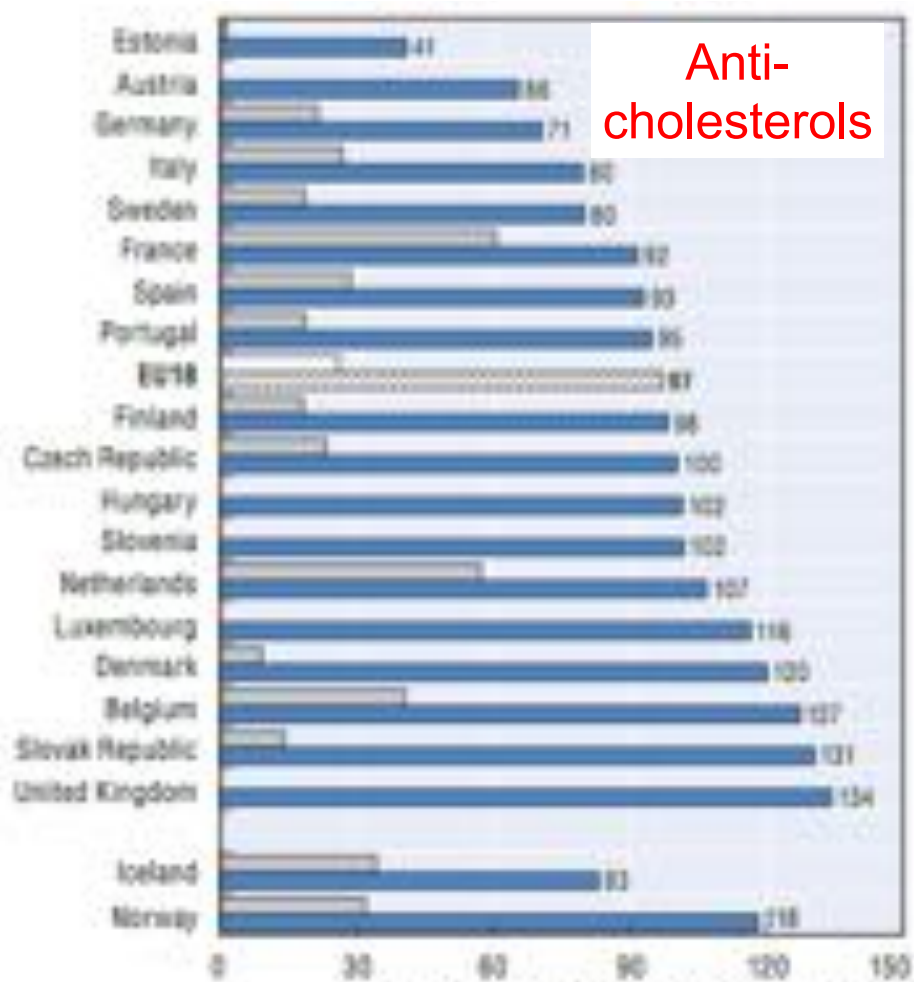
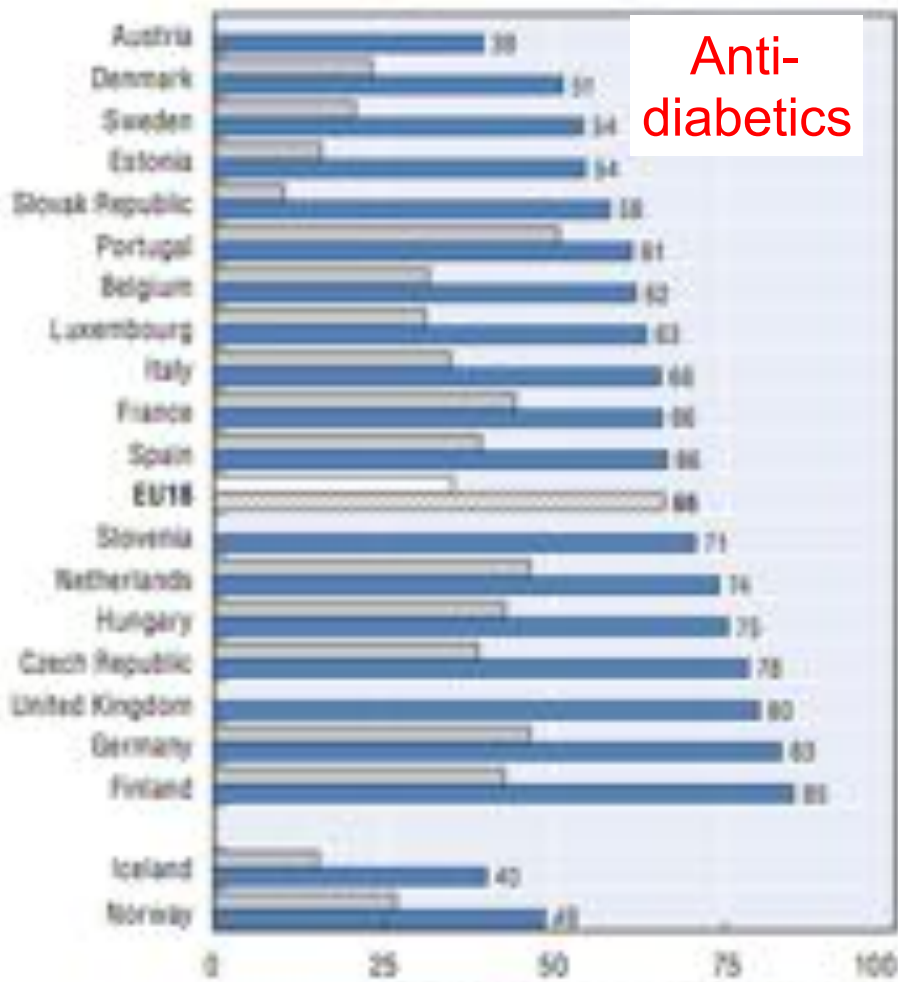
# Less Usage-Feasible!

