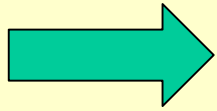


**Pharmaceuticals and Personal Care Products (PPCP) –
Candidate Environmental Pollutants with Increasing Impact**

Heinrich Hühnerfuss

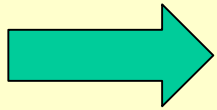
*Institute of Organic Chemistry
University of Hamburg*

Due to the demographic development the average life-span of people is increasing continuously

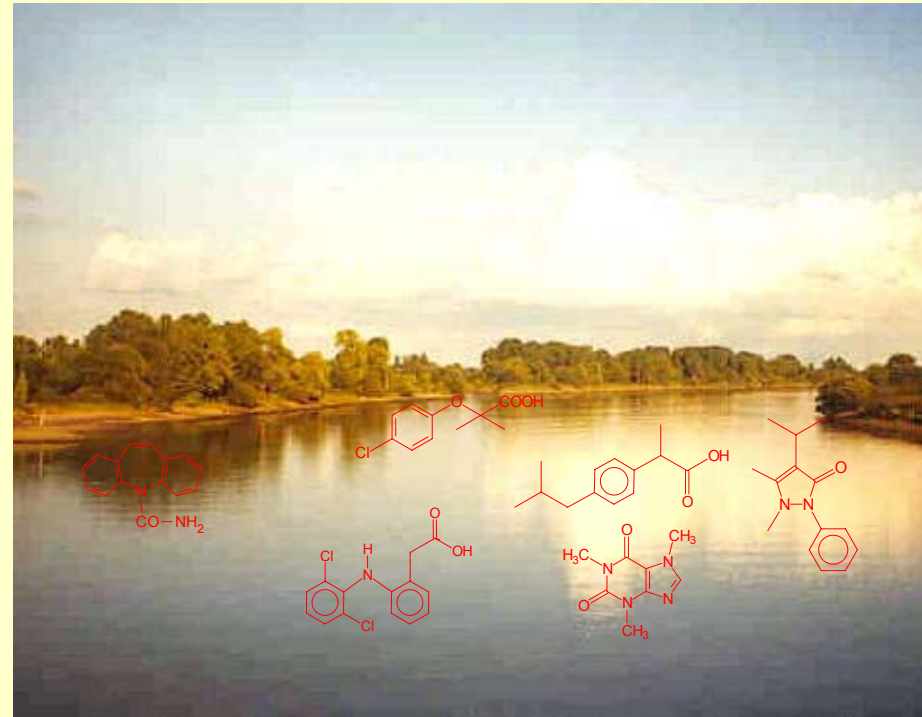
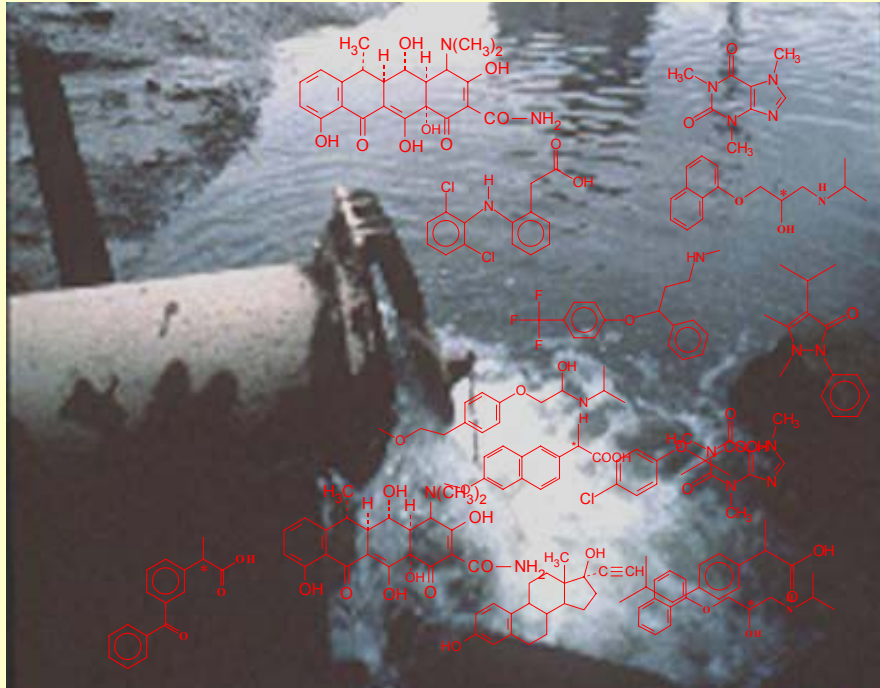


