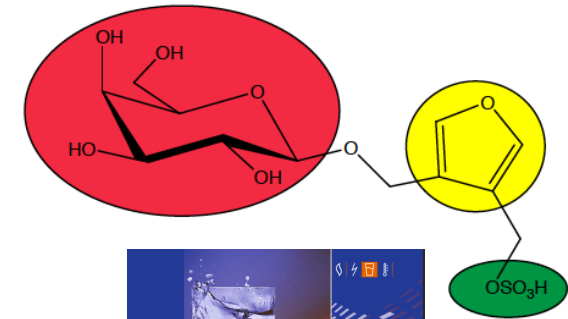
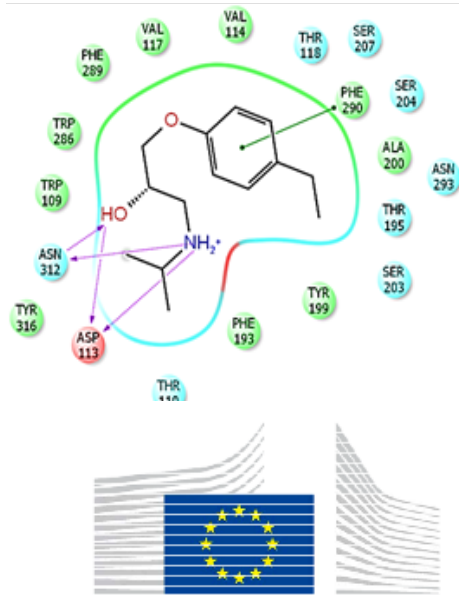


Herausforderung Mikroschadstoffe

Praktische Beiträge der Nachhaltigen Pharmazie



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 Klaus.Kuemmerer@uni.leuphana.de



gefördert vom
 Bundesministerium
 für Bildung
 und Forschung

NaWaM
 Nachhaltiges Wassermanagement

RiSKWa
 Risikomanagement von neuen Schadstoffen und Krankheitserregern im Wasserkreislauf

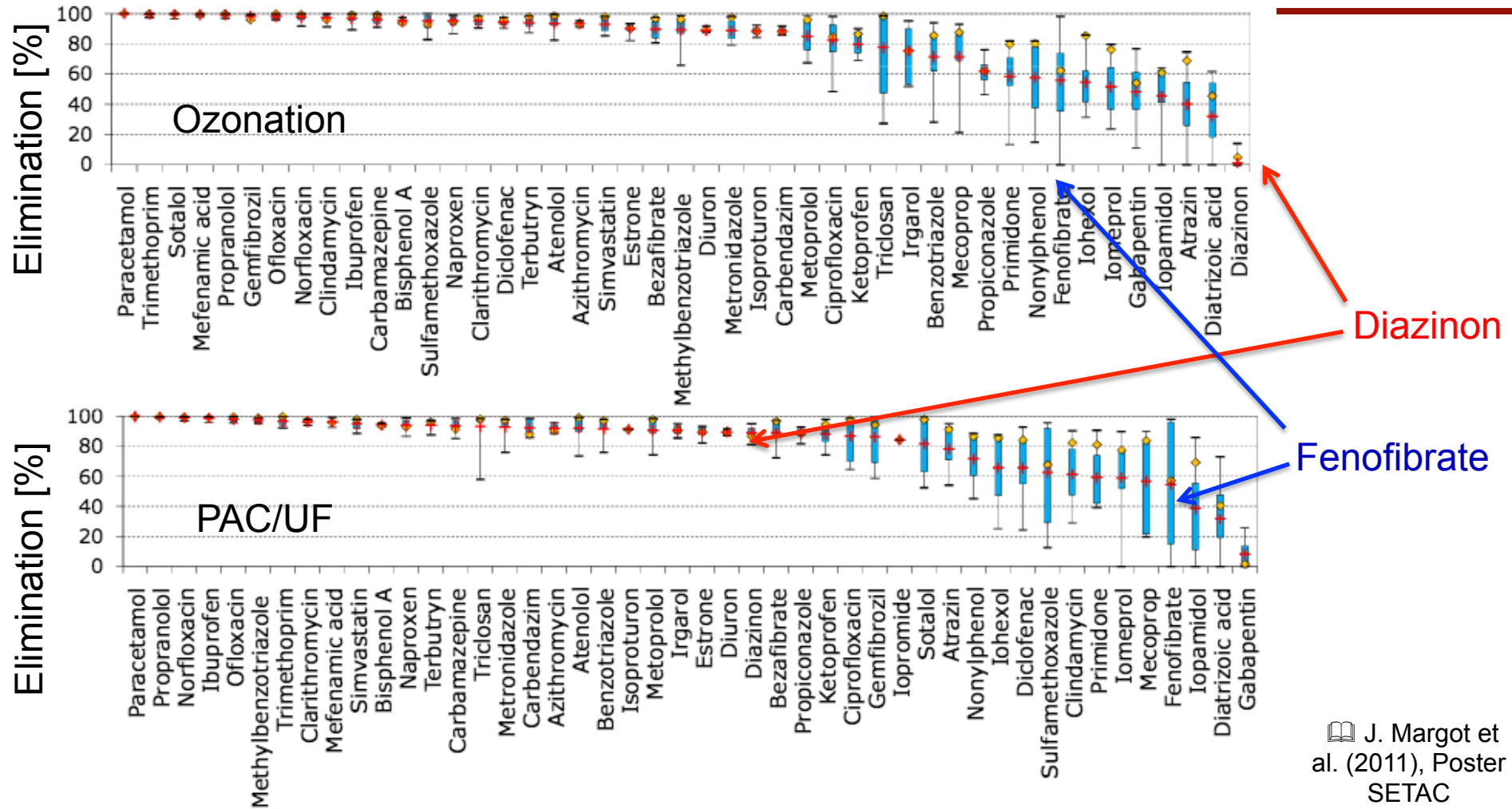
FONA
 BMBWF

Innovative Konzepte und Technologien für die separate Behandlung
 von Abwasser aus Einrichtungen des Gesundheitswesens

