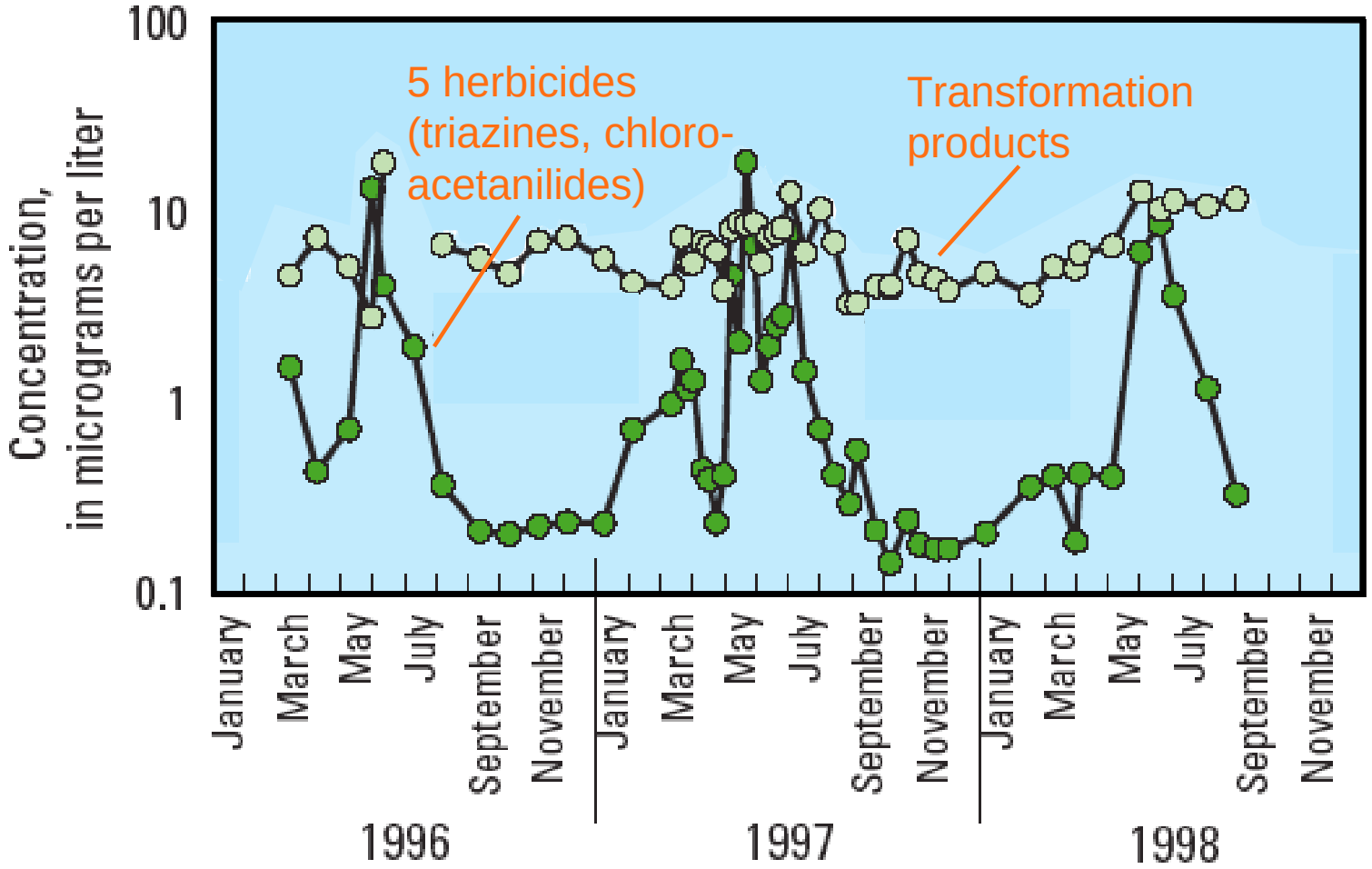
Transformation products of organic contaminants – Relevant risk factors?

Kathrin Fenner

Eawag,
Swiss Federal Institute of Aquatic Science and Technology

Occurrence of transformation products

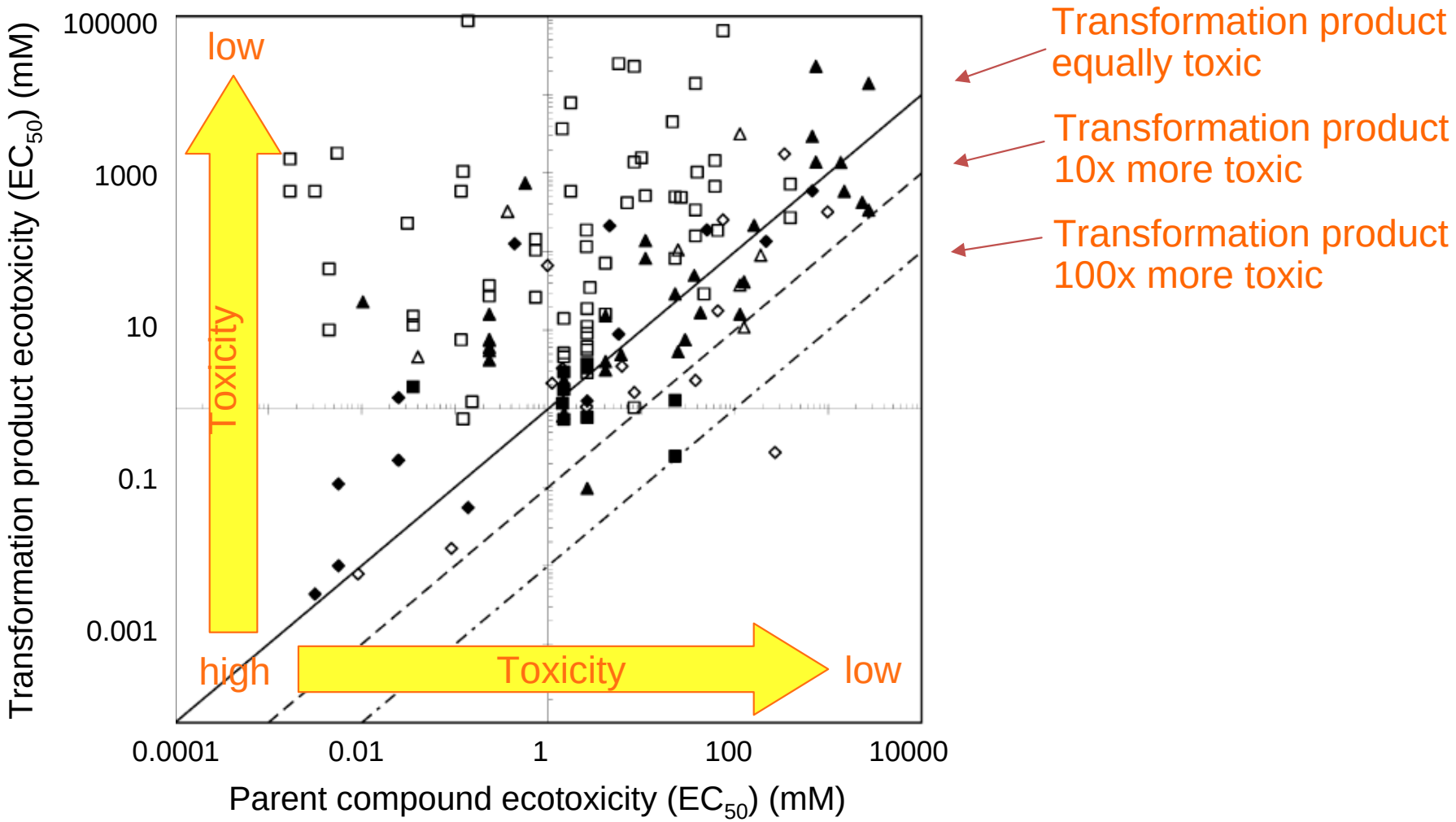
- Some herbicide transformation products detected in higher concentrations and more frequently than the parent pesticides in groundwater and surface water



Gilliom et al. (2005) *USGS Circular* 1291

How toxic are transformation products?

- 30% of transformation products more toxic than parent pesticide to fish, daphnids and algae



Sinclair and Boxall (2003) *Environ Sci Technol* 37: 4617-4625

How are transformation products regulated?