This goes in line with an increase in consumption of pharmaceuticals



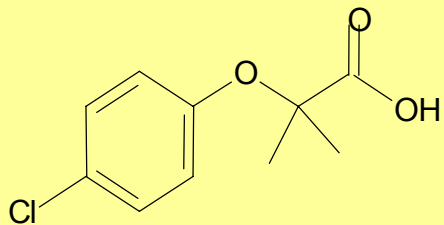


After consumption, further fate



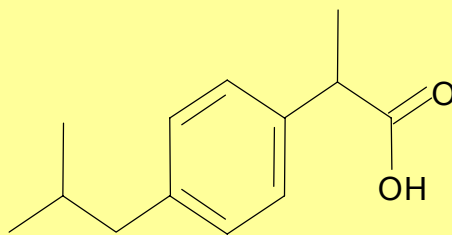
Prominent examples for pharmaceuticals

in the aquatic ecosystem



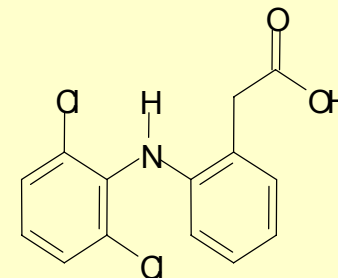
Clofibric acid

*Metabolite of Ethylclofibrate
reduction of plasma
cholesterol and triglyceride*



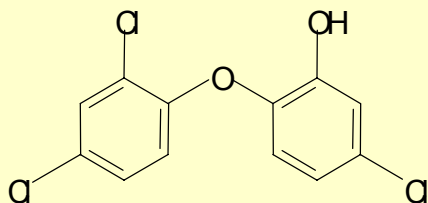
Ibuprofen

*antiphlogistic, analgesic
and antipyretic properties*



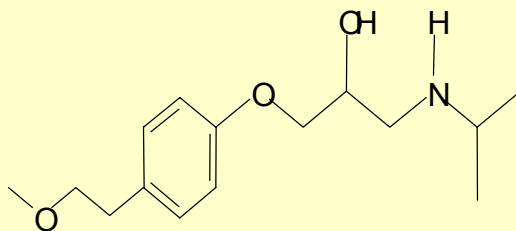
Diclofenac

*antiphlogistic and analgesic
effect*



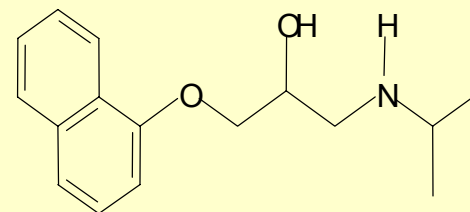
Triclosan

*Antibacterial effect in
soaps, toothpaste etc.*



Metoprolol

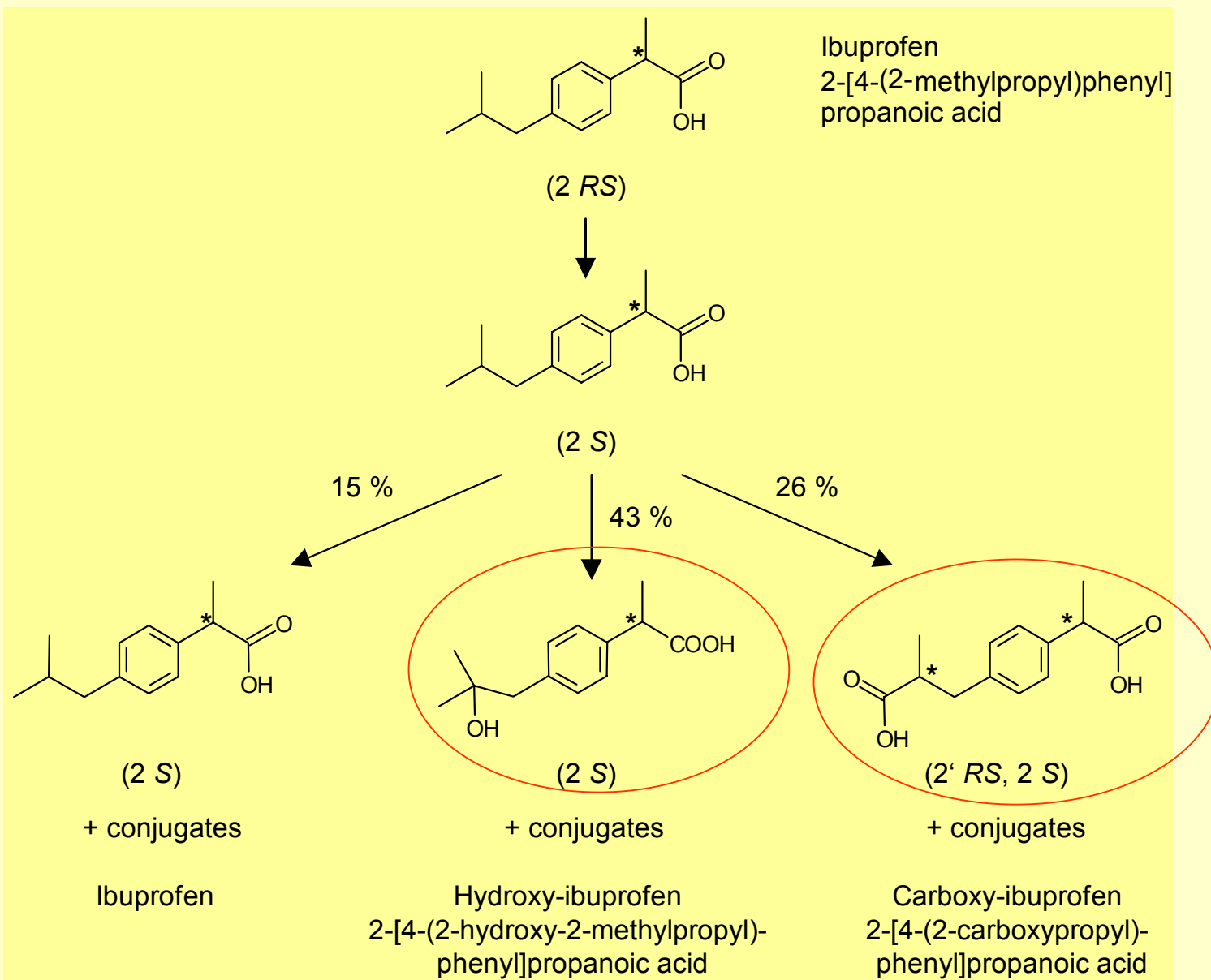
adrenergic β -receptor blocker



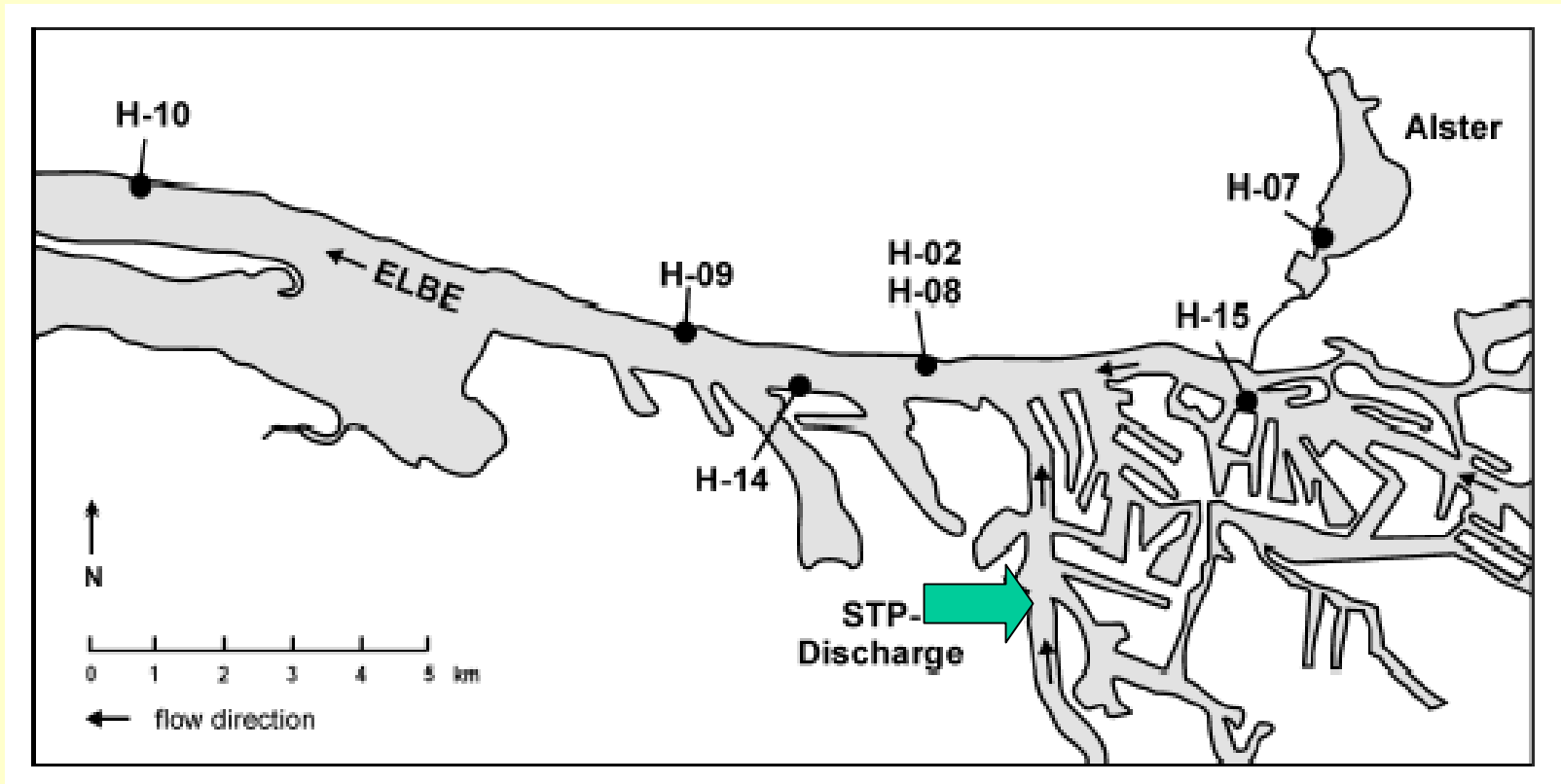
Propranolol

adrenergic β -receptor blocker

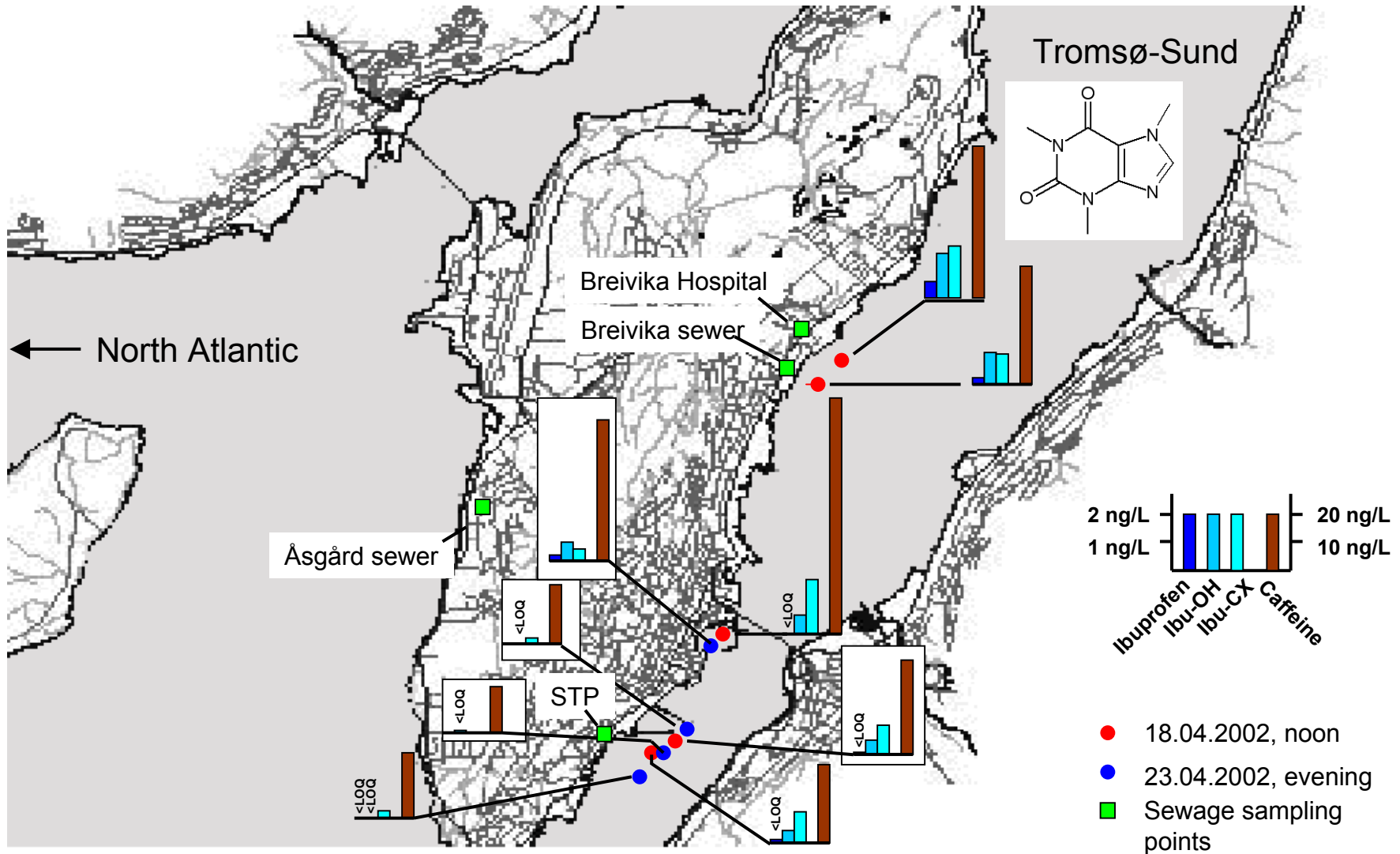
Enzymatic transformation of ibuprofen in humans



Sampling stations STP Hamburg and River Elbe



Hydrophilic Organic Pollutants – A Threat to the Arctic?