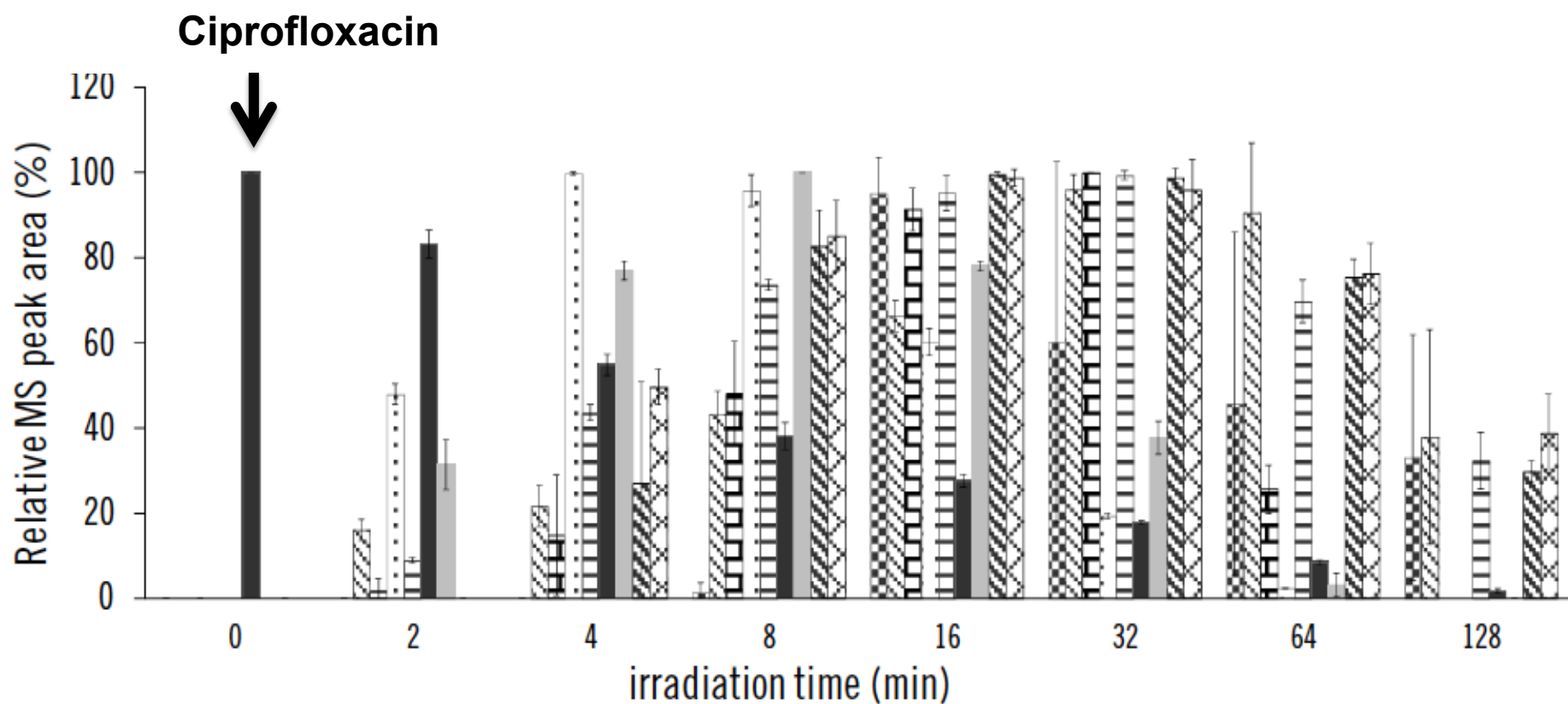
SAUBER+



Elimination of Micro-Pollutants in Advanced Waste Water Treatment



UV-Photolysis of Ciprofloxacin (Mediated by \bullet OH-Radicals)

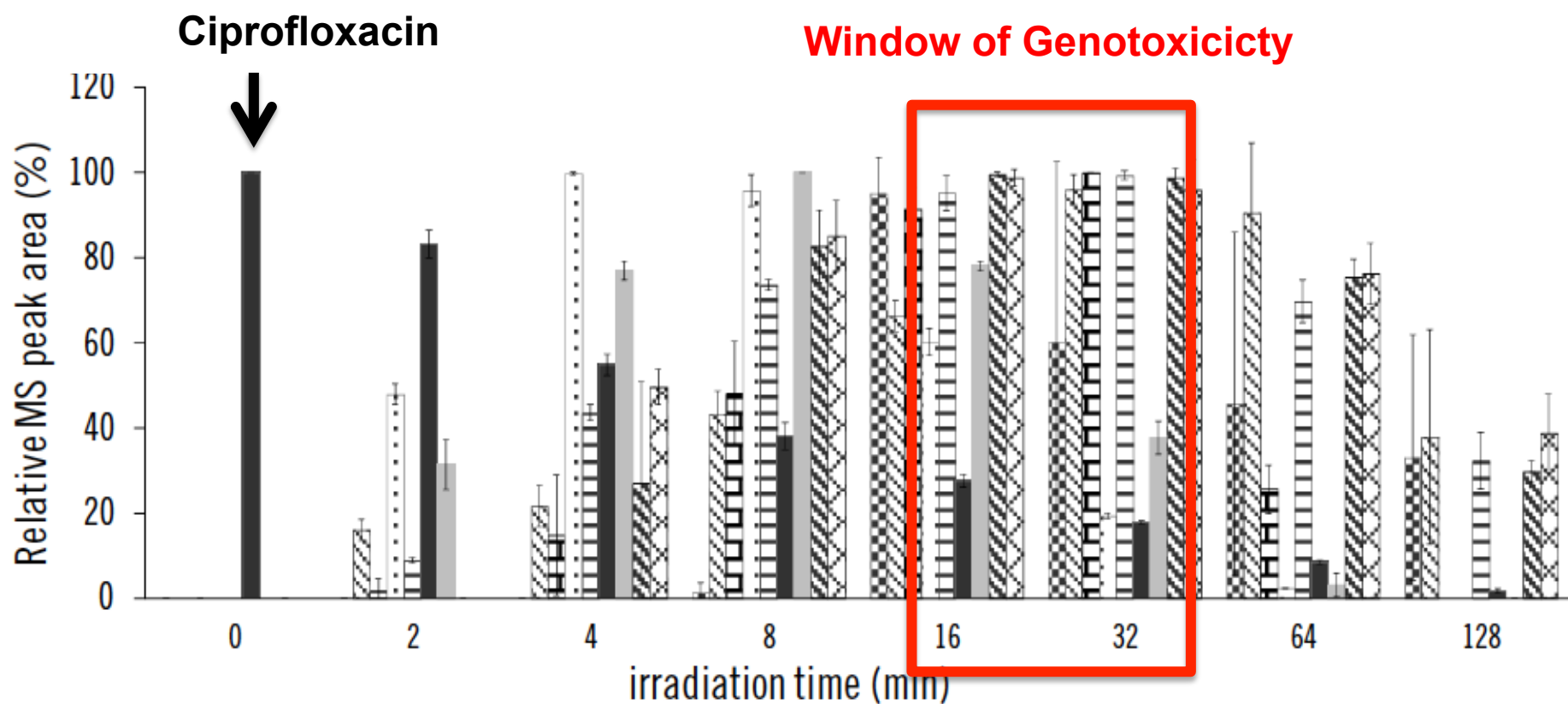


362.4(3.3)
 362.4(4.4)
 316.8(6.1)
 330.3(6.3)
 346.2(7.5)
 332.2(8.0)
 344.7(11.3)
 316.3(11.7)
 330.3(12.3)