- Pesticide Directive (91/414/EEC):

  - Identification of relevant transformation products mandatory
  - Clear guidance on assessing their relevance

- Industrial chemicals (REACh):

  - Identification of transformation products requested for products > 100 t/y
  - No guidance on assessment

- Human and veterinary medicines (EMEA):

  - Consideration of environmental transformation products subject to expert judgment

Open questions, challenges and opportunities

- Research goals
  - Assess exposure to transformation products
  - Identify relevant transformation products

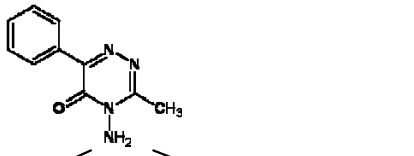
- Challenges
  - Which products?
  - Lack of analytical standards
  - Scarcity of experimental fate data

- Opportunities
  - Read-across from parent compound properties

⇒ Develop toolbox to adequately and efficiently assess transformation products

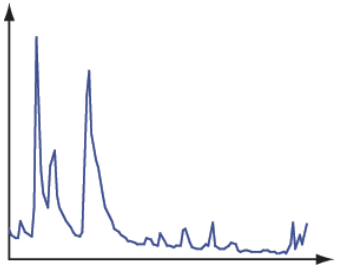
Strategy for assessing transformation products

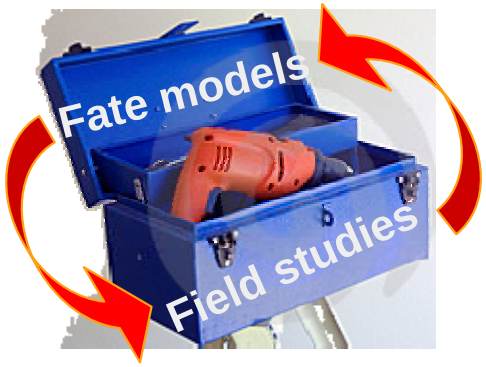
Identification



Exposure assessment

PEC/MEC

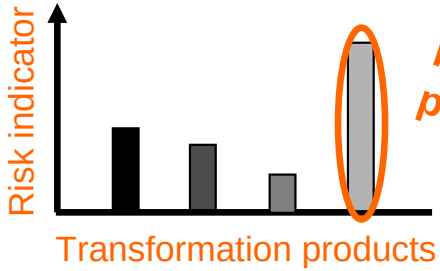




Effect assessment

PNEC

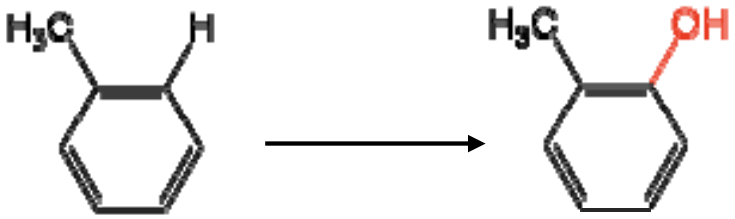
Risk assessment



Relevant transformation product!

Structure-biodegradation relationships

- Artificial intelligence tools



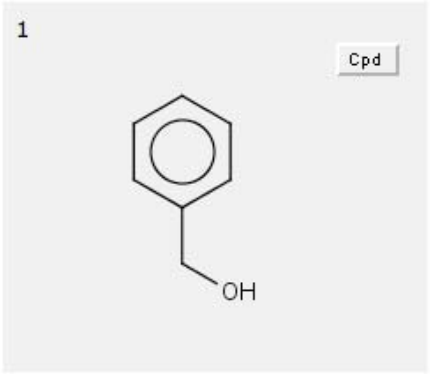
Set of transformation rules

- University of Minnesota Pathway Prediction System (UM-PPS)
  - About 200 transformation rules
  - Derived from database of experimentally elucidated biotransformation pathways (UM-BBD)
  - Publicly available, transparent, continuously developed
  - http://umbbd.msi.umn.edu/predict/index.html

Structure-biodegradation relationships

University of Minnesota Pathway Prediction System (UM-PPS)

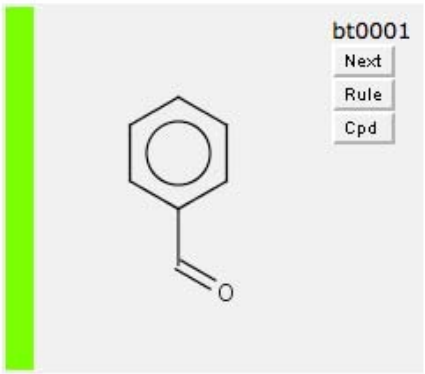
The predicted pathway:

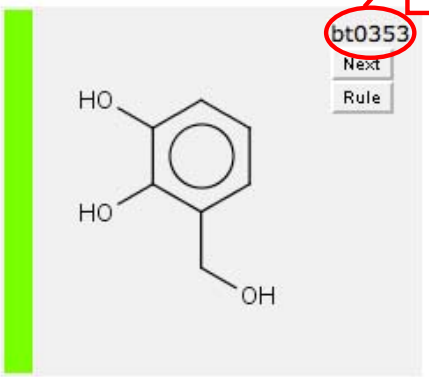


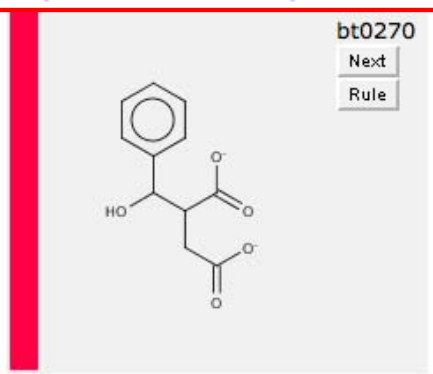
Aerobic Likelihood:

Very likely | Likely | Neutral | Unlik

Choose the next reaction step:

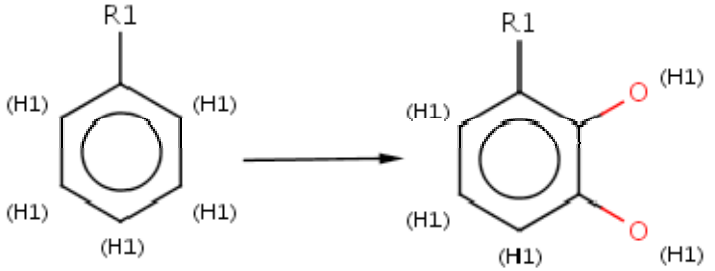






Rule bt0353

[Pathway Prediction Engine] [All Rules List] [BBD Main Menu]



All patterns

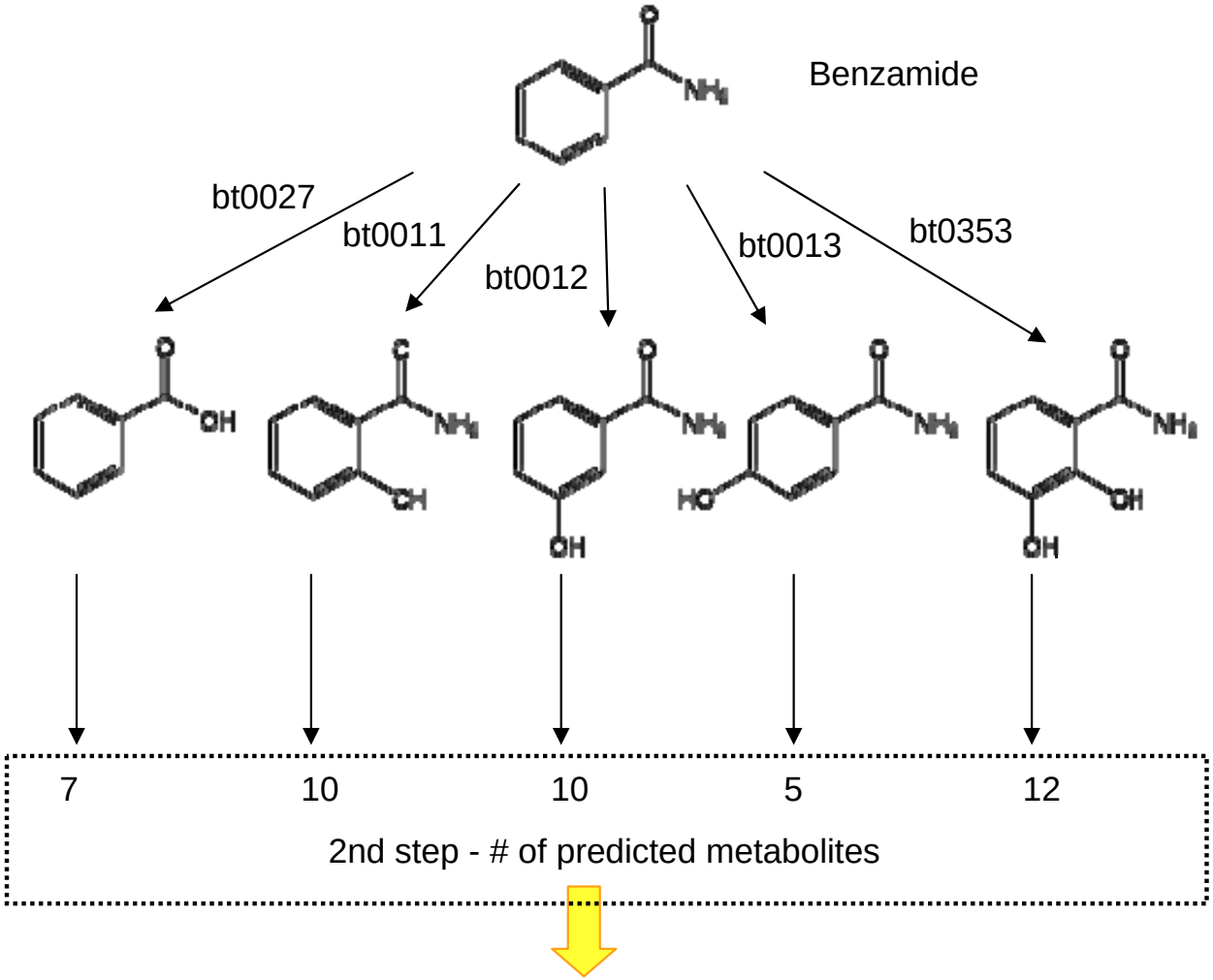
mono-carbon-substituted Benzenoid -> 1-substituted-2,3-dihydroxy Benzenoid
mono-halo-substituted Benzenoid -> 1-halo-2,3-dihydroxy Benzenoid
mono-pseudohalo-substituted Benzenoid -> 1-pseudohalo-2,3-dihydroxy Benzenoid

Aerobic Likelihood: Likely

Styrene -----> Styrene *cis*-glycol (reacID# r0256)
Toluene -----> Toluene-*cis*-1,2-dihydrodiol (reacID# r0253)
Biphenyl -----> *cis*-2,3-Dihydro-2,3-dihydroxybiphenyl (reacID# r0388)

Structure-biodegradation relationships

The challenge: Combinatorial explosion

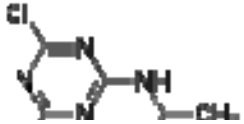


Method to limit combinatorial explosion needed!