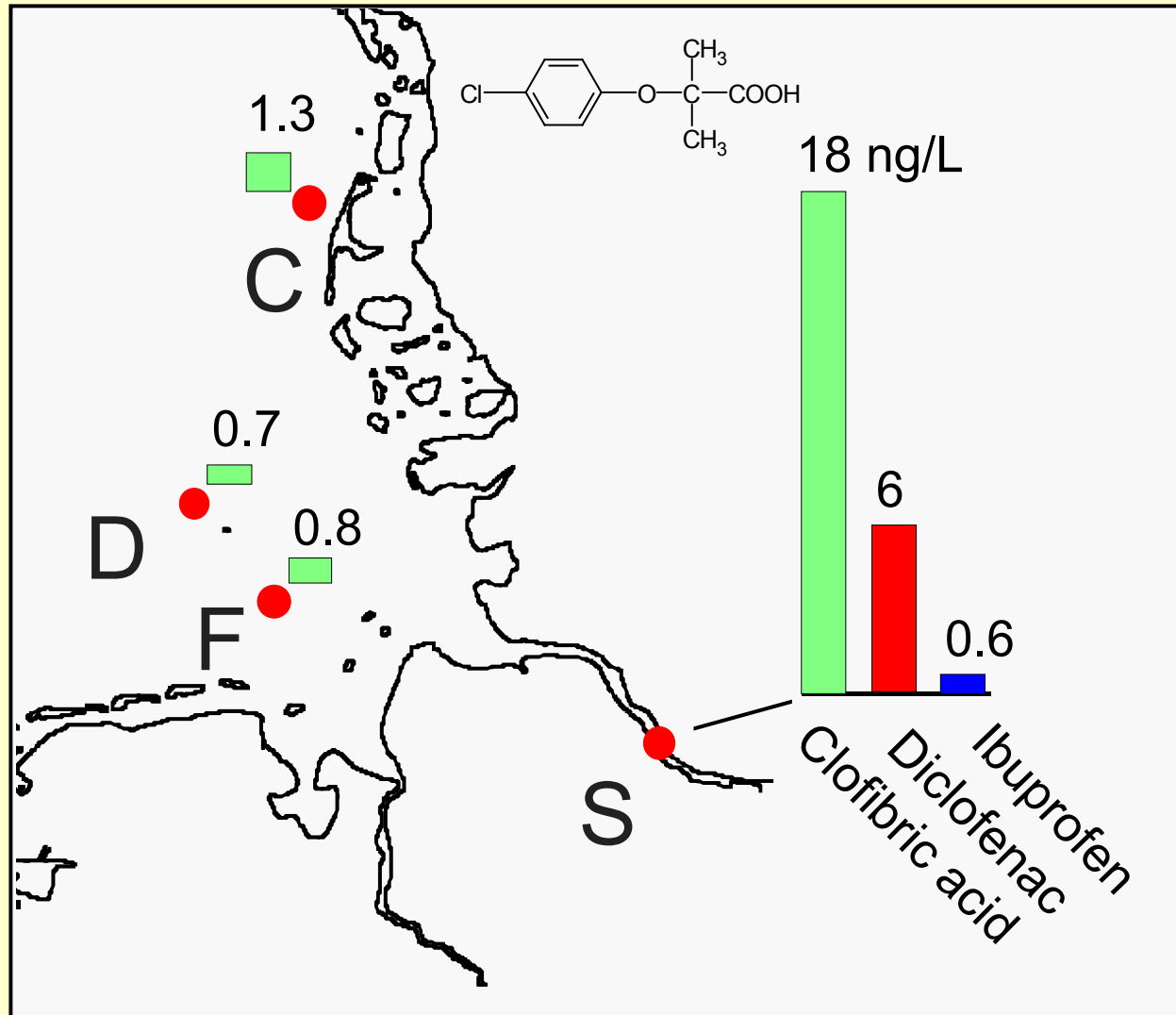
Comparison: STP influents and effluents in Tromsø and Hamburg

Sampling location	Date	Ibuprofen	Ibu-OH	Ibu-CX
STP influent HH	Nov 18 th 2002	1.6 µg/L	6.8 µg/L	23.0 µg/L
STP effluent HH	Nov 19th 2002	30 ng/L	90 ng/L	n.d.
STP effluent Tromsø	Oct 8th 2002	310 ng/L	590 ng/L	70 ng/L

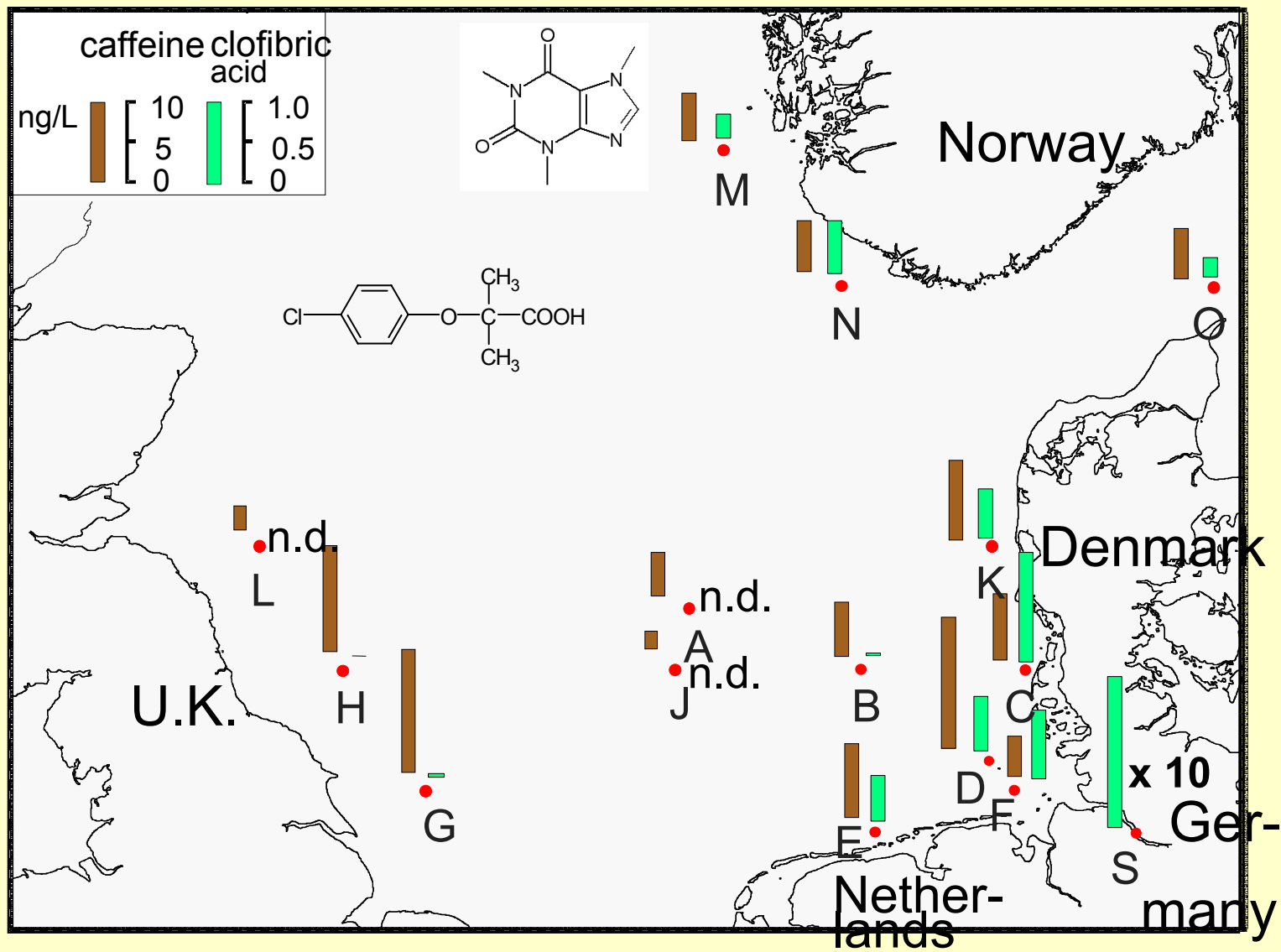
Which substances are reaching the open sea ?



Acid Pharmaceuticals in the German Bight

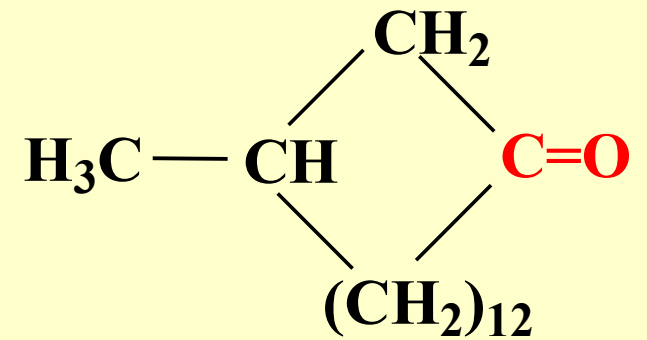


Distribution of Clofibric acid and Caffeine in the North Sea



Personal Care Products:

Musk Fragrances



Muscone

**Robert =
our working group mascot**



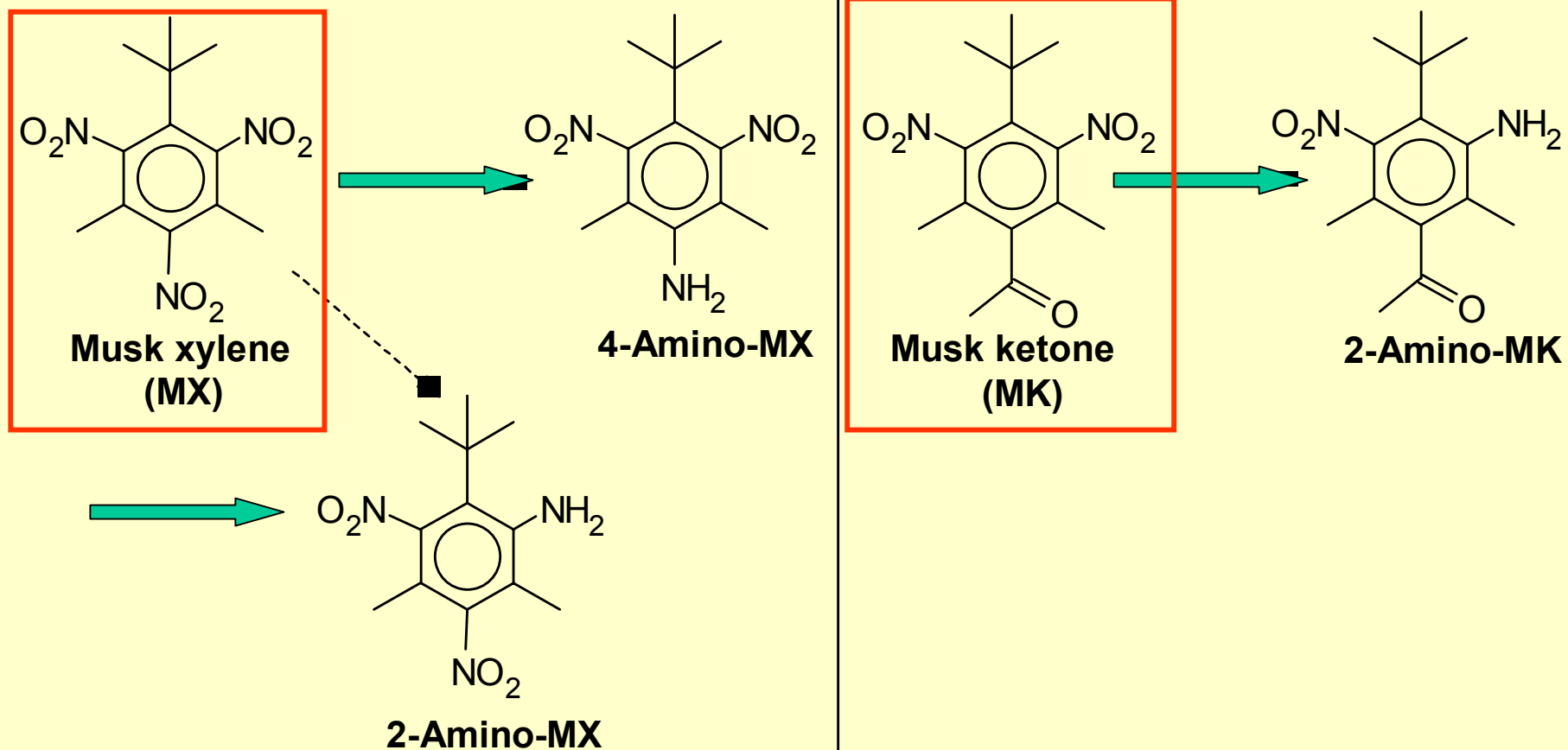
ROYAL COPENHAGEN MUSK For Men By ROYAL COPENHAGEN

ROYAL COPENHAGEN created ROYAL COPENHAGEN MUSK in 1976. It is the result of the following top fragrance Notes: basil, bergamot and jasmine. The middle notes are: freesia, sage and clove and the base of the fragrance is: nutmeg, moss and cedar. ROYAL COPENHAGEN MUSK *is recommended for romantic use.*



Transformation of the nitro musks to the corresponding amino compounds

1. Microbiological reduction

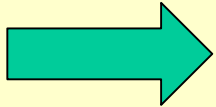


Concentrations (ng/L) of nitro musks and their amino metabolites in the influent and effluent of the sewage treatment plant Hamburg and in the Elbe river (Germany)

Substance	Sewage Plant		Elbe River
	influent [ng/L]	effluent [ng/L]	(3 samples) [ng/L]
MX	150	10	nq – 2
2-amino-MX	nq	10	nq – 1
4-amino-MX	nq	34	1 – 9
MK	550	6	nq – 4
2-amino-MK	nq	250	7

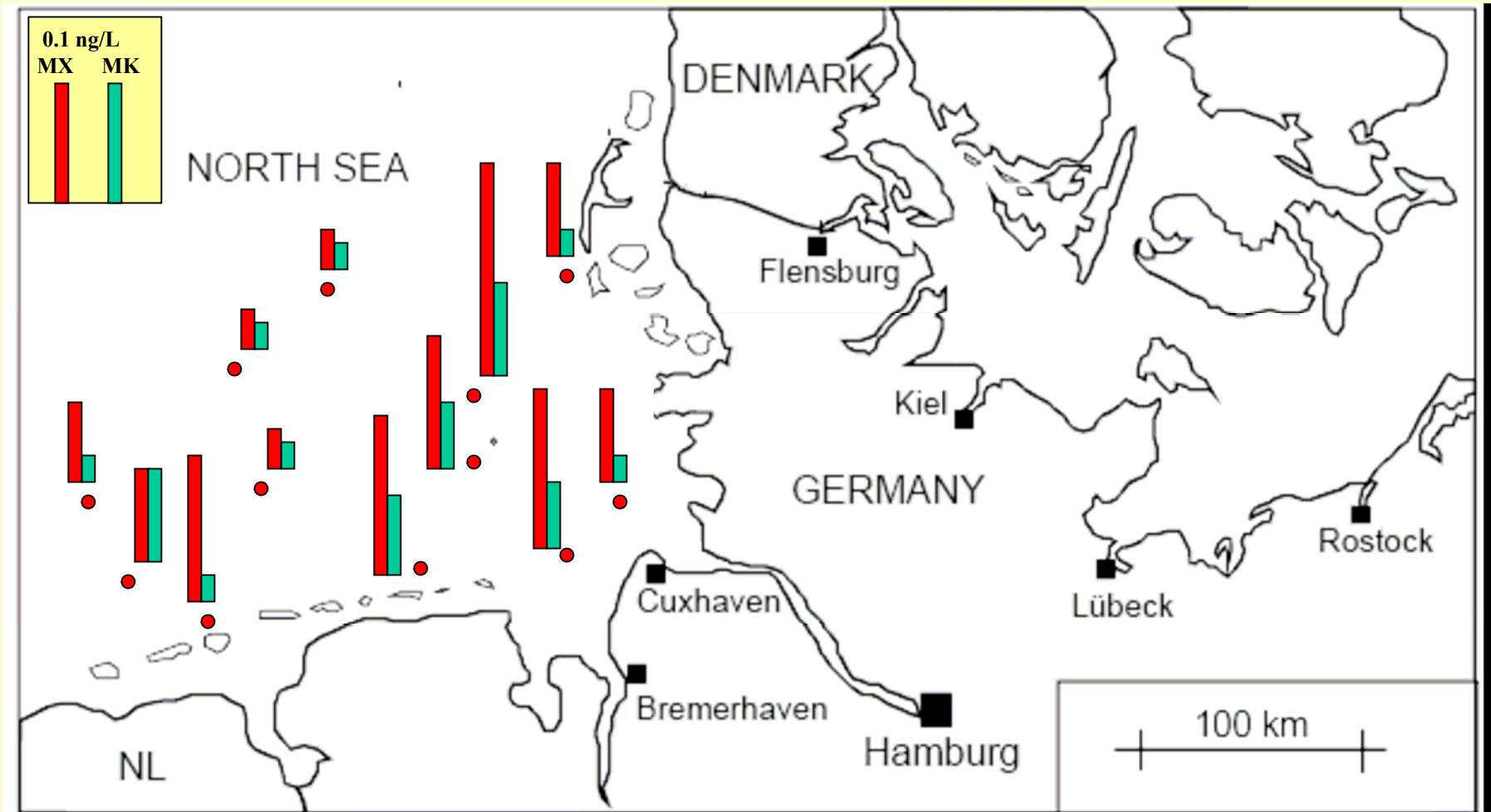
Facit:

„away is not away!“

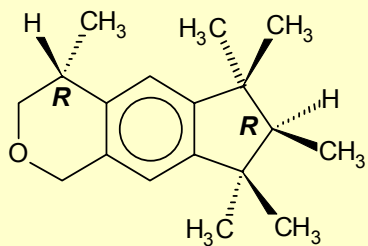


A comprehensive risk assessment has to include the transformation products

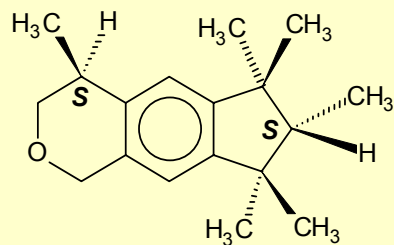
Distribution of musk xylene (MX) and musk ketone (MK) in the German Bight (summer 1993)



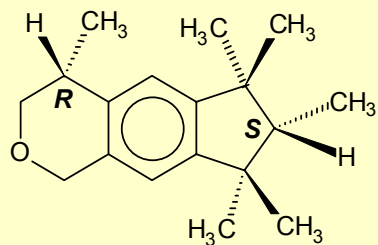
HHCB



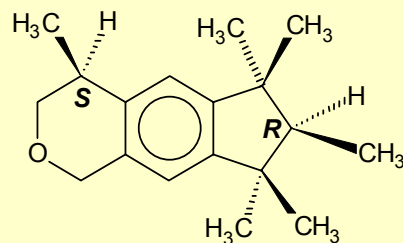
4R, 7R



4S, 7S



4R, 7S



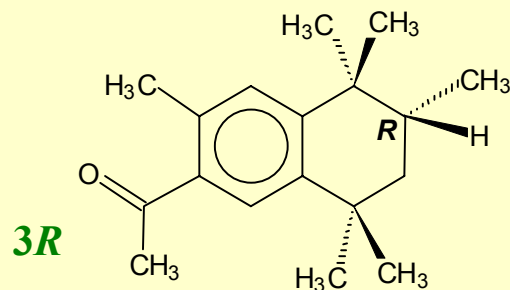
4S, 7R

Personal Care Products:

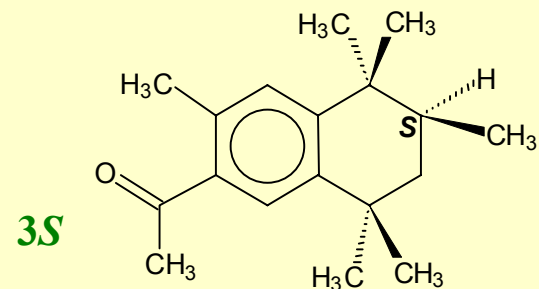
Musk fragrances



AHTN

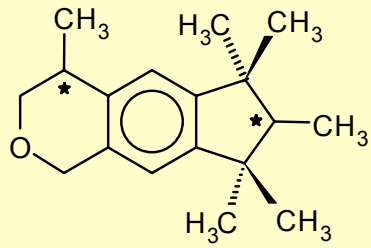


3R

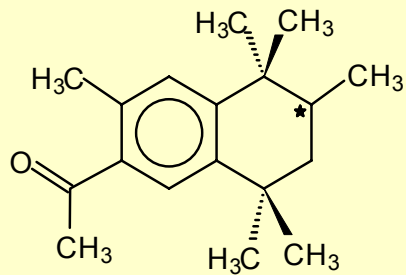


3S

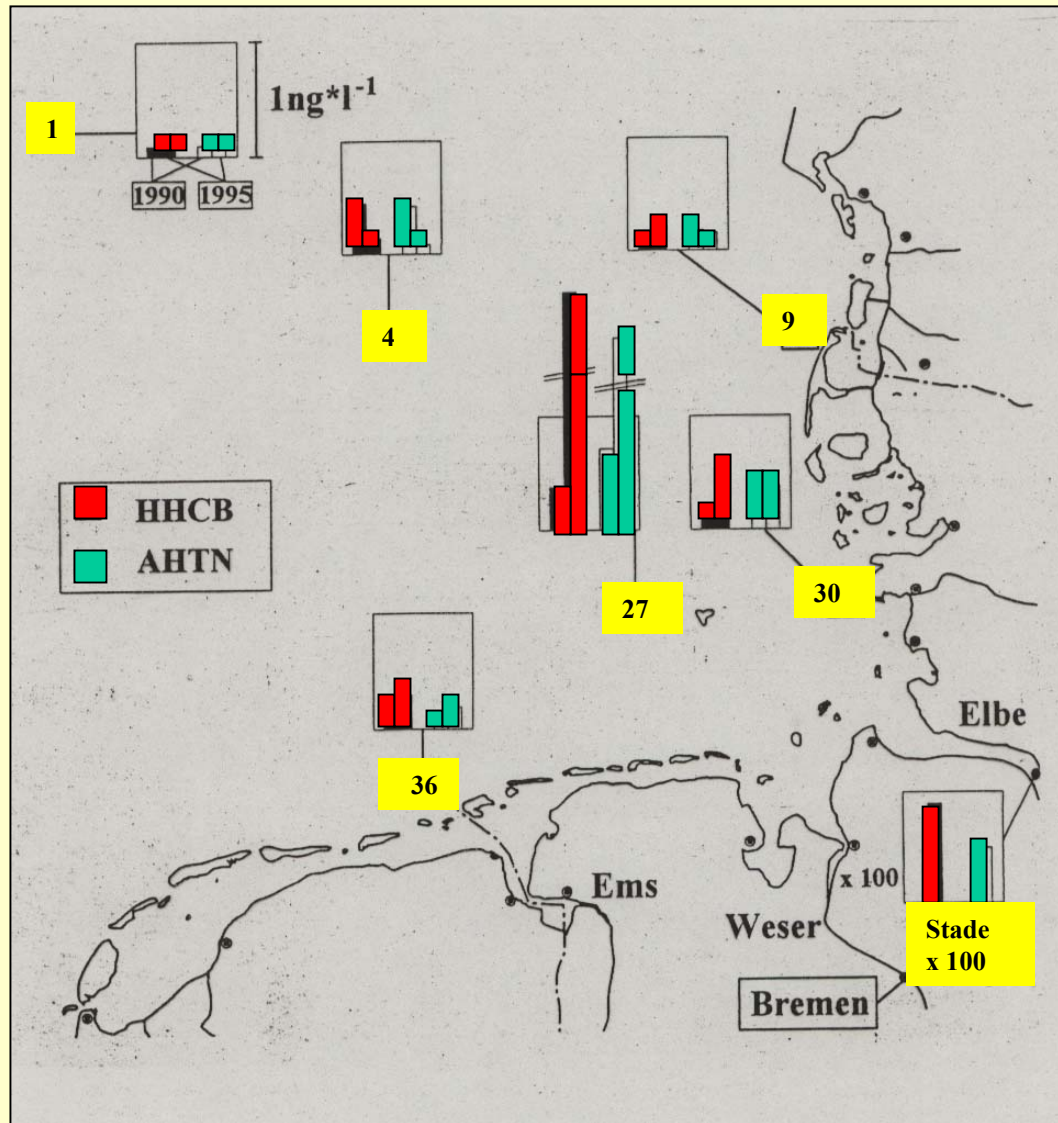
Moschusduftstoffe HHCB und AHTN in der Deutschen Bucht



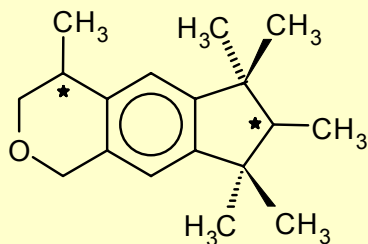
■ HHCB
(Galaxolide®)



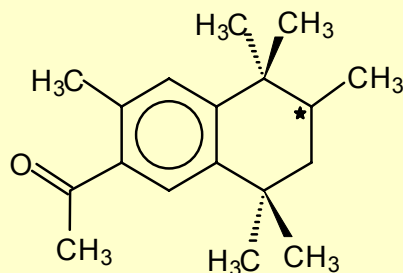
■ AHTN
(Tonalide®)



Concentrations [conc; $\mu\text{g/g}$ lipid] and enantiomeric ratios (ER) of HHCB, *trans*- and *cis*-HHCB, AHTN, *trans*-ATHI, and AHDI in biota caught in the pond of a municipal waste water treatment plant in summer 1997

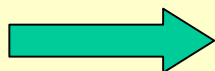


HHCB
(Galaxolide®)



AHTN
(Tonalide®)

Species	HHCB	<i>trans</i> -HHCB	<i>cis</i> -HHCB	AHTN		<i>trans</i> -ATHI		AHDI	
	conc	ER	ER	conc	ER	conc	ER	conc	ER
Rudd	6.2	0.66	1.24	5.0	0.94	0.5	0.99	0.3	0.90
Rudd	7.1	0.55	1.10	5.7	0.91	0.5	0.98	0.3	1.12
Rudd	7.5	0.57	1.07	6.1	0.80	0.5	0.97	0.3	0.95
Tench	150	1.06	0.98	30	1.65	2.3	0.60	2.2	1.31
Tench	160	1.10	0.95	32	1.97	2.0	0.38	1.9	1.47
Tench, liver	72	1.01	0.85	16	1.98	1.1	0.33	0.9	1.78
Tench	160	0.88	1.00	35	1.74	2.2	0.51	2.1	1.30
Tench	150	1.03	0.98	42	1.65	2.6	0.46	2.5	1.28
Crucian carp	39	0.12	0.44	26	1.05	1.2	0.05	1.8	0.65
Crucian carp	59	0.12	0.42	31	1.24	1.5	0.08	2.7	0.81
Crucian carp	91	0.19	0.54	31	1.19	1.9	0.20	3.1	0.94
Crucian carp	71	0.14	0.48	30	1.15	1.4	0.10	2.5	0.78
Crucian carp	50	0.10	0.41	34	1.19	1.6	0.06	2.4	0.71
Crucian carp	66	0.10	0.46	40	1.14	1.5	0.05	2.3	0.66
Crucian carp	84	0.13	0.51	34	1.15	1.9	0.07	3.0	0.64
Cr. carp liver	69	0.10	0.48	31	1.29	1.6	0.06	2.5	0.63
Eel	4.8	0.98	1.27	2.6	0.87	0.3	1.95	0.2	0.73
Eel	4.6	0.79	1.15	2.7		0.3	1.50	0.2	0.48
Mussel	120	0.91	1.26	45	0.90	3.4	0.67	2.3	1.02

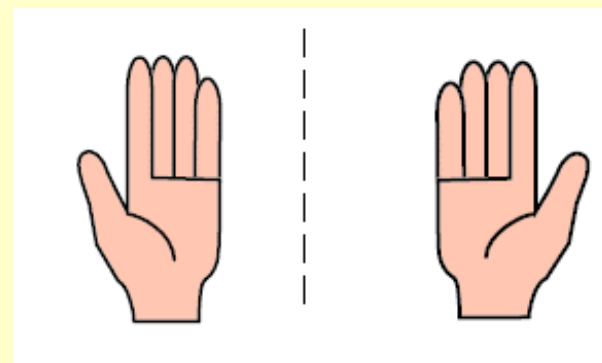
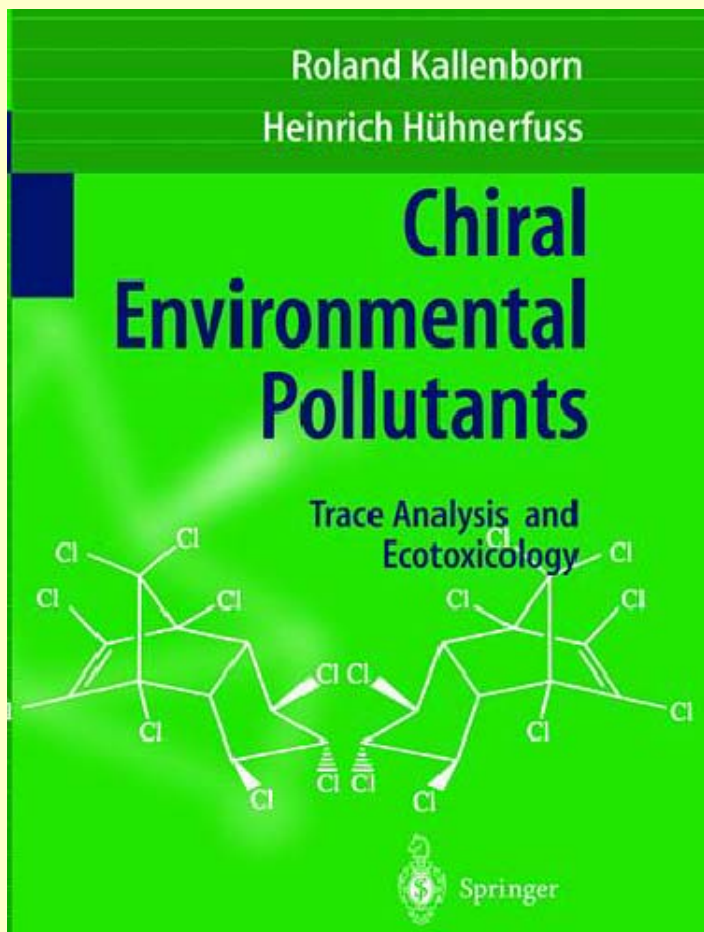