📖 Haddad and Kümmerer, Chemosphere (2015) 115, 40-46



UV-Photolysis of Ciprofloxacin (Genotoxicity of Transformation Products)



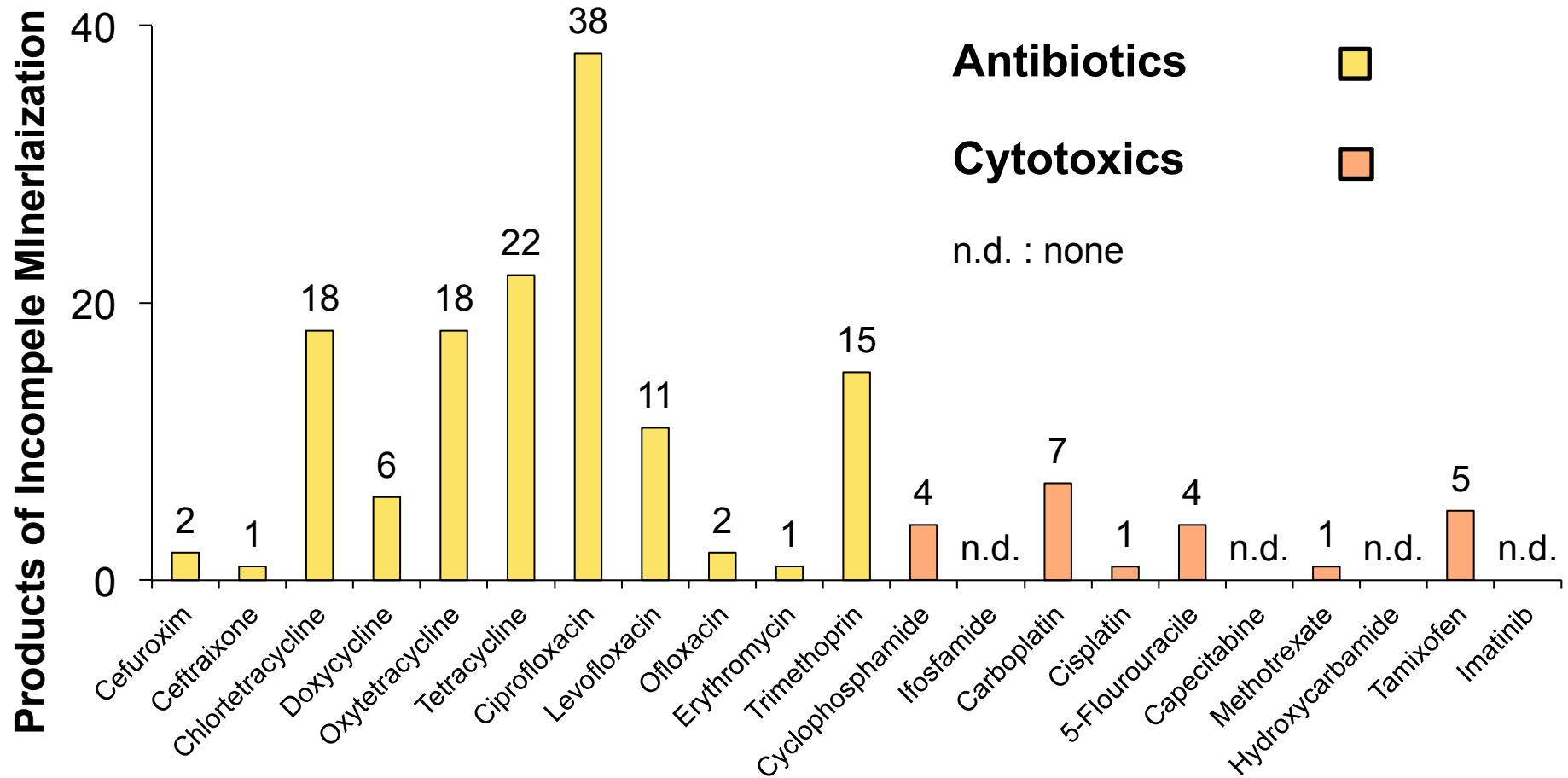
▣ 362.4(3.3)
▣ 362.4(4.4)
▣ 316.8(6.1)
▣ 330.3(6.3)
▣ 346.2(7.5)
▣ 332.2(8.0)
▣ 344.7(11.3)
▣ 316.3(11.7)
▣ 330.3(12.3)

📖 Garcia-Käufer M, Haddad T, Gupta P, Gminski R, Kümmerer K, Mersch-Sundermann V, *ESPR* (2012) 19, 1719-1727



Products of Incomplete Mineralization

(Advanced Effluent Treatment, reported until 2012)



Haddad T, Baginska E, Kümmerer K; Water Research, 2015



Wir stoßen zunehmend an Grenzen!

1. Jedes Verfahren entfernt nur eine jeweils spezifische Minderheit von Substanzen
 2. Bei oxidativen Verfahren wird eine Vielzahl von Abbauprodukten mit unbekanntem Eigenschaften und Toxizität gebildet
 3. Die Stoffe der Zukunft kennen wir nicht
-

4. Ca. 35 000 Stoffe relevant, pro Stoff 5 Abbauprodukte?
welche und wieviele Toxizitätsendpunkte mit welchem Test?



Measures at the Source

Member States **should tackle the sources of pollution ... This is much preferable to using end-of-pipe treatment ...** while avoiding high treatment costs and protecting the environment.