Structure-biodegradation relationships

Finding rule priorities through data mining

- Use knowledge from experimentally elucidated pathways to learn about rule priorities
- Define rule priorities: If two rules are applicable, only apply the one more likely according to known pathways
- Find pairs of rules with clear rule priority over all known transformations



bt0063 > bt0036
bt0022 > bt0036

$$R'_A = \{(r_i > r_j) \mid |O_i \cap T_j| \geq 10 \wedge |T_i \cap O_j| = 0\}$$

$$R_B = \{(r_i > r_j) | (r'_i > r'_j) \in R_A \wedge r_i \in \text{group}(r'_i) \wedge r_j \in \text{group}(r'_j)$$

$$\wedge |T_i \cap T_j| \geq 1 \wedge (\neg\exists c: c \notin O_i \wedge c \in O_j) \wedge ((|O_i \cap T_j|$$

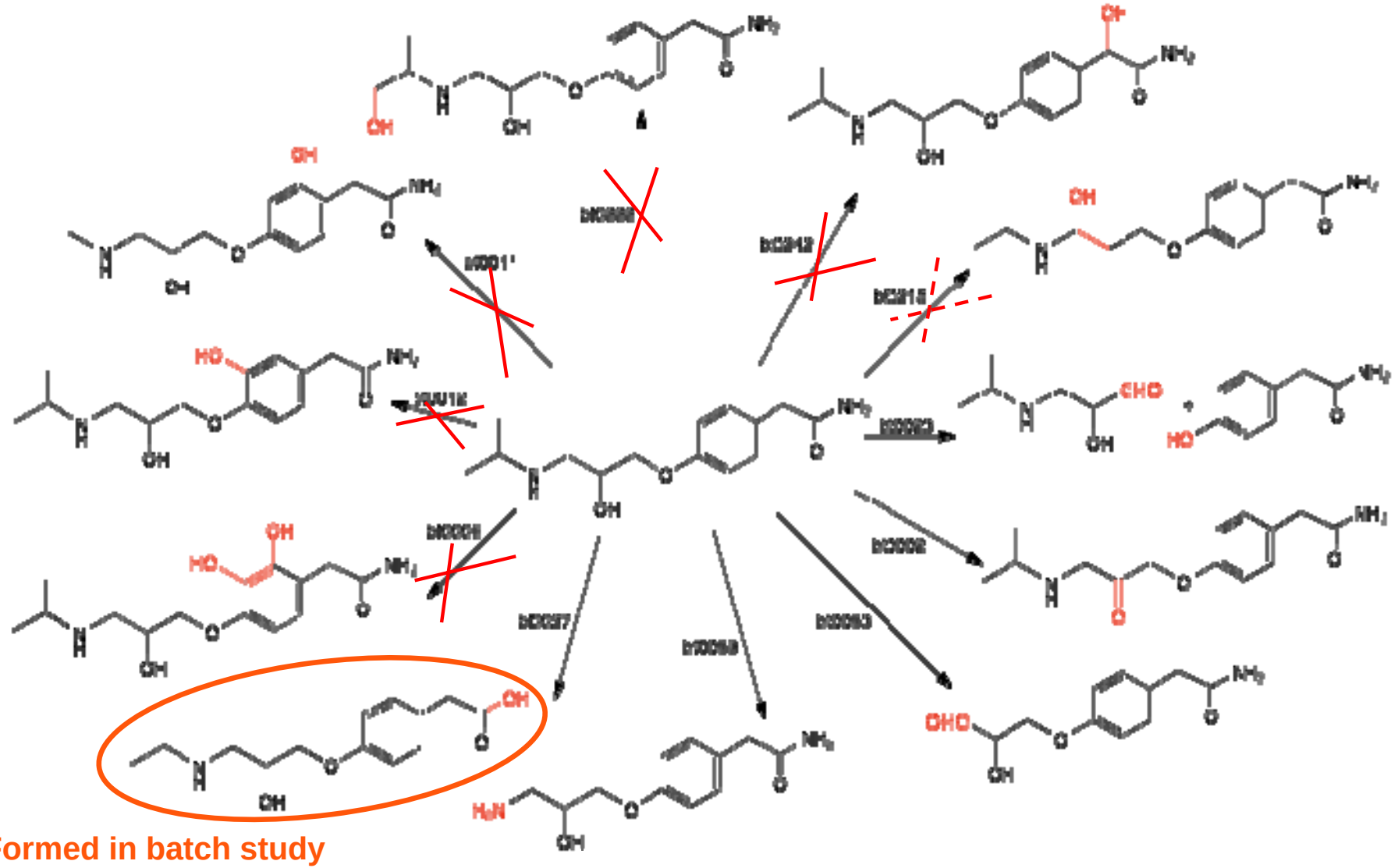
$$\geq 5 \wedge |T_i \cap O_j| = 0) \vee r_i = r'_i \vee r_j = r'_j)\}$$

"Known" products

"Unknown" products

Structure-biodegradation relationships

UM-PPS: Results from implementation of rule priorities



Formed in batch study with activated sludge

Fenner et al., *Bioinformatics*, 2008

Structure-biodegradation relationships

UM-PPS: Results from implementation of rule priorities

- 15% reduction

	n	Predicted reactions
Original		
Pesticides	24	280
With relative reasoning		
Pesticides	24	240

Fenner et al., *Bioinformatics*, 2008

Structure-biodegradation relationships

UM-PPS: Results from implementation of rule priorities

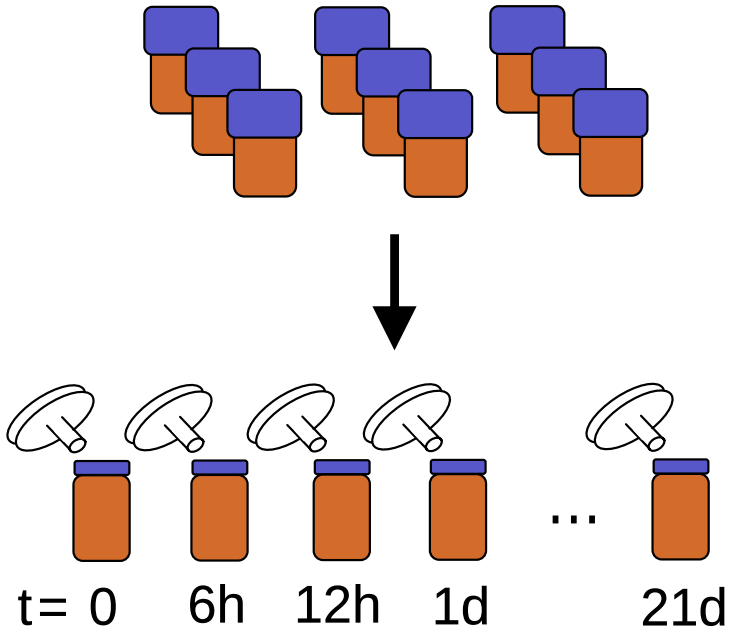
- 15% reduction
- Sensitivity stable
- Selectivity improved

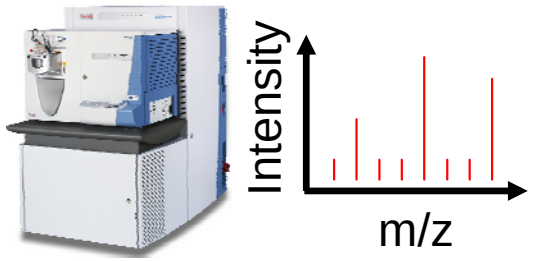
	n	Predicted reactions	Known products		Sensitivity (%)
			predicted	not predicted	
Original					
Pesticides	24	280	43	15	74.1
With relative reasoning					
Pesticides	24	240	43	15	74.1