## Use Patterns (DDD per 1000 people per day)

2000

2012

Source: OECD Health Statistics 2014, <http://dx.doi.org/10.1787/health-data-en>



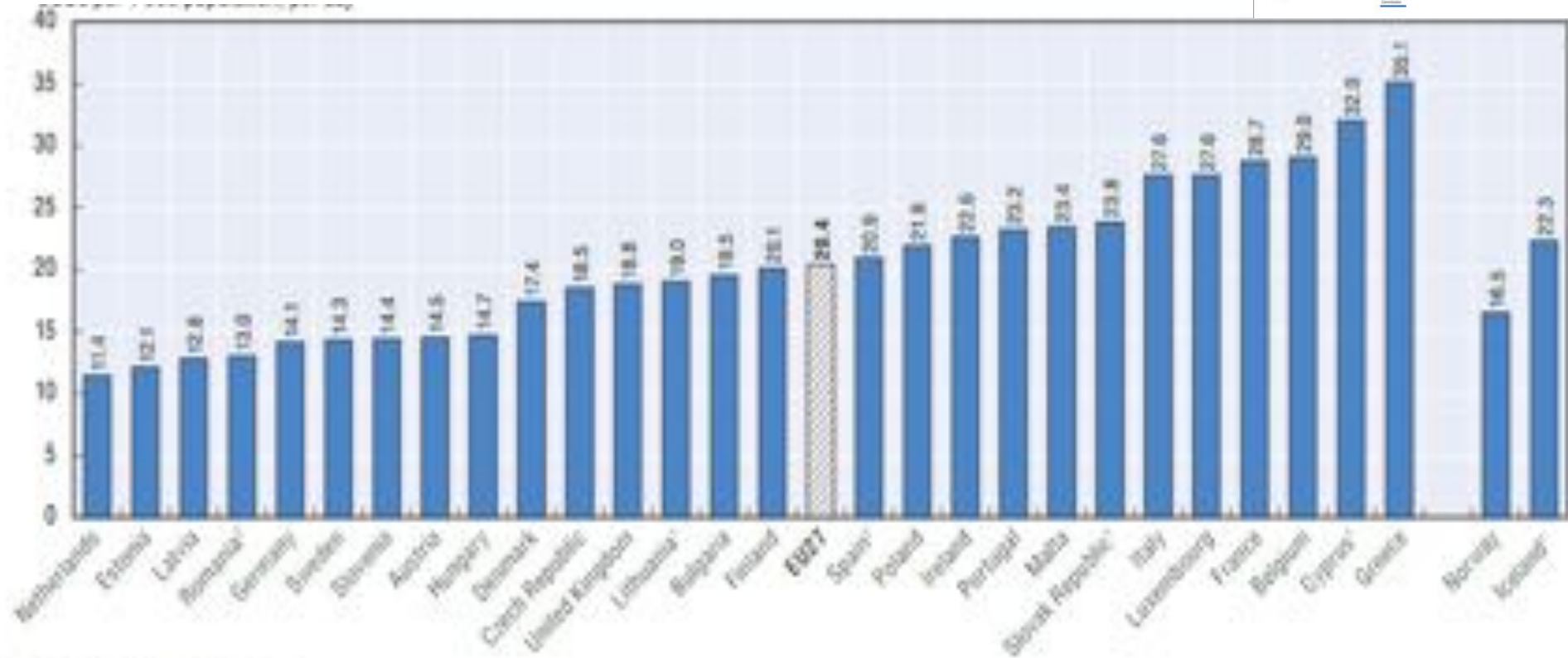


# Less Usage-Feasible!

## Use patterns (DDD per 1000 people) Antibiotics 2011

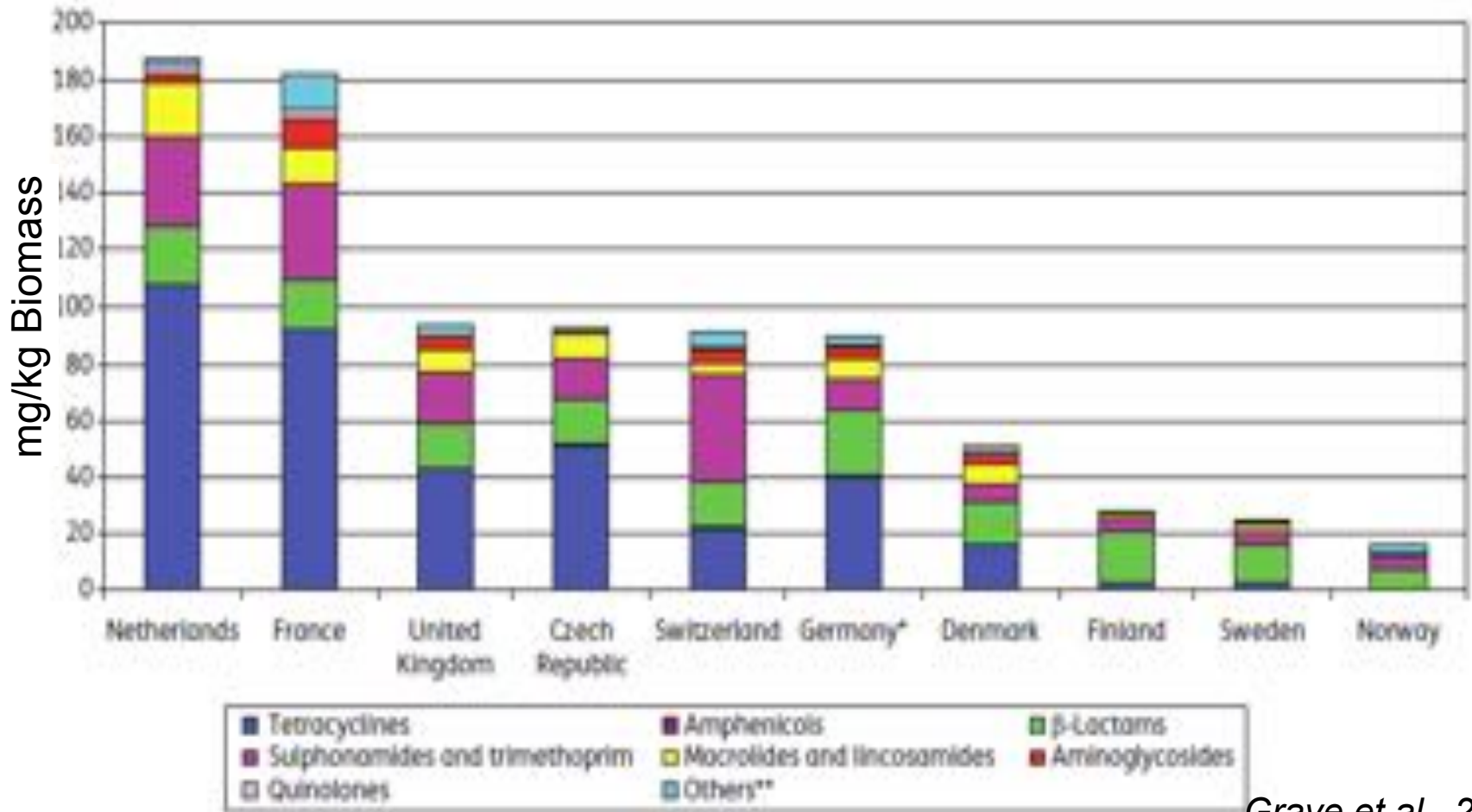


DDDs per day per 1000 population



# Less Usage-Feasible!

## Use Patterns Veterinary Antibiotics (EU) (mg/kg Biomass)



Grave et al., 2010

# In the Patient

## Less excretion

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- 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

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## What Is the Problem ?