Both concentrations and ER show a species dependency

New Approach for the Study of Transformation Processes

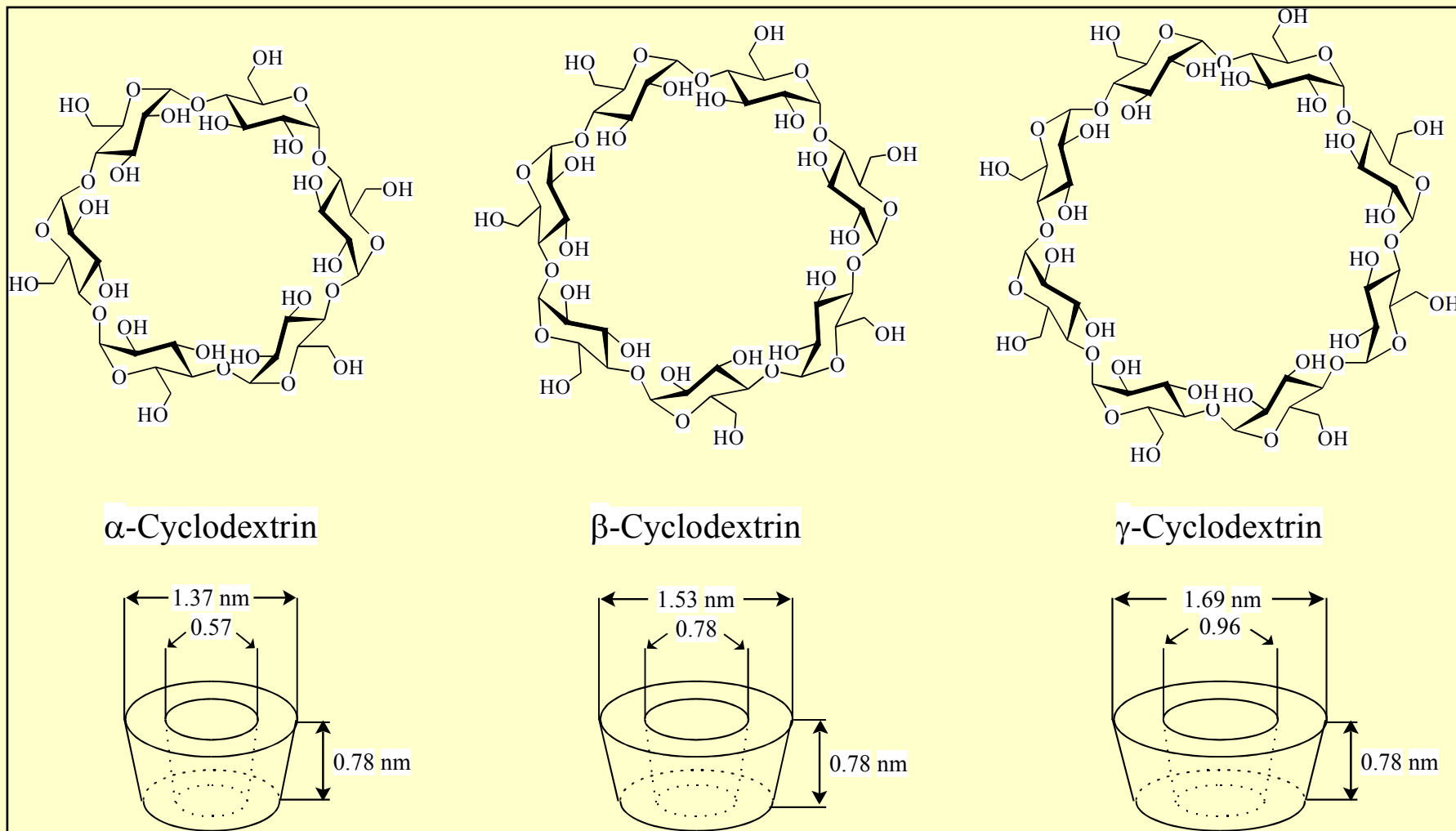


Enantioselective Chromatography for *Chiral Environmental Pollutants*

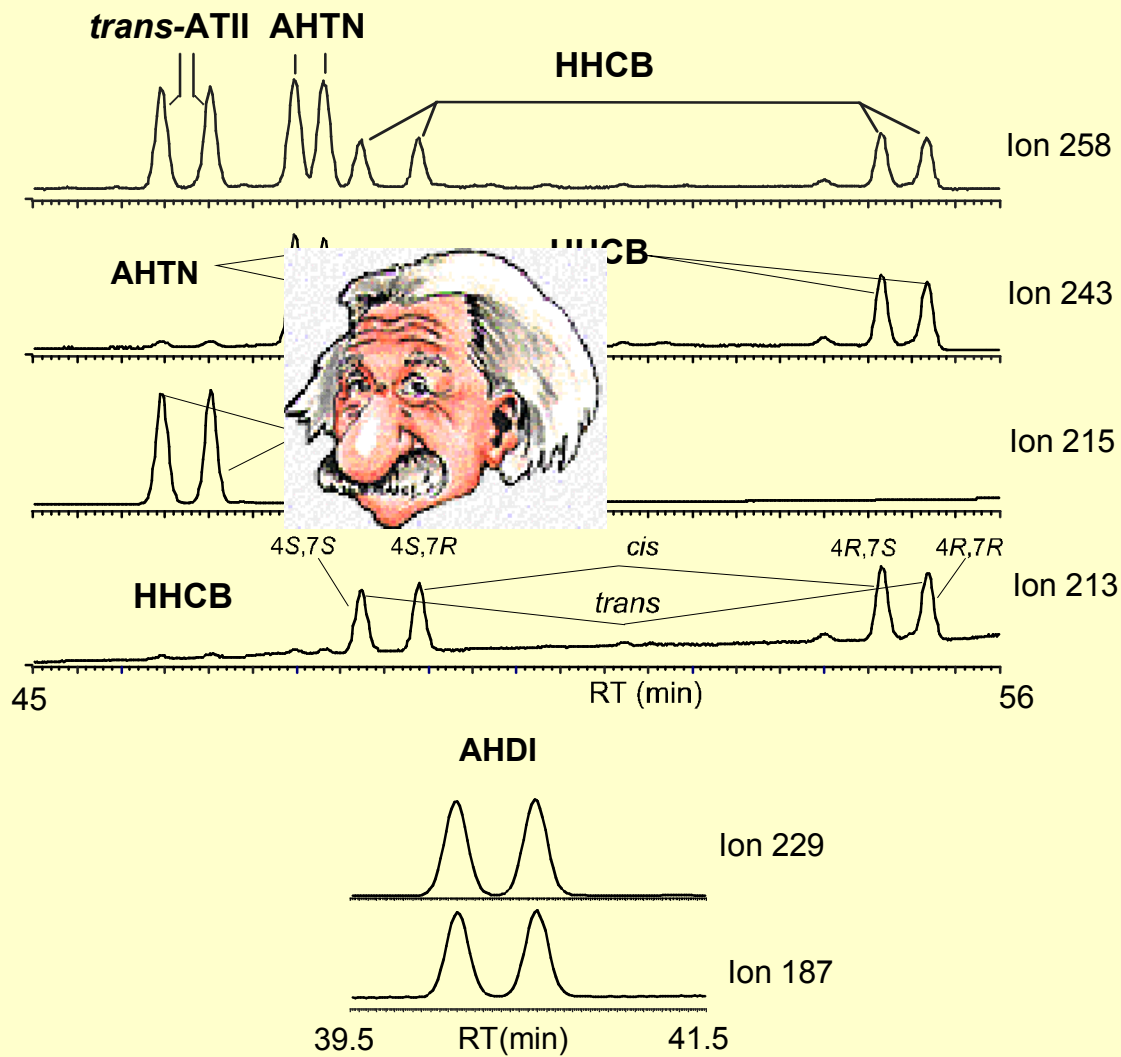


*Principle of
Chirality*

Chiral cyclodextrin phases to be derivatized yet

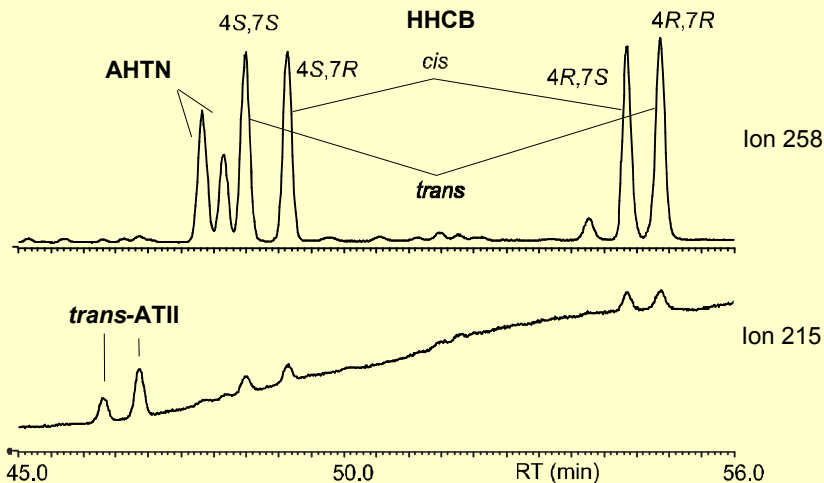


SIM fragmentograms of a standard mixture containing HHCb, AHTN, *trans*-ATII, and AHDI (1 ng/ μ L each), stationary phase: 1:1 mixture of OV 1701/heptakis(6-*O*-*tert*-butyl-di-methyl-silyl-2,3-di-*O*-methyl)- β -cyclodextrin