Fenner et al., *Bioinformatics*, 2008

Experimental elucidation of rule priorities

Experimental setup





High resolution mass spectrometry

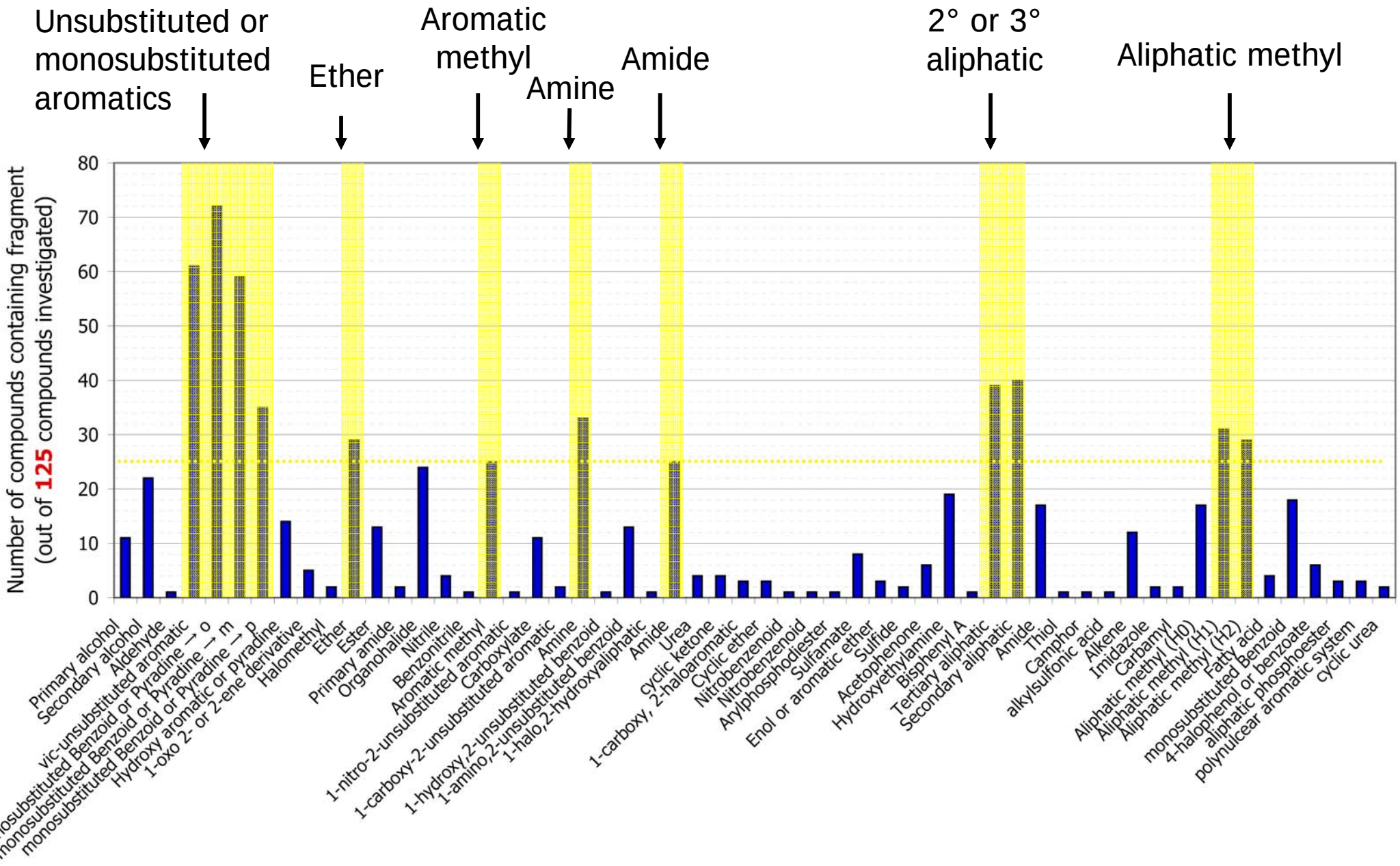
Bioreactor considerations:
- ✓ Control pH, temperature, dissolved oxygen
- ✓ Sludge (active biomass) concentration
- ✓ Spiked compound concentration
- ✓ Sorption and abiotic controls

Sample preparation considerations:
- ✓ Sample volume – SPE
- ✓ Compound sorption to syringe
- ✓ Compound sorption to filter material
- ✓ Sample storage

Analytical method:
- ✓ Previously developed screening method
- ✓ UM-PPS predicted TP masses
- ✓ Identification with exact mass and MS/MS
- ✓ No need for reference standards

Experimental elucidation of rule priorities

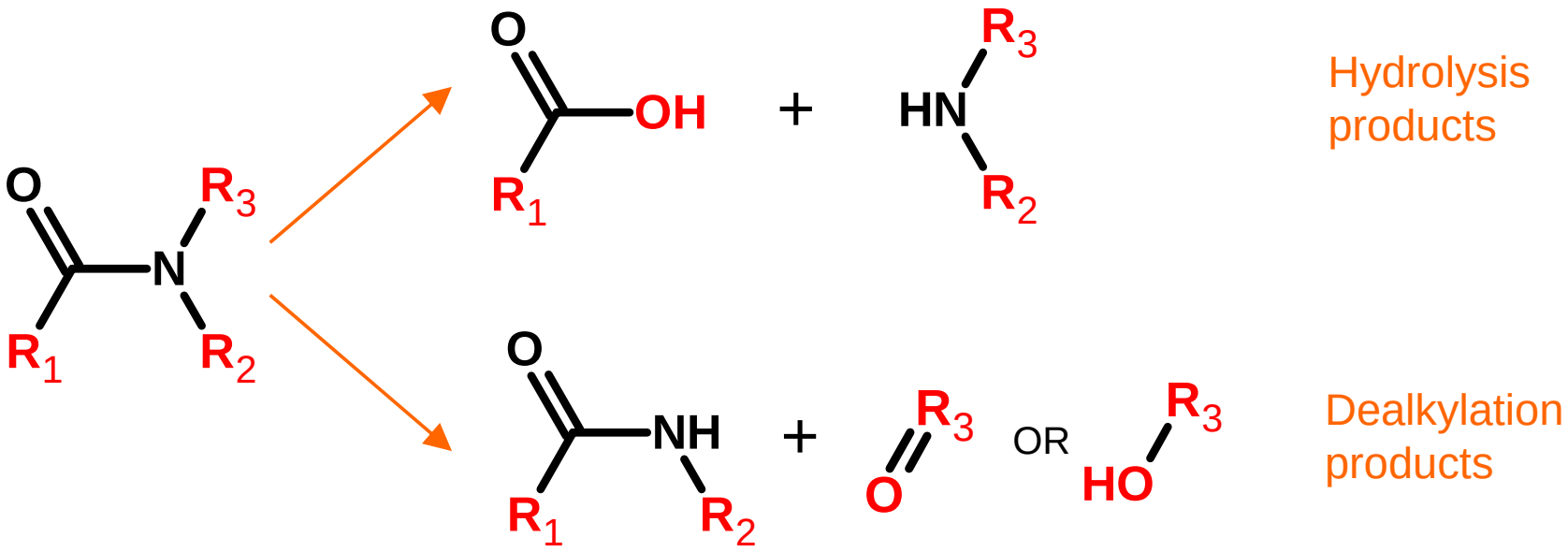
Selection of pertinent rule priorities



Experimental elucidation of rule priorities

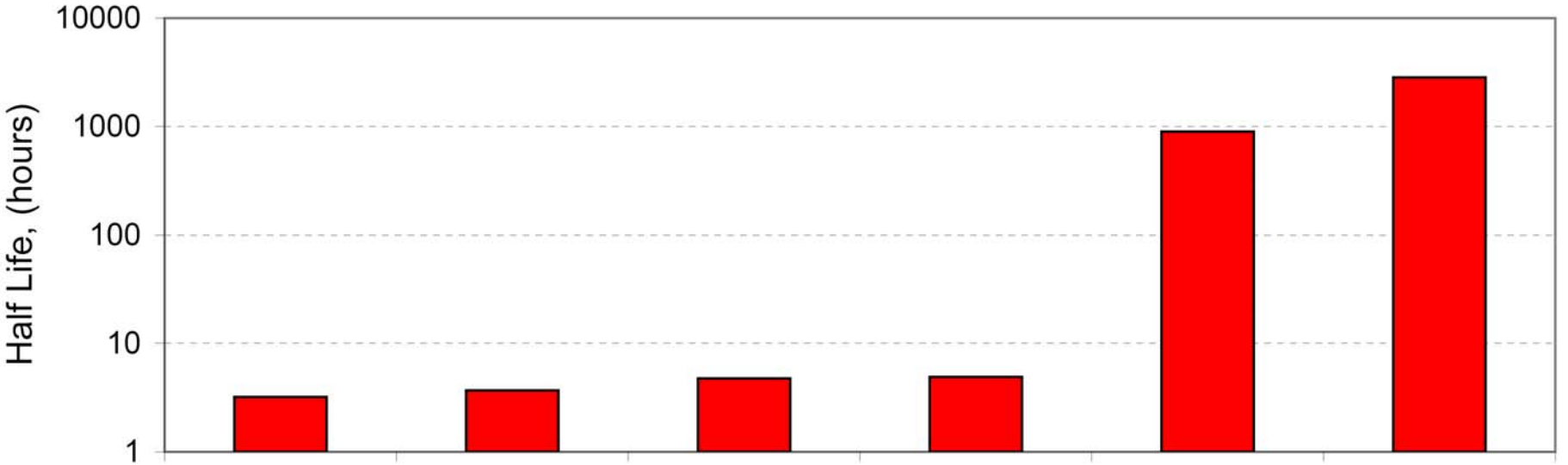
Case study: Amides

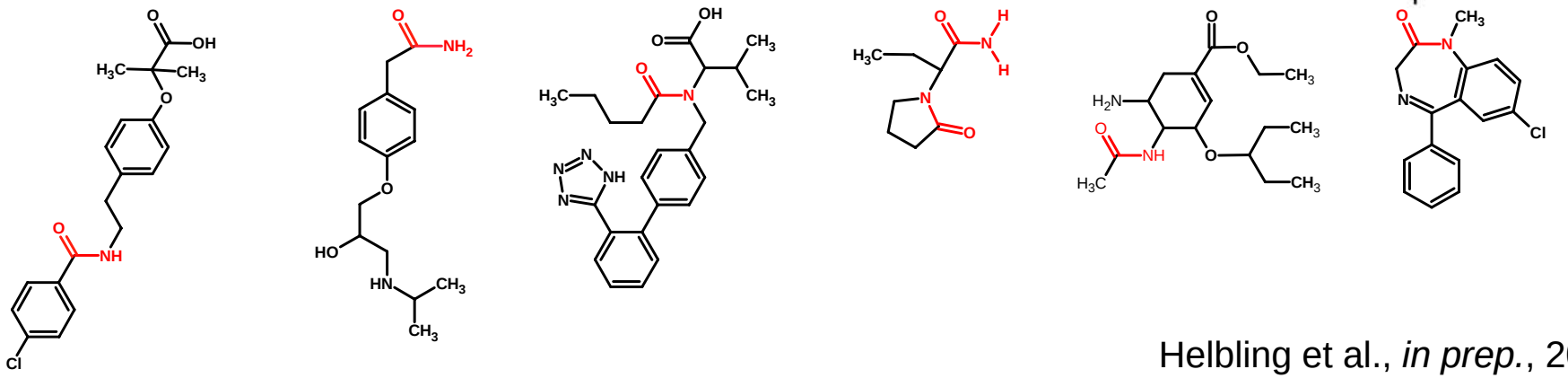
- No transformations with priorities over amide fragments within UM-PPS
- Specific biodegradation pathway of amides remains ambiguous
- Starting hypothesis: 1° and 2° amides hydrolyze rapidly, 3° amides dealkylate