9.3.2015



COMMUNICATION FROM THE COMMISSION TO THE EUROPEAN PARLIAMENT AND THE COUNCIL
The Water Framework Directive and the Floods Directive: Actions towards the 'good status' of EU water
and to reduce flood risks /* COM/2015/0120 final */., 9.3.2015



Eintragsreduktion durch Information und Ausbildung

Information Bevölkerung
Patient-Arzt-Interaktion
Ärztefortbildung
Ärzteausbildung

Abfallwirtschaft und Stadtreinigung Freiburg GmbH
 Hermann-Müller-Strasse 26
 79108 Freiburg
 Telefon 07 01 7 07 07 40
 www.abfallwirtschaft-freiburg.de

Abwasserzweckverband Breisgau-Bucht
 Hartwegstraße 6
 79108 Freiburg
 Telefon 07 01 52 17 10
 www.abzw-breisgau.de

Landesärztekammer Baden-Württemberg
 Ausschuss Prävention und Umwelt
 Jochenstraße 40
 70597 Stuttgart
 Telefon 07 14 74 98 90
 www.aerztekammer-bw.de

Landesapothekerverband Baden-Württemberg e.V.
 Hölderstraße 15
 70174 Stuttgart
 Telefon 07 14 23 34 77
 www.apotheker.de

Stadterhebung Freiburg i. Br.
 Egonstraße 25
 79115 Freiburg
 Telefon 07 01 51 44 01
 www.stad-freiburg.de

Uniklinik Freiburg
 Institut für Umweltmedizin und Krankheitshygiene
 Breisacher Straße 135 B
 79106 Freiburg
 Telefon 07 01 2 10 82 95
 www.uk-freiburg.de

Landesinstitut für Umweltmedizin und Krankheitshygiene, Section Angewandte Umweltforschung, Universität Leirichium Freiburg
 www.lub.uni-freiburg.de

Landesapothekerverband Baden-Württemberg e.V.
 Landesapothekerverband Baden-Württemberg e.V.
 www.lav-bw.de

Freiburg
 www.freiburg.de

Uniklinik Freiburg
 www.uk-freiburg.de

Arzneimittel – Wasser – Umwelt
 > So schützen wir vorsorglich unser Trinkwasser

badenova
 Energie. Tag für Tag

GEFÖRDERT VOM
Bundesministerium für Bildung und Forschung

NaWaM
 Nachhaltiges Wassermanagement

RiSKWa
 Risikomanagement von neuen Schadstoffen und Krankheitserregern im Wasserkreislauf

FONA
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Innovative Konzepte und Technologien für die separate Behandlung
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SAUBER+

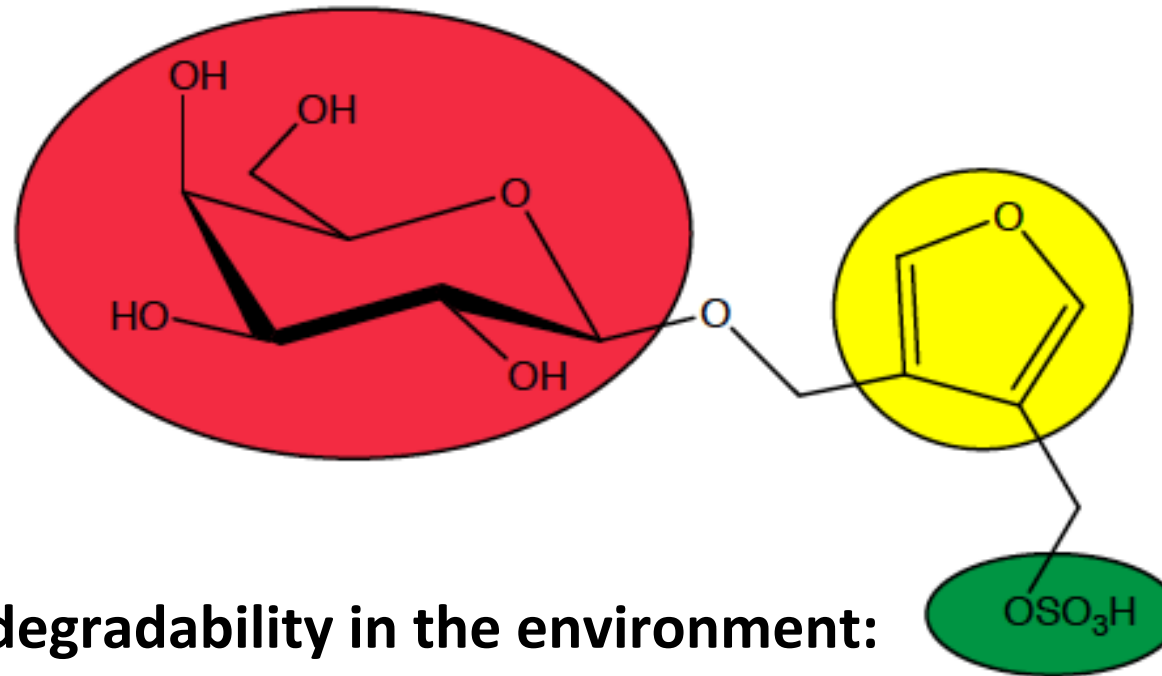


Meeting the Hygienical Standard



De-Novo Design - Targeted Synthesis

New Lead Structure by Ligand Variation



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?**

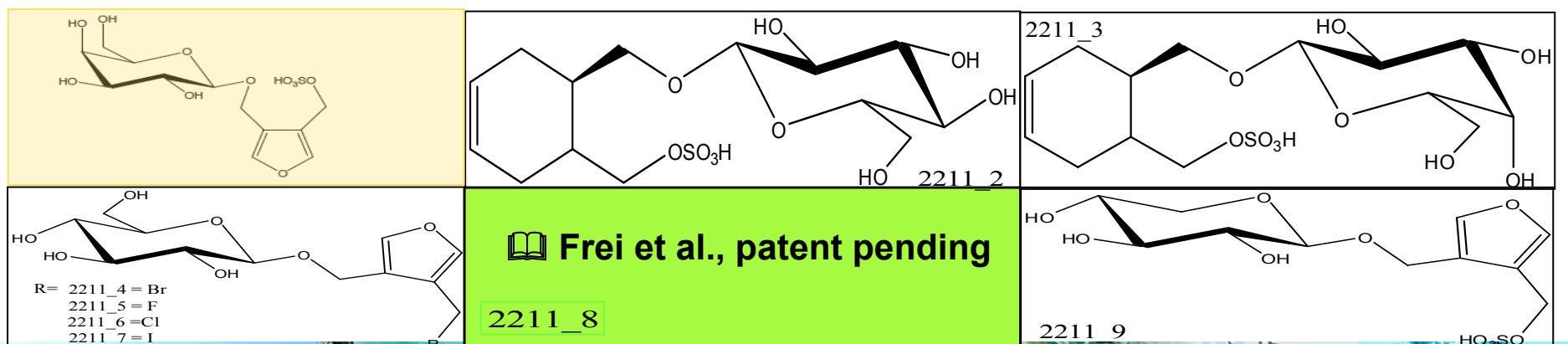
📖 Kümmerer K, Frei E, Marano G, in preparation