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# Persistence

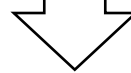
# Avoiding Environmental Persistence

**Chemical**



**Fast and complete mineralization in the environment**

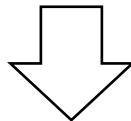
**No Exposition**



**No Effect**



**No Risk**





Sustainable Chemistry and Pharmacy 2 (2015) 31–36

Contents lists available at ScienceDirect

## Sustainable Chemistry and Pharmacy

journal homepage: [www.elsevier.com/locate/scp](http://www.elsevier.com/locate/scp)



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# 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\*

Sustainable Chemistry and Material Resources, Institute of Sustainable and Environmental Chemistry, Leuphana University Lüneburg, C13, Schambornstraße 1, DE-21335 Lüneburg, Germany

# 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

 Kümmerer K., In: Kümmerer K., Hempel M. (Eds) Green and Sustainable Pharmacy , Springer 2010)

# Rational Drug Design - Revisited

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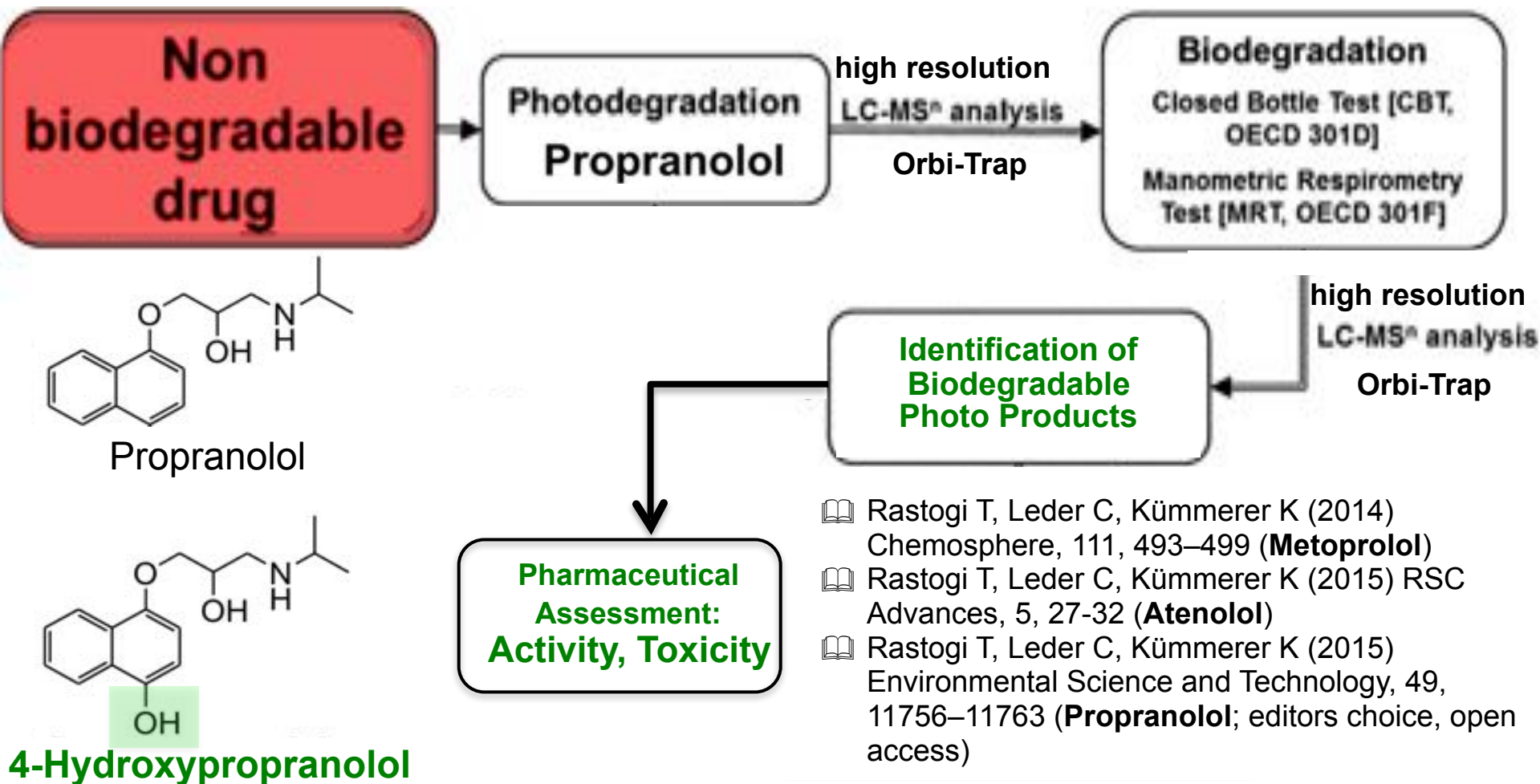
- High oral absorption
- Effective and efficient
- Receptor specific
- Reduced/no unwanted side-effects
- metabolized to harmless metabolites
- ...
- High degree of mineralization after introduction into the environment