Experimental elucidation of rule priorities

	Bezafibrate	Atenolol	Valsartan	Levetiracetam	Oseltamavir	Diazepam
Hydrolysis	✓	✓	✓	✓		
Dealkylation			✓			✓
Other					✓	

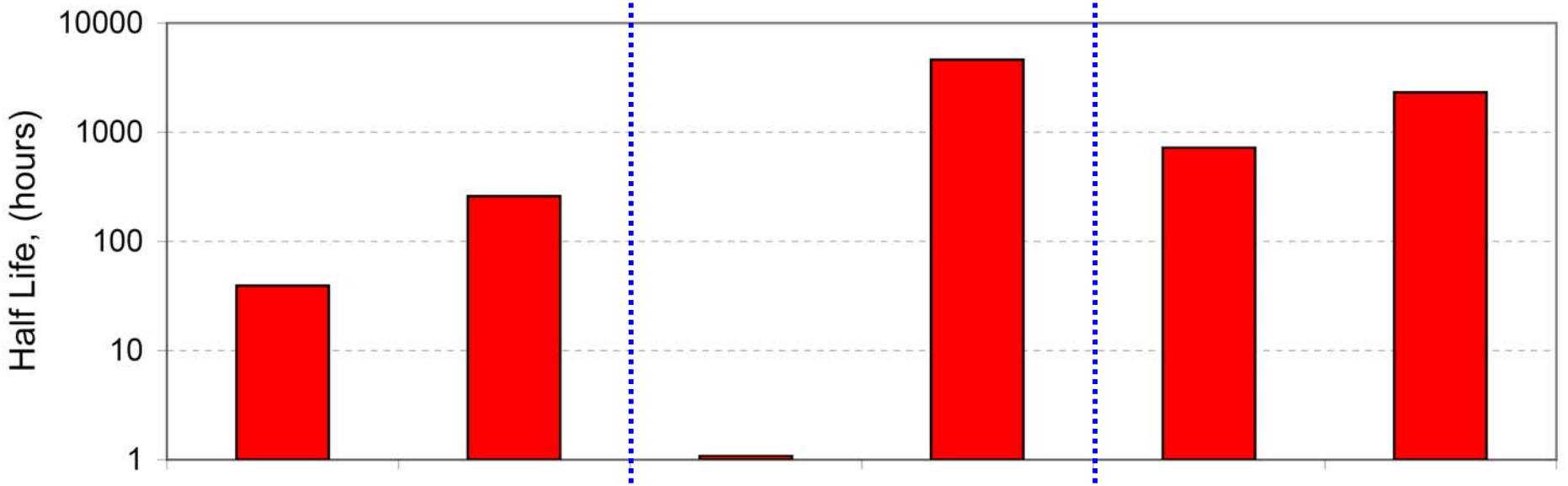


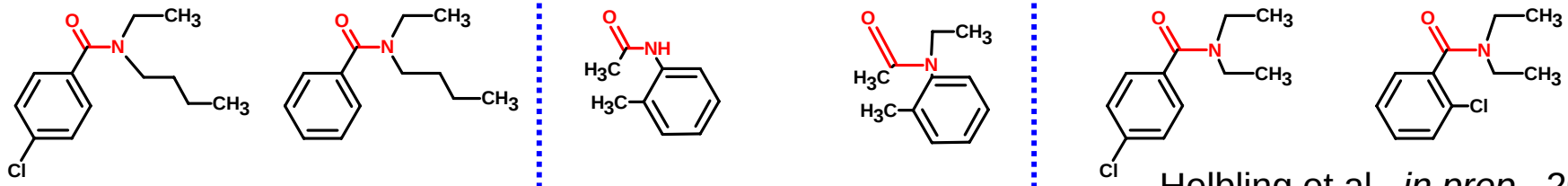


Helbling et al., *in prep.*, 2009

Experimental elucidation of rule priorities

	BEclB	BEB	mPH2	EmP2	EEclB	EEclB2
Hydrolysis	✓	✓	✓		✓	
Dealkylation					✓	✓
Other				✓		



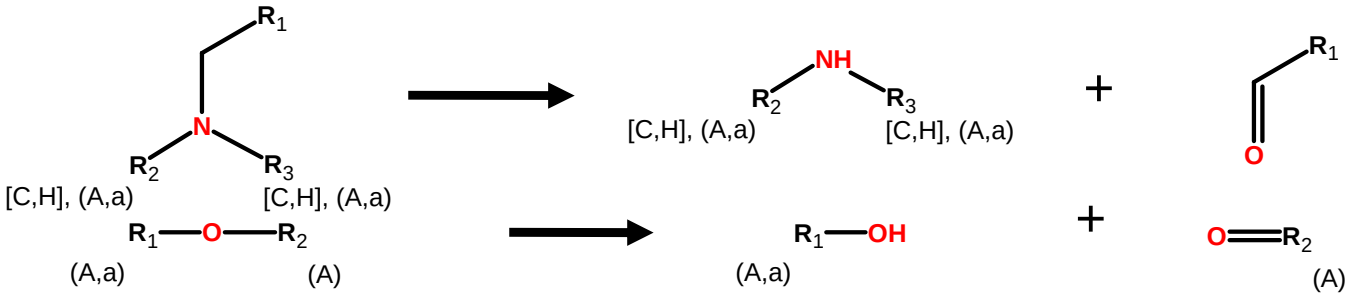


Helbling et al., *in prep.*, 2009

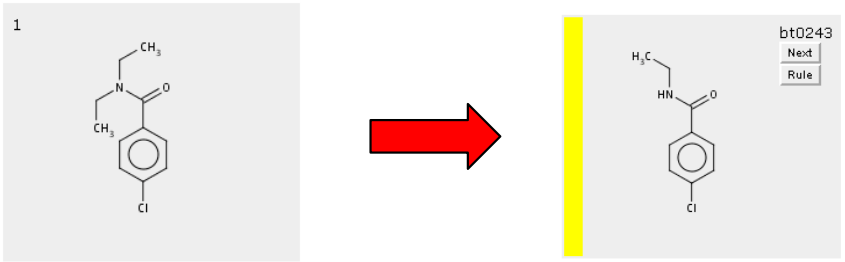
Structure-biodegradation relationships

Outlook and further work

- New case study for amines and ethers



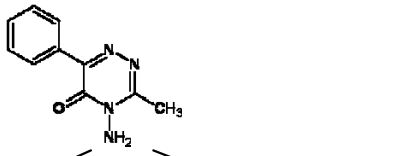
- Feedback loop into UM-PPS



- UM-PPS mirror at ETH Zürich
  - More “environmental realism”
  - Validation and further development based on data from soil and activated sludge simulation studies

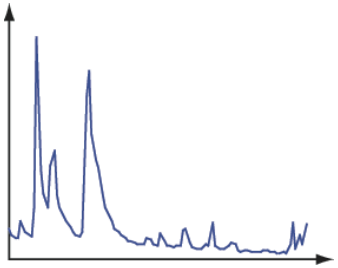
Strategy for assessing transformation products

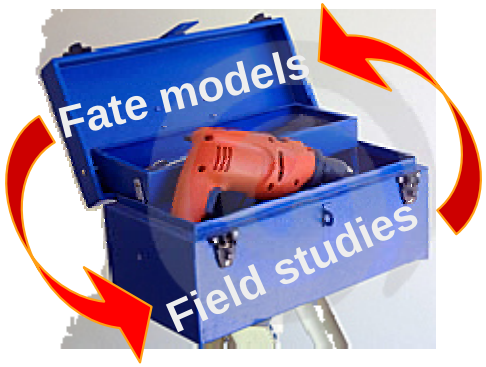
Identification



Exposure assessment

PEC/MEC

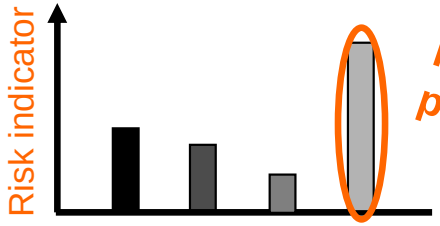




Effect assessment

PNEC

Risk assessment

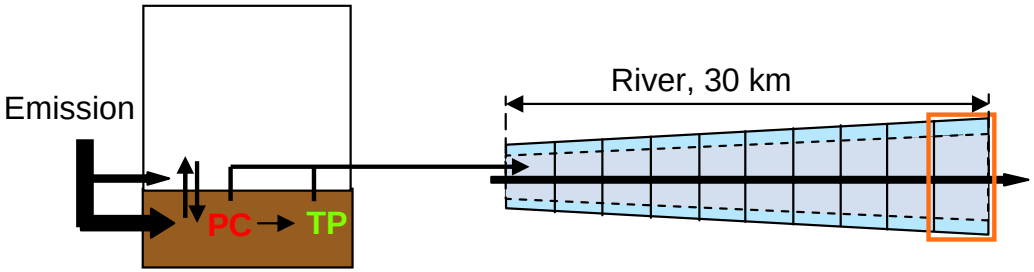


Relevant transformation product!