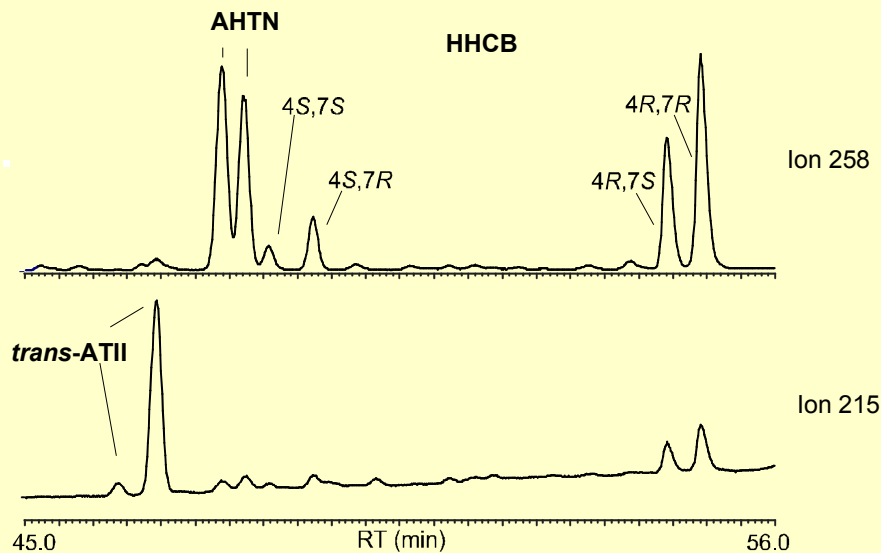


SIM fragmentograms of tench and crucian carp sample extracts, stationary phase: 1:1 mixture of OV 1701/ heptakis(6-*O*-*tert*-butyl-dimethyl-silyl-2,3-di-*O*-methyl)- β -CD

Sample: Tench

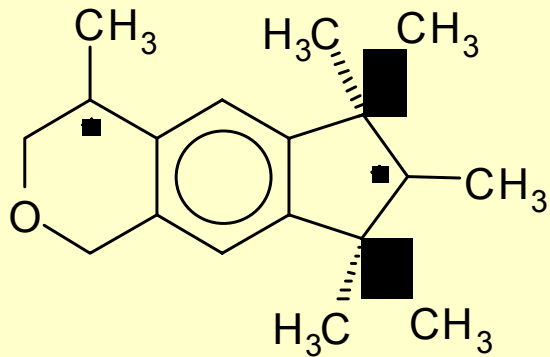


Sample: Crucian carp



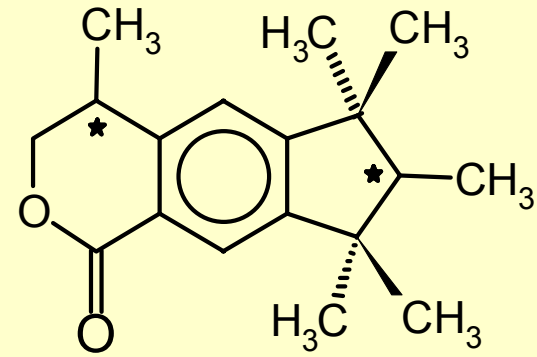
Transformation von HHCB

HHCB



(Galaxolide[®])

HHCB-Lacton

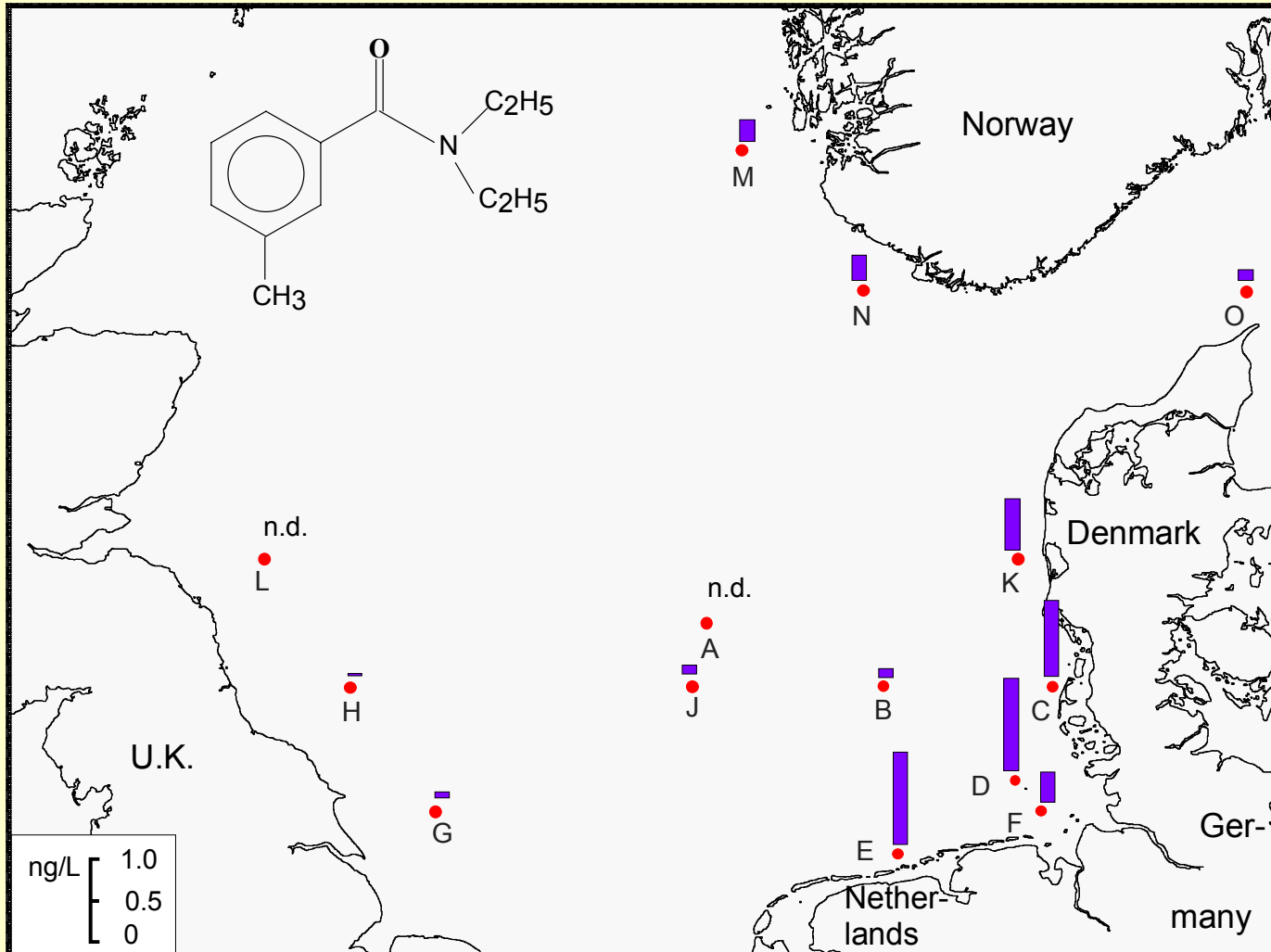


**Average concentrations for HHCB and HHCB-lactone,
and enantiomeric ratios (ER) of HHCB-lactone in different samples
stemming from the pond of a sewage treatment plant**

Sample	HHCB Conc [µg/g lipid]	HHCB-lact. Conc [µg/g lipid]	<i>trans</i>-HHCB-lact ER	<i>cis</i>-HHCB-lact. ER
Rudd (n = 3)	6.9	8	0.65	1.19
Tench (n = 4)	155	33	0.68	0.99
Crucian carp (n = 7)	66	24	0.39	0.83
Eel (n = 2)	4.7	4	0.59	1.51
Zeb.mussel (pooled)	120	33	0.81	0.91
SPMD (n = 12)	166 (n = 12)	8 (n = 9)	0.81	1.01

„Personal Care Products“

Distribution of the Insect Repellent DEET in the North Sea

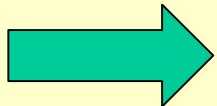
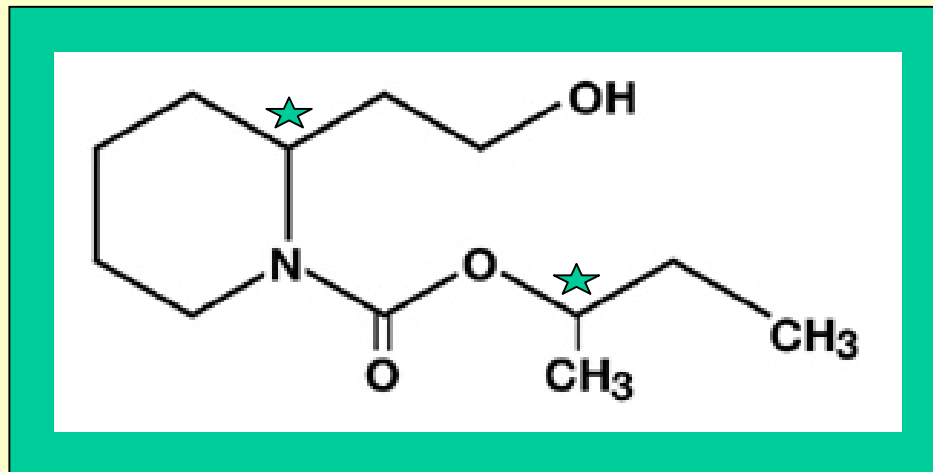