# What Would that do to the Drug Discovery Process?

- Starting from (already known?) lead structure
- Optimization as usual ( e.g. by chemo informatics)
- **New:** including after use life at early stage
  - Challenging
  - Paradigm shift
  - Fascinating problem (not toxic/envionmenatllly biodegradable)

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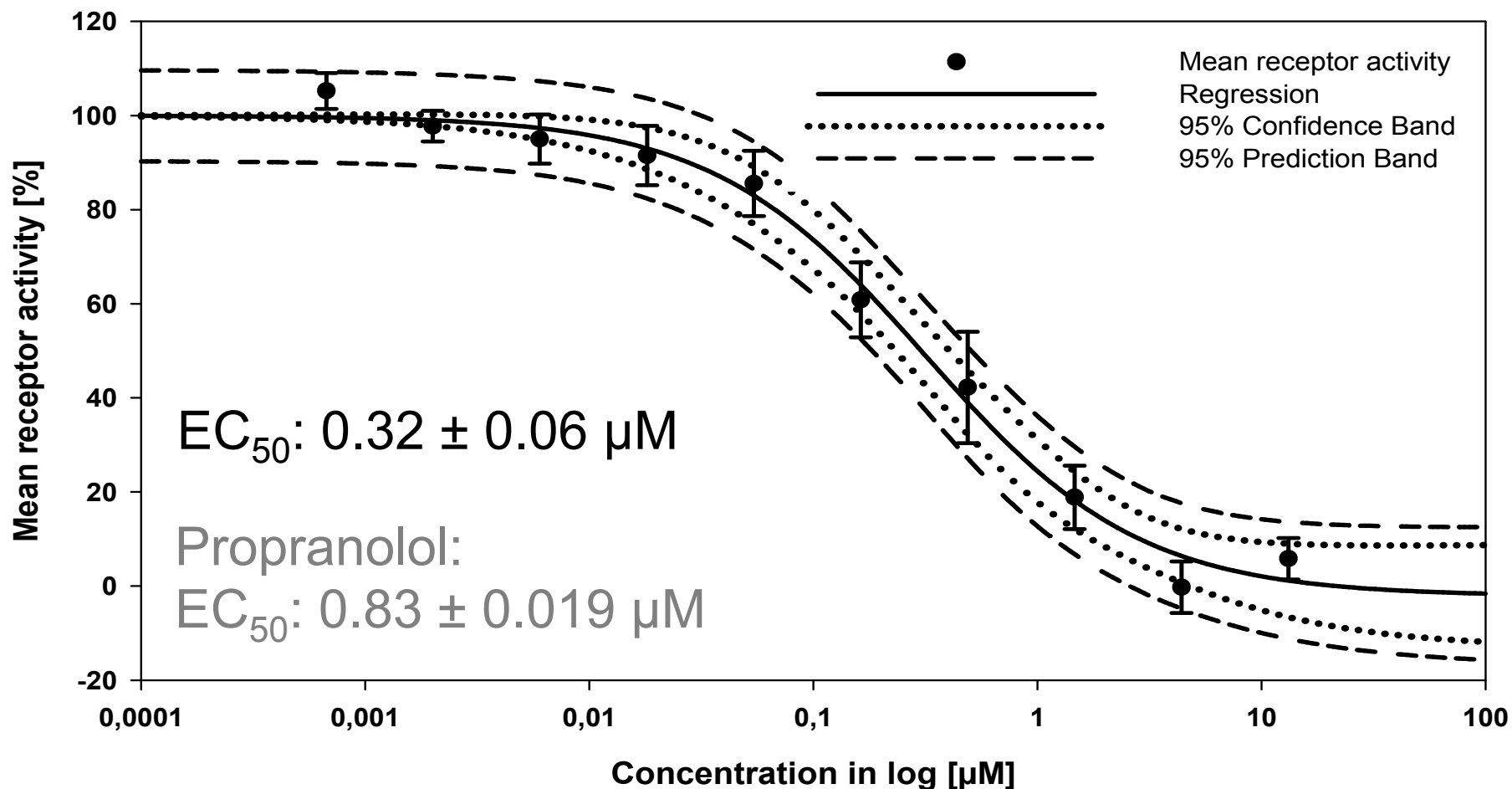
# “Non Systematic” Re-Design