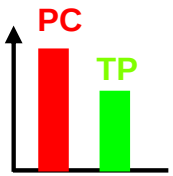
Finding products with relevant aquatic exposure

Tools

Mass balance model to predict concentration ratios of parent pesticide and transformation products



Measure for exposure to transformation product:
Relative concentration in last box of river model

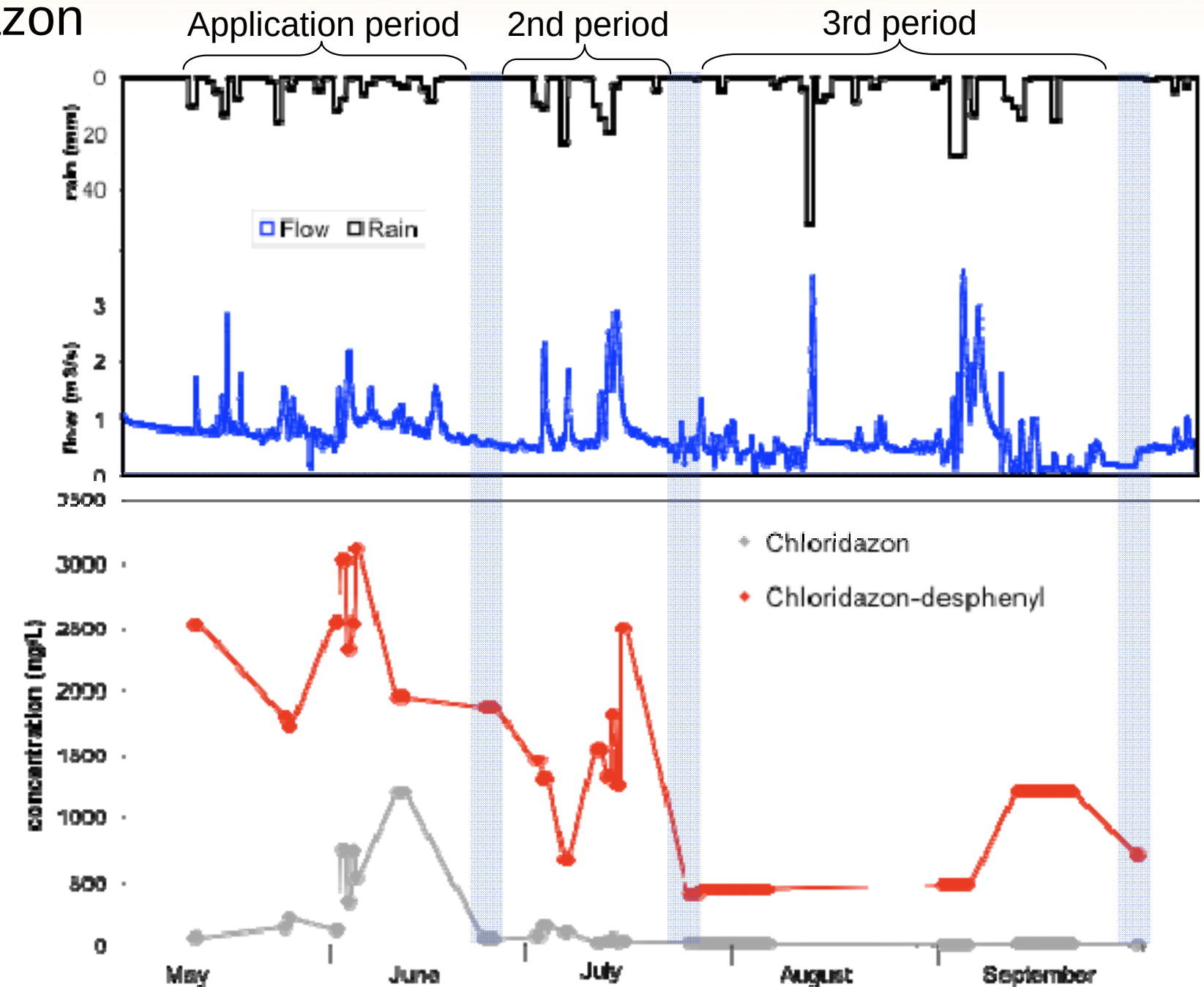


Field study La Petite Glâne; Chemical analysis for 12 events and 6 pairs of parent compounds and transformation products

Gasser et al., *ES&T*, 2007; Kern et al., *in prep*., 2009

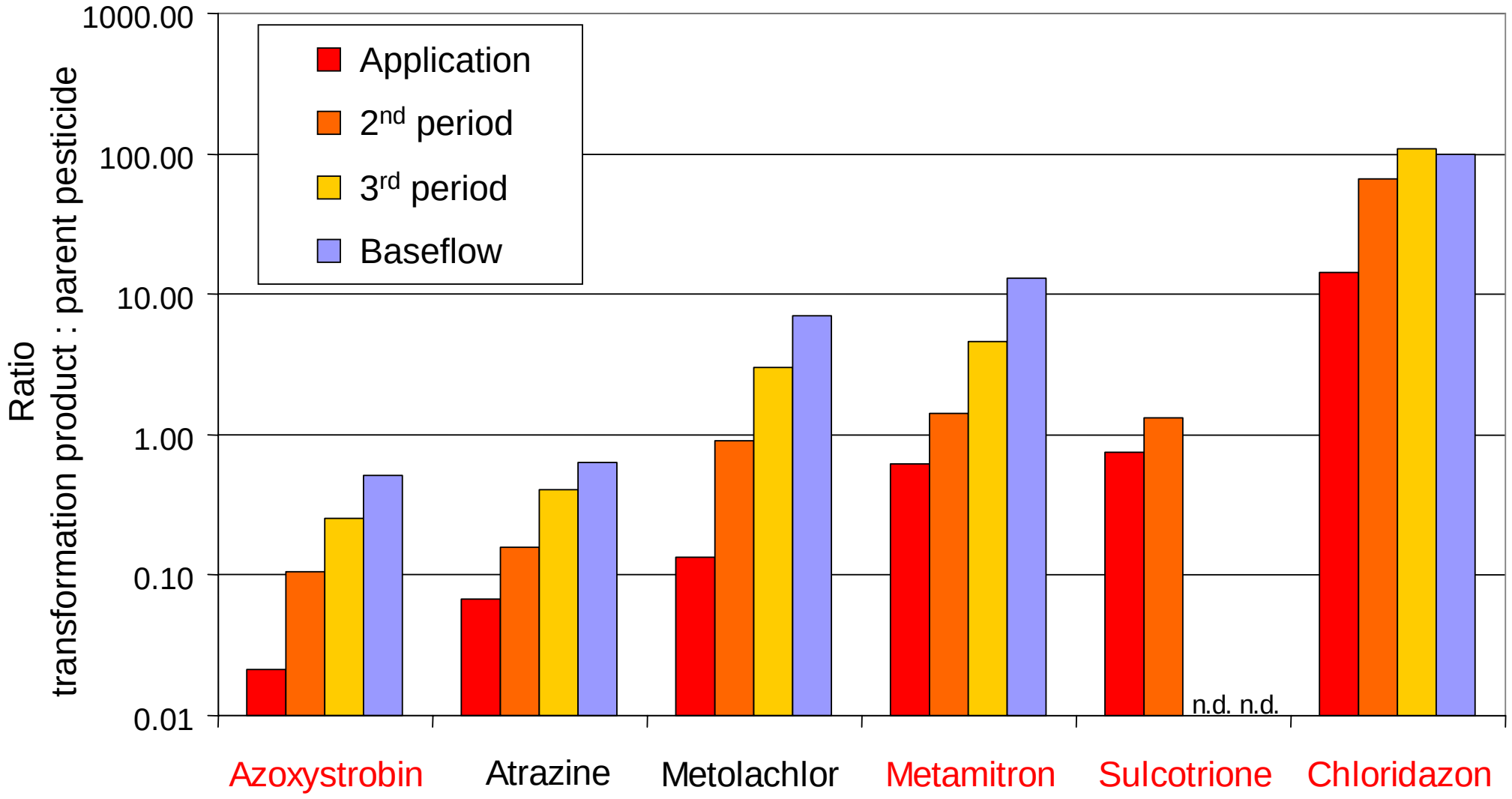
Finding products with relevant aquatic exposure