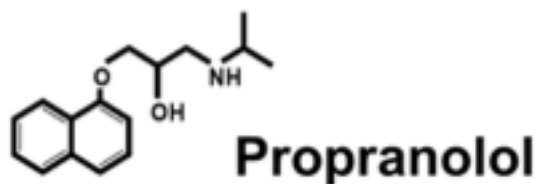
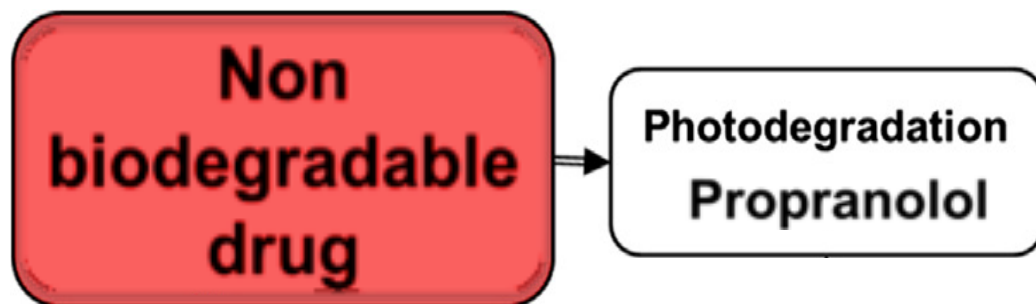
Targeted Structure Variation


📖 Kümmerer K, Frei E, Marano G, in preparation

Structure ID	Log Kow	Effect threshold (rel. units)	Biodegradation[%]
GSF	-2.1	1	19
2211_2 (Glu ,Cyclohex)	-1.8	> 1	37
2211_3 (Gal, Cyclohex)	-1.8	> 1	37
2211_4 (Glu-Br)	-0.5	> 1	14
2211_5 (Glu-F)	-0.9	> 1	14
2211_6 (Glu-Cl)	-0.7	> 1	14
2211_7 (Glu-I)	-0.5	> 1	14
2211_8	-2.0	<0,01	54
2211_9 (Desoxyglu)	-1.5	> 1	31



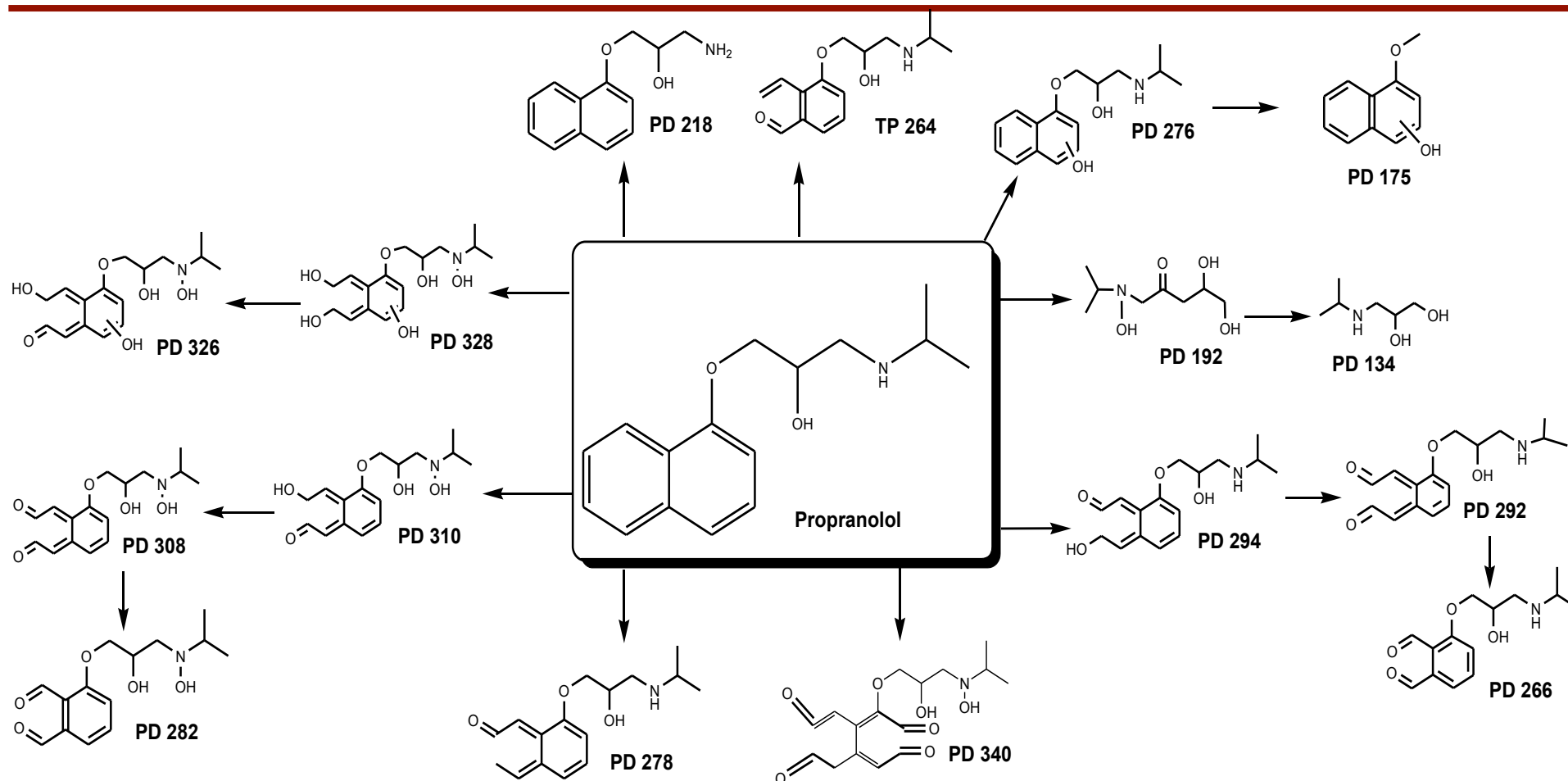
Re-Design



 Rastogi T, Leder C, Kümmerer K (2015), ES&T, 49, 11756–11763 (open access)