- 📖 Rastogi T, Leder C, Kümmerer K (2014) Chemosphere, 111, 493–499 (**Metoprolol**)
- 📖 Rastogi T, Leder C, Kümmerer K (2015) RSC Advances, 5, 27-32 (**Atenolol**)
- 📖 Rastogi T, Leder C, Kümmerer K (2015) Environmental Science and Technology, 49, 11756–11763 (**Propranolol**; editors choice, open access)

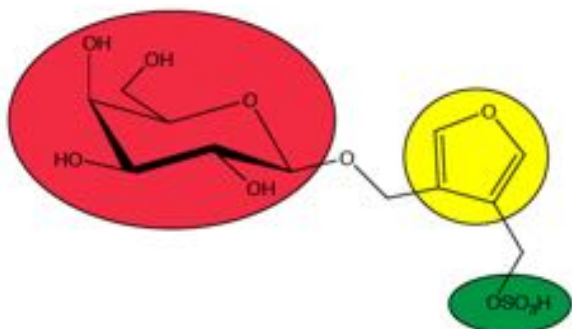
# Pharmacological Activity of 4-Hydroxypropranolol

## *In Vitro* Analysis



# Re-Design and De-Novo Design Examples

## Anti-Cancer Drugs: patent



📖 Kümmerer K, Frei E, Marano G, Wiessler M., in preparation

## Antibiotics: Two patent applications pending

ENVIRONMENTAL  
Science & Technology

## β-Blockers:

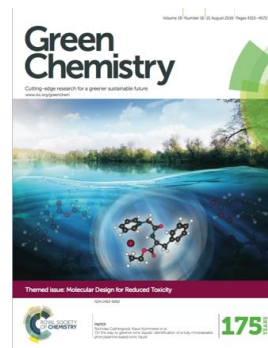
ACS EST  
Article  
pubs.acs.org/est

### Re-Designing of Existing Pharmaceuticals for Environmental Biodegradability: A Tiered Approach with β-Blocker Propranolol as an Example

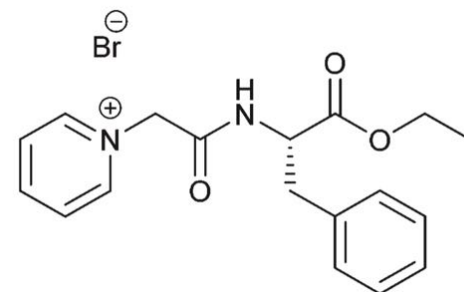
Tushar Rastogi, Christoph Leder, and Klaus Kümmerer\*