Chloridazon



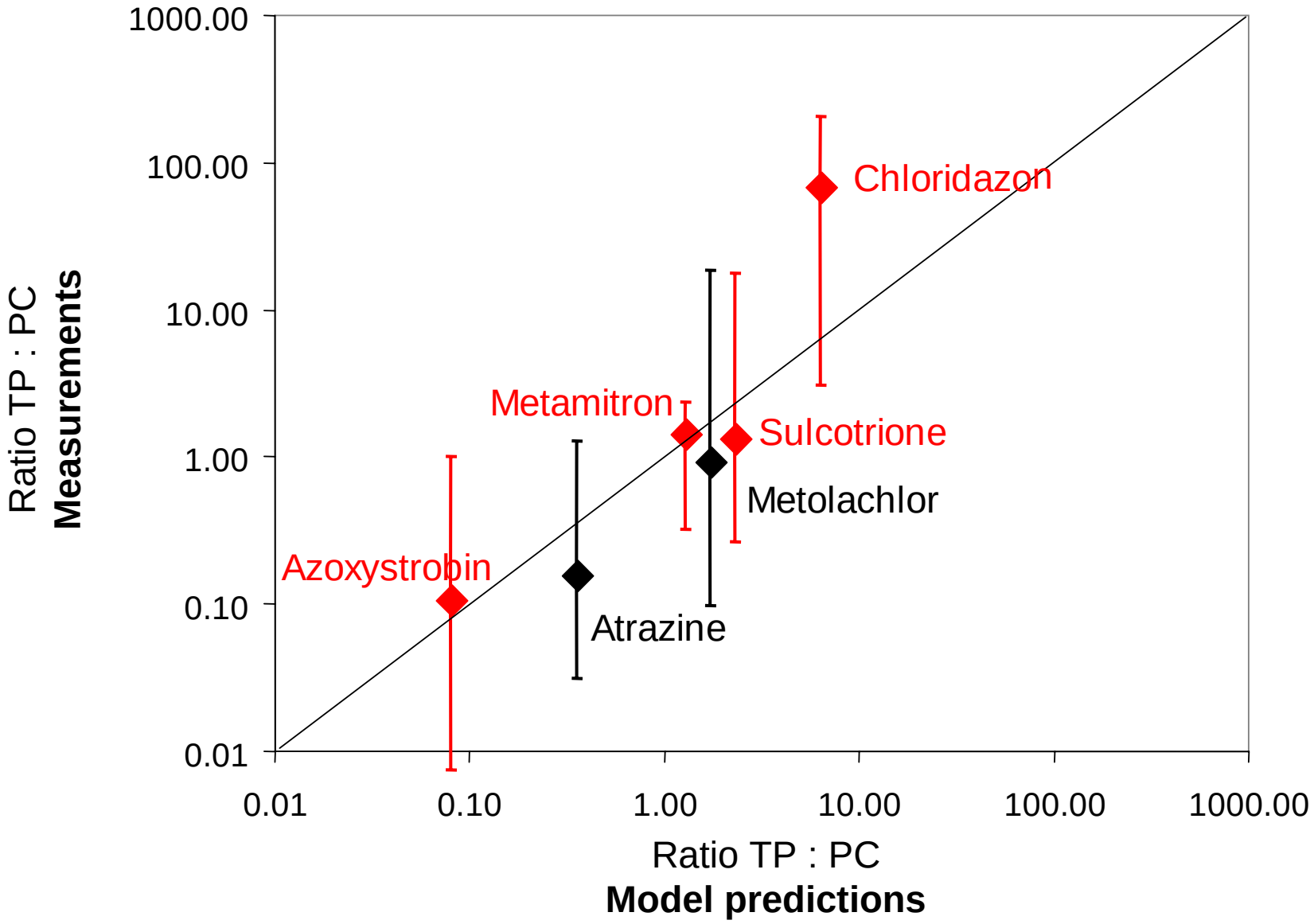
Finding products with relevant aquatic exposure

Summary of field study results



Finding products with relevant aquatic exposure

Comparison model – measurements



Strategy for assessing transformation products

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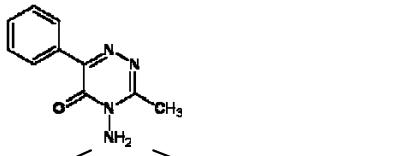

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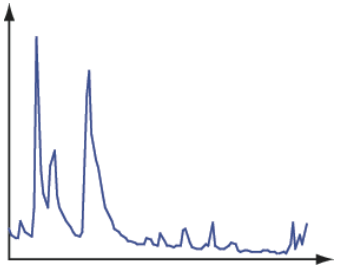
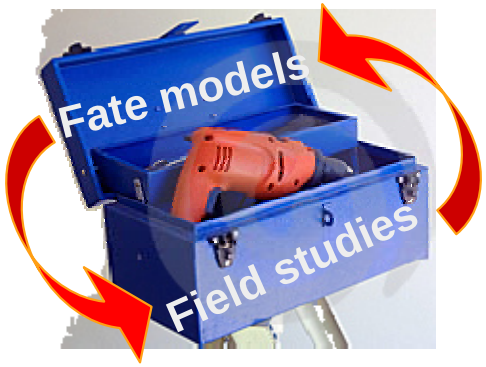
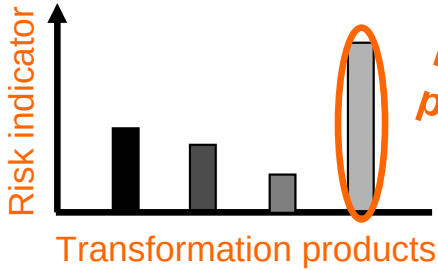




Effect assessment

PNEC

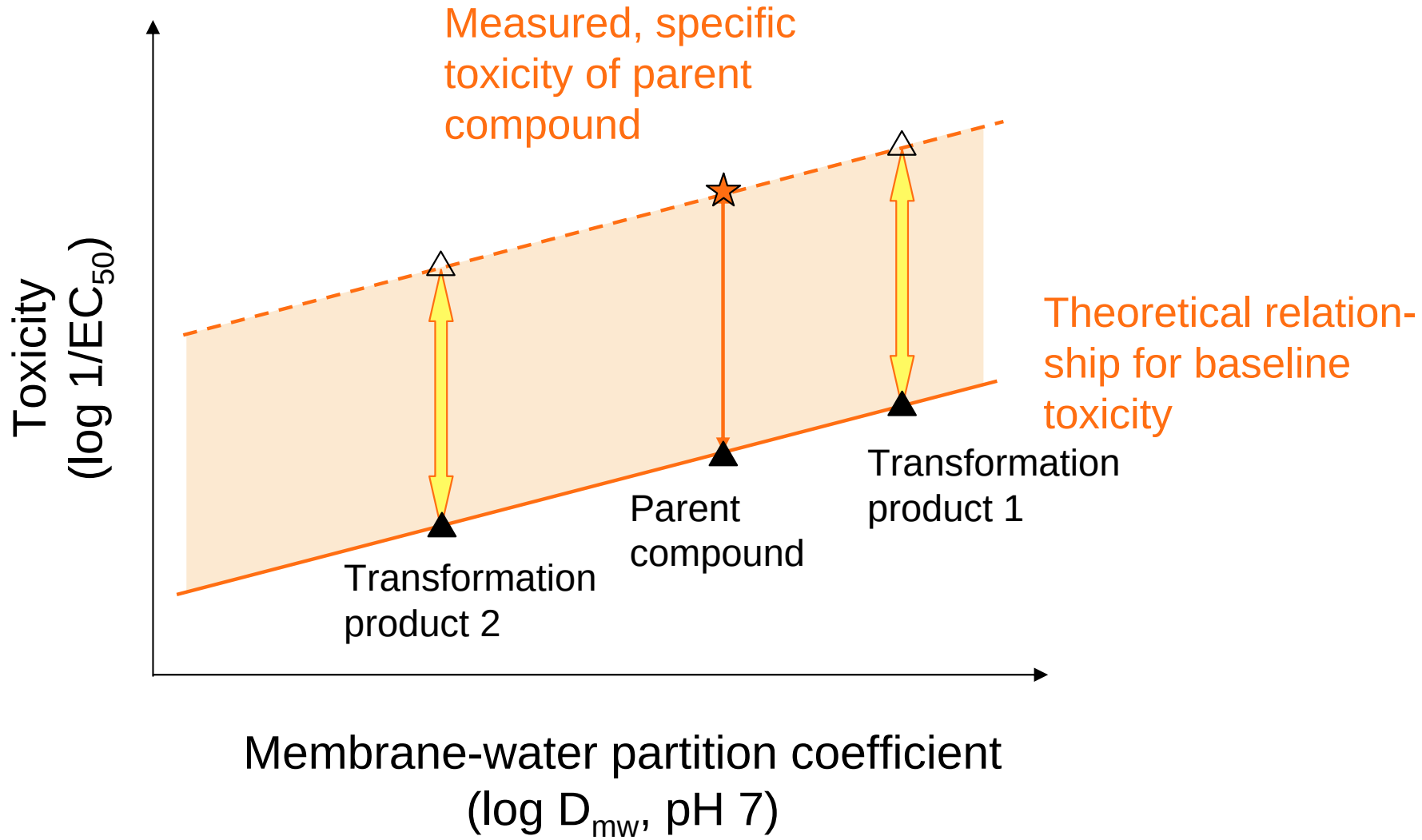
Risk assessment



Relevant transformation product!