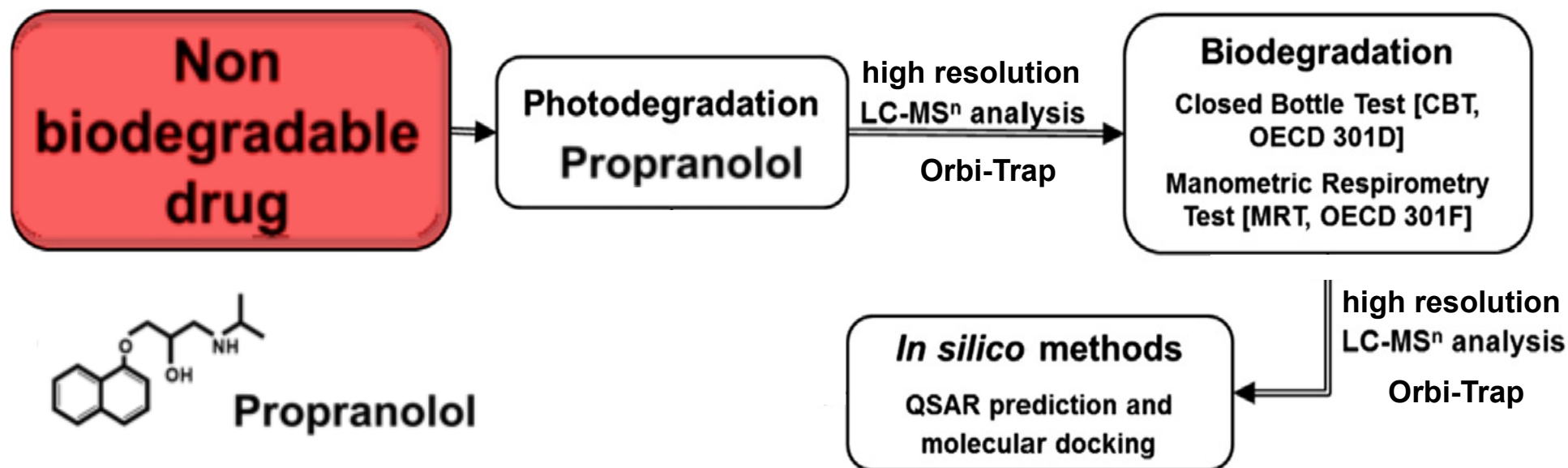
Non-targeted Generation of Derivatives of Propranolol



📖 Rastogi T, Leder C, Kümmerer K (2015), ES&T, 49, 11756–11763 (open access)



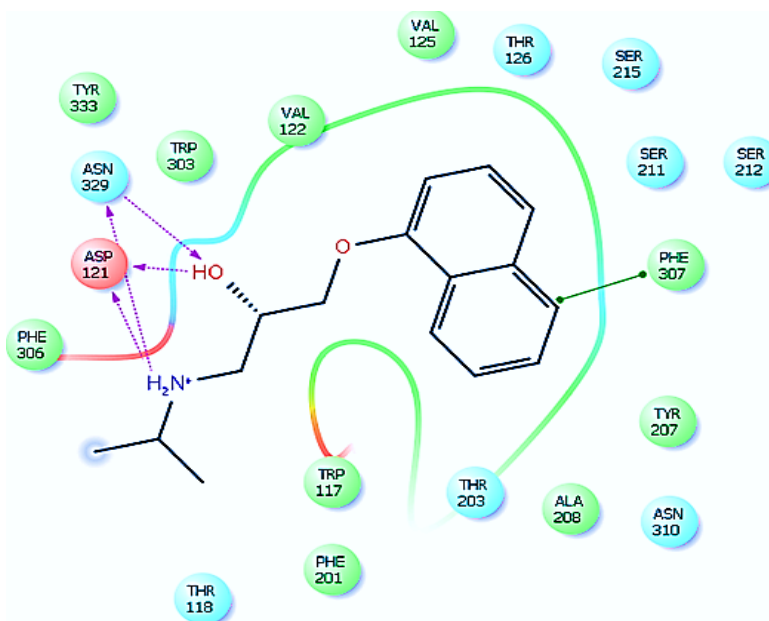
Methods



📖 Rastogi T, Leder C, Kümmerer K (2015), ES&T, 49, 11756–11763 (open access)



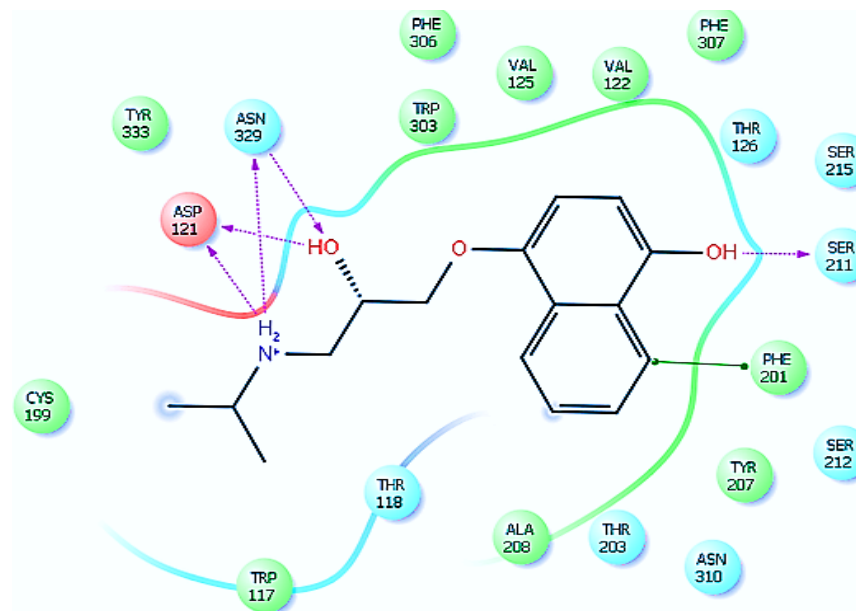
Docking



PPL (S)

Docking Score:

- 9.1



4-OH PPL (S)

Docking Score:

- 9.3

📖 Rastogi T, Leder C, Kümmerer K (2015), ES&T, 49, 11756–11763 (open access)



Toxicity Assessment 4-Hydroxypropranolol (In Silico Prediction)