Sustainable Chemistry and Material Resources, Institute of Sustainable and Environmental Chemistry, Leuphana University Lüneburg, C13, DE-21335 Lüneburg, Germany

- 📖 Rastogi T, Leder C, Kümmerer K (2014) Chemosphere, 111, 493–499 (**Metoprolol**)
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## Ionic liquids:





# Carrots

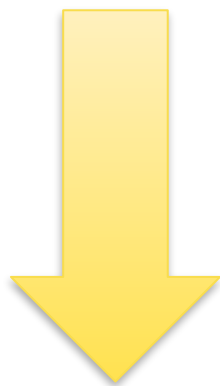
- Prolonged patent life-time
- Fast track authorization
- Precautionary principle (subset of arguments)
- Important contribution to CSR
- Increased reputation
- Vision: „next generation“ is greener!



 US- Department of Agriculture

# Incentives

New compound



New business opportunity



# Carrots



## Opportunity/business case

VS.

**falling behind**



# ... and Sticks

- EMA: Revision of EMEA guideline (EU Parliament)?
- EEA Report 1/2010:  
„Pharmaceuticals in the Environment
- Legislation (e.g. EU Water Framework Directive)
- U.S. Senate Hearing
- The greener consumer



<http://www.eea.europa.eu/publications/pharmaceuticals-in-the-environment-result-an-eea-workshop>

# Schering-Plough (Press release 2007)

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- 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**,

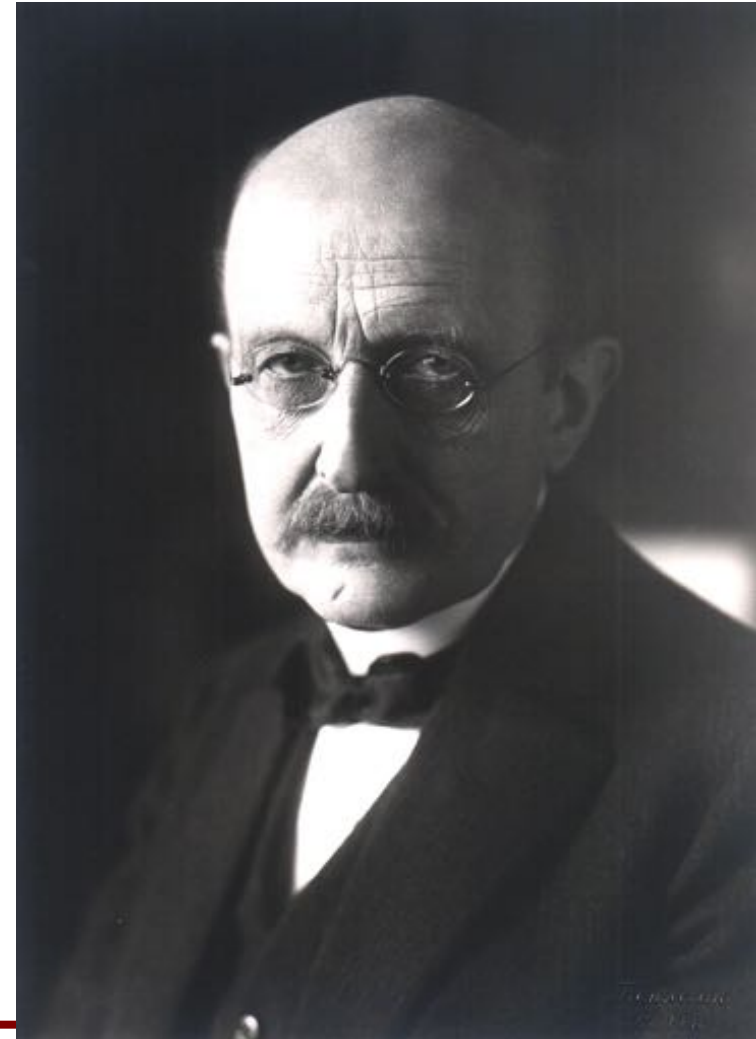
(1) **already more than one compound on the market for most groups** (e.g. sartanes)

(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



# Take-Home Message

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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!**