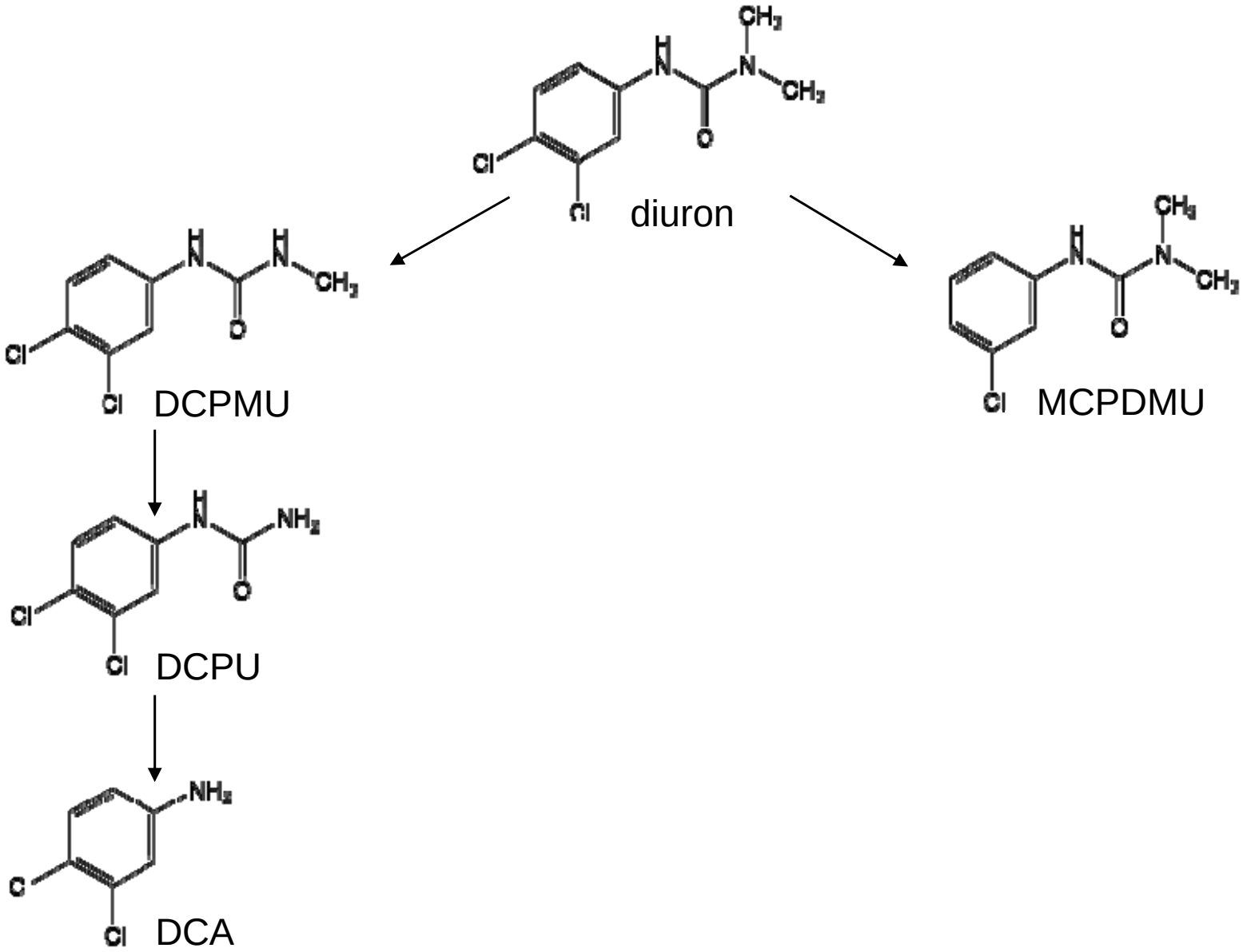
Effect and risk assessment

Predicting toxicity range of transformation products using read-across



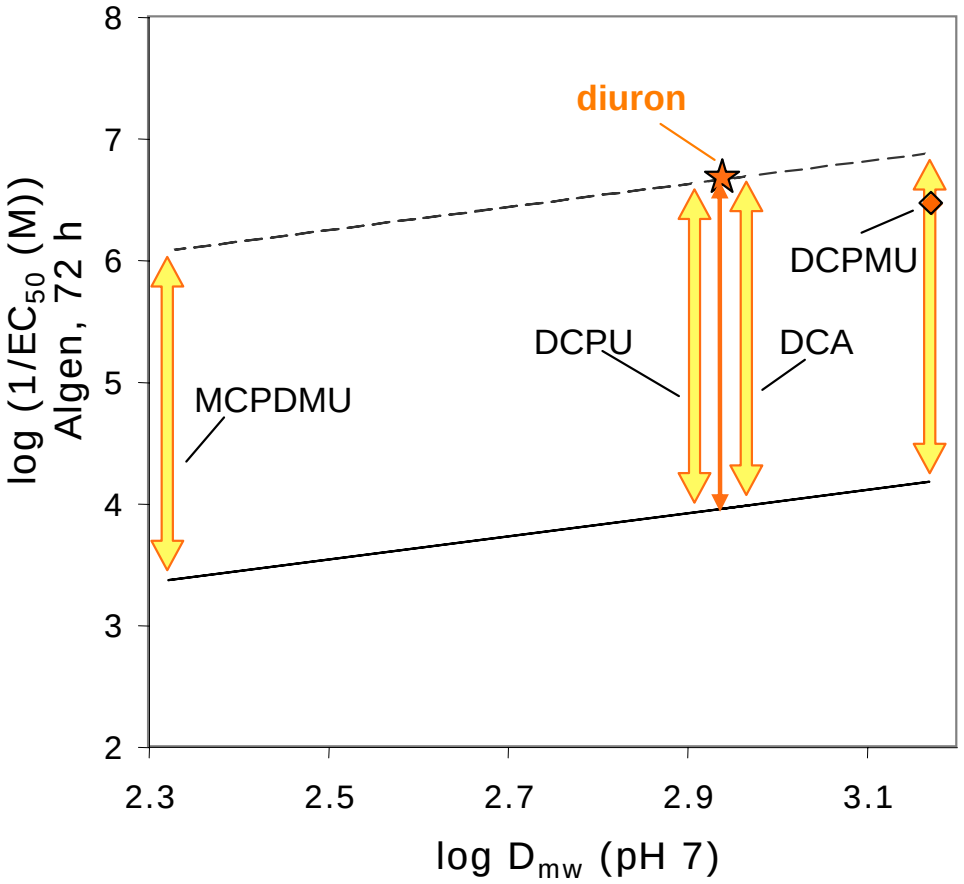
Effect and risk assessment

Case study diuron



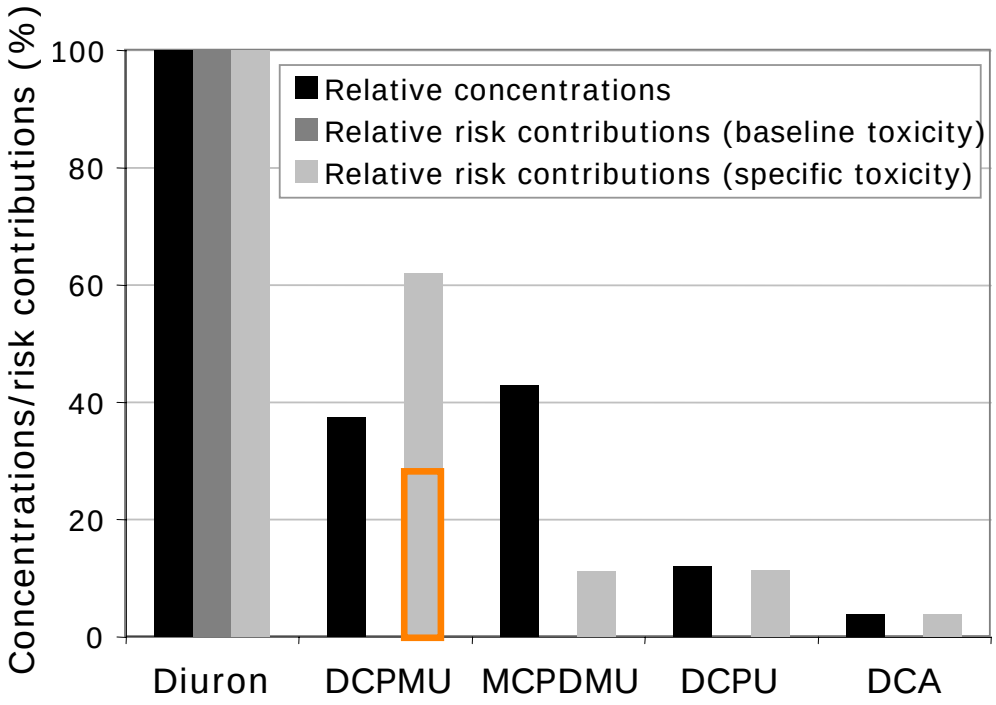
Effect and risk assessment

Modeling effects, concentrations and risk contributions



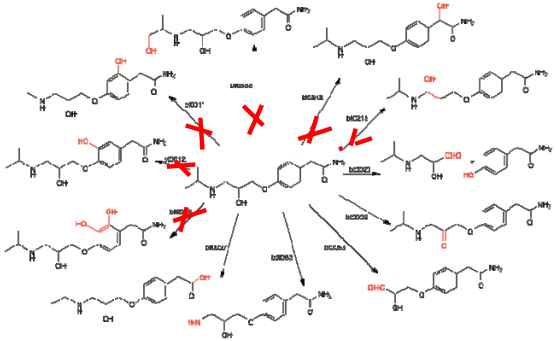
Risk contribution:

$$\frac{EC_{50}\,(\text{product})}{\text{Concentration (product)}} \Big/ \frac{EC_{50}\,(\text{diuron})}{\text{Concentration (diuron)}}$$



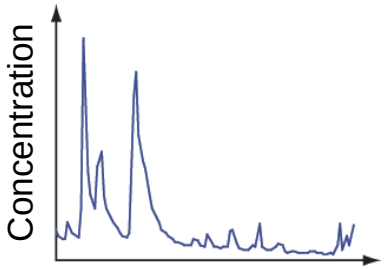
Conclusions

- Prediction of biodegradation products



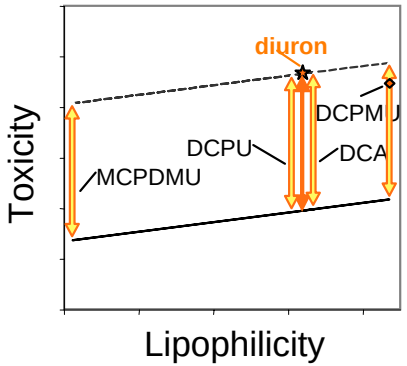
  - Restriction of prediction space through data mining and targeted experiments

- Characterization of exposure to transformation products



  - Combination of modeling and monitoring
  - Importance of groundwater component!

- Procedure for risk assessment of transformation products



  - Prediction of relative concentrations
  - Prediction of toxicity range through read-across
  - Targeted toxicity studies

Thank you!

KoMet team:

- Susanne Kern
- Judith Neuwöhner
- Beate Escher, Juliane Hollender, Heinz Singer

Swiss Federal Office for the Environment (Bafu):

- Michael Schärer
- Paul Liechti, Christof Studer, Reto Muralt, Christian Pillonel, Daniel Traber