QSAR Software	Models	End points	Propranolol	4-OH Propranolol
CASE Ultra v. 1.5.2.0 (as per ICH M7 guidelines)	Salmonella mutagenicity	Mutagenicity	Known negative	Negative
	A-T site mutation	Mutagenicity	Inconclusive	Negative
	Expert rules for genotoxicity	Genotoxicity	Known negative	Positive
	E.coli mutagenicity	Mutagenicity	Negative	Negative
Leadscope Model Applier Version: 1.8.6 (as per ICH M7 guidelines)	Salmonella mutagenicity	Mutagenicity	Known negative	Negative
	ICH M7 Genetox Consensus	Genetox Consensus	Negative	Negative
	E Coli - Sal 102 A-T mutagenicity	Mutagenicity	Negative	Negative
	Salmonella mutagenicity	Mutagenicity	Negative	Negative
	Bacterial Mutation	Mutagenicity	Negative	Negative
CASE Ultra v.1.4.5.1	Human carcinogenicity	Carcinogenicity	Negative	Negative
	Micronucleus formation in vivo composite	Genotoxicity	Positive	Negative
OASIS Catalogic	Chromosome aberration in vitro composite	Mutagenicity	Marginal positive	Negative
	In vitro Ames model	Mutagenicity	Negative	Negative

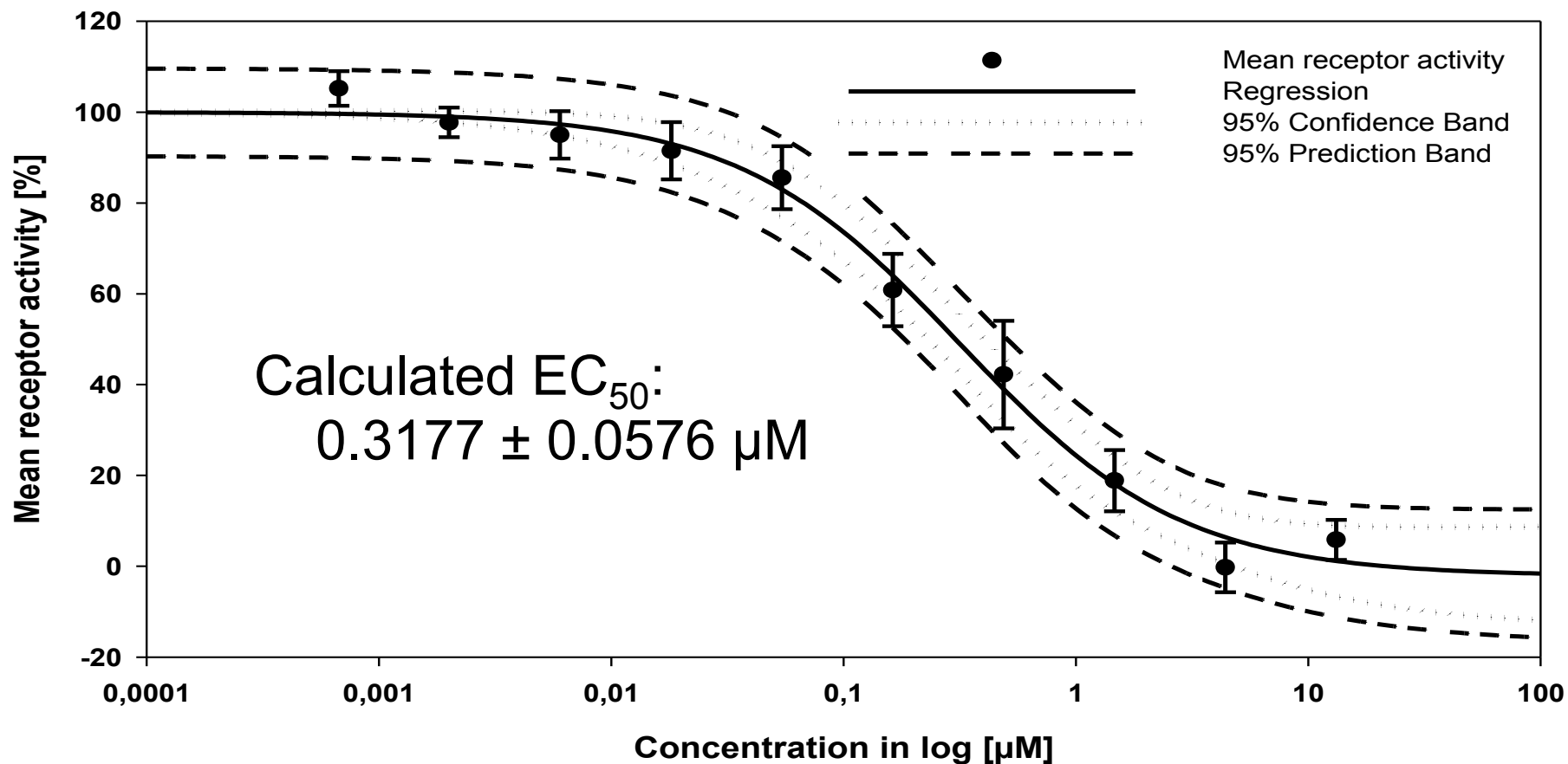


ADME Properties of 4-Hydroxypropranolol (In Silico Prediction)

ADME properties	Description	Range or recommended values	Atenolol	Metoprolol	Propranolol	4-Hydroxy propranolol
Rule of 5	Lipinski's rule of five.	Fewer or no violations	0	0	0	0
Rule of 3	Jorgensen's rule of three.	Fewer or no violations	0	0	0	0
log P_{o/w}	Octanol/water partition coefficient.	-2.0 to 6.5	0.17	1.9	3.1	2.1
log S	Aqueous solubility	-6.5 to 0.5	-1.3	-1.4	-3.5	-2.1
log HERG	IC50 value for blockage of HERG K ⁺ channels.	Concern below -5	-4.5	-6.1	-5.9	-5.9
P Caco	Apparent Caco-2 cell permeability	<25 poor and >500 great	33.9	733.9	1147.9	320.7
log BB	Brain/blood partition coefficient	-3.0 to 1.2	-1.21	-0.22	0.22	-0.4
P MDCK	Apparent MDCK cell permeability	<25 poor and >500 great	32.0	391.7	635.3	160.1
log K_p	Skin permeability	-8.0 to -1.0	-5.2	-3.2	-2.6	-3.7
Human-oral absorption		1, 2, or 3 for low, medium or high, respectively	2	3	3	3
log K_{hsa}	Binding to human serum albumin	-1.5 to 1.5	-0.76	-0.15	0.05	-0.12
CNS	Central nervous system activity	-2 (inactive) to 2 (active)	1	-2	1	0



Pharmacological Activity of 4-Hydroxypropranolol (In Vitro Analysis)

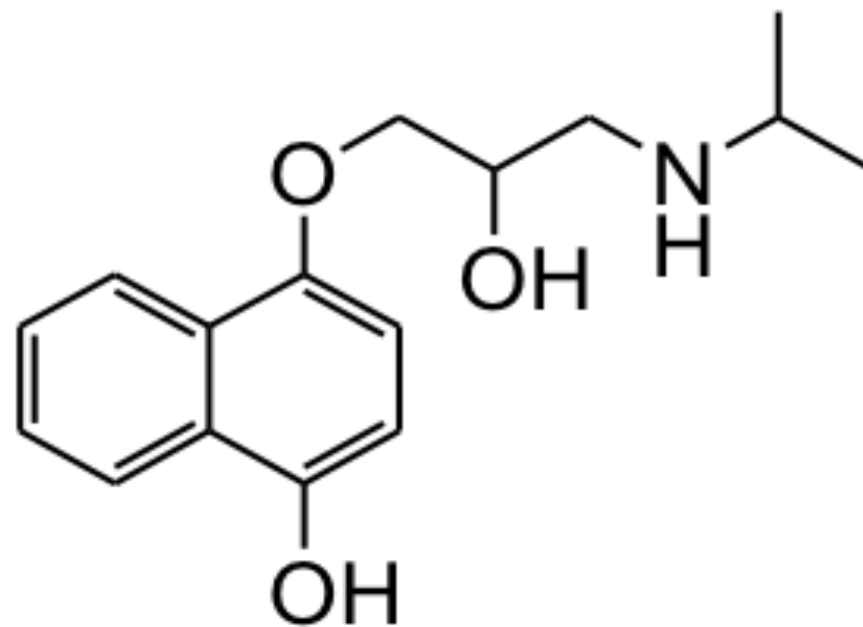



📖 Rastogi T, Leder C, Kümmerer K (2015), ES&T, 49, 11756–11763 (open access)



4-Hydroxypropranolol

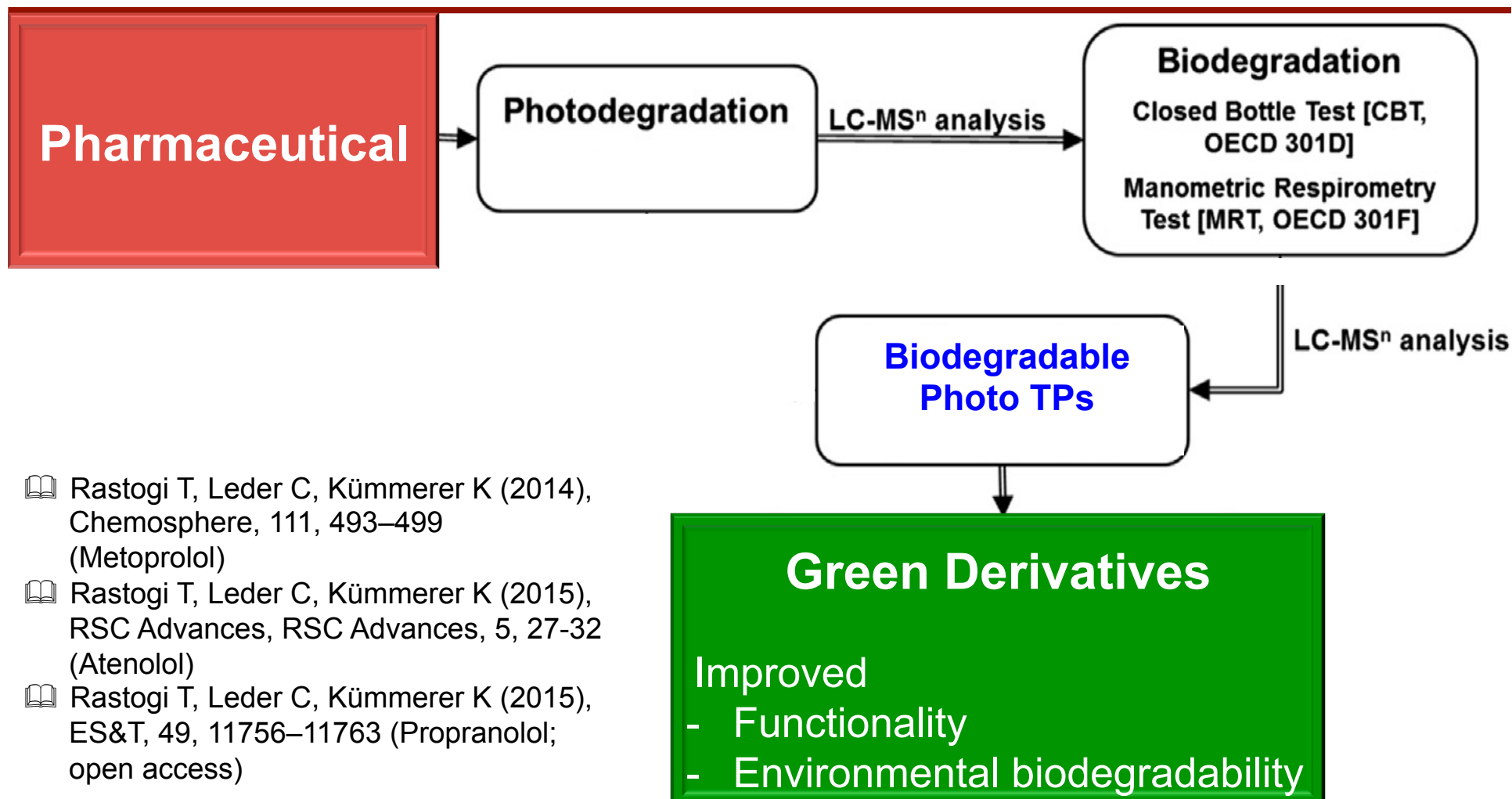
Pharmaceutically
active and
environmentally
biodegradable photo
transformation product
Including metabolite



 Rastogi T, Leder C, Kümmerer K (2015), ES&T, 49, 11756–11763 (open access)



Re-Design



- 📖 Rastogi T, Leder C, Kümmerer K (2014), Chemosphere, 111, 493–499 (Metoprolol)
- 📖 Rastogi T, Leder C, Kümmerer K (2015), RSC Advances, RSC Advances, 5, 27-32 (Atenolol)
- 📖 Rastogi T, Leder C, Kümmerer K (2015), ES&T, 49, 11756–11763 (Propranolol; open access)



Zusammenfassung

1. (Erweiterte) Abwasserreinigung kann die Probleme nicht lösen
2. Information und Ausbildung kann zur Reduktion beitragen
3. Re-Design kann zu umweltverträglichen Wirkstoffen führen
4. Umweltverträglichkeit kann bei neuen Wirkstoffen gezielt eingebaut werden