„Personal Care Products“

Insect Repellents:

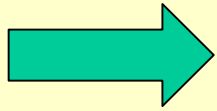
Precursor of DEET in the „new Autan“:

BAYREPEL®

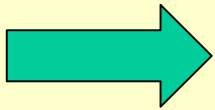


in the river Elbe this compound was already found in concentrations of about 25 ng/L

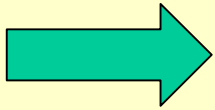
Conclusions



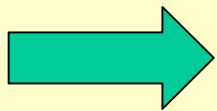
**PCPPs have been detected
in all marine environmental compartments**



**PCPPs often showed
surprisingly high concentrations**



**A risk assessment with regard to PCPPs has to take
into account their transformation pathways and thus
to include the transformation products**



**Enantioselective Chromatography allows deeper
insight into transformation pathways**

Acknowledgements:

Prof. Dr. Wilfried König †

Dr. Kai Bester

Sonja During

Jan Kuhlmann

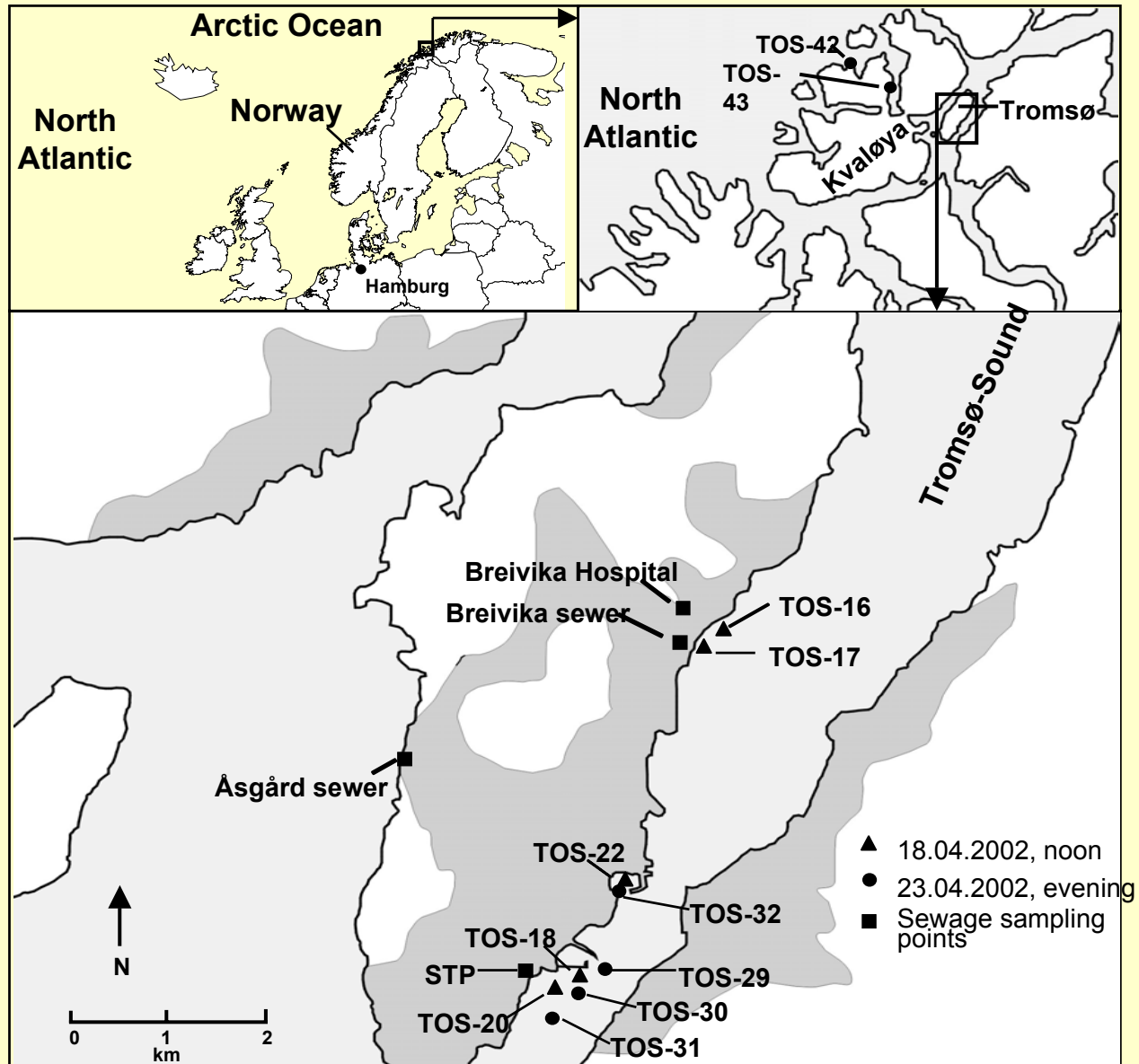
Stephanie Selke

Dr. Hai Pham-Tuan

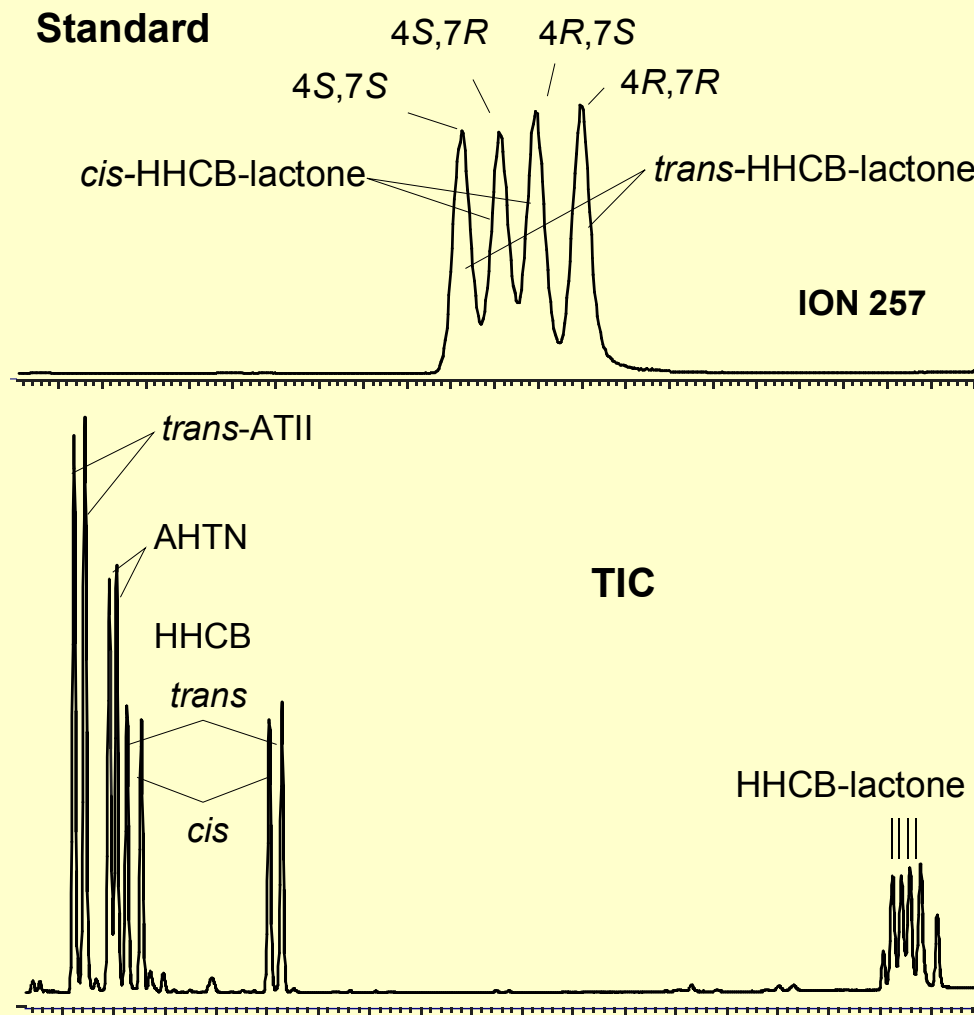
Dr. Stefan Weigel

The End

Sampling stations in the Tromsø-Sund (Norway)

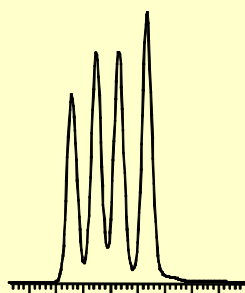


top: SIM fragmentogram of a HHCB-lactone standard (ion 257);
below: standard mixture containing HHCB, AHTN, *trans*-ATII, and HHCB-lactone (TIC)
phase: 1:1 mixture of OV 1701/heptakis(6-*O*-*tert*-butyl-dimethylsilyl-2,3-di-*O*-methyl)- β -CD

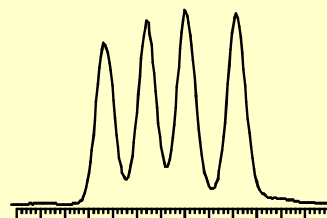


**SIM fragmentogram of HHCB-lactone
in various fish, mussel and SPMD extracts; stationary phase: 1:1 mixture of
OV 1701/heptakis(6-*O*-*tert*-butyl-dimethylsilyl-2,3-di-*O*-methyl)- β -cyclodextrin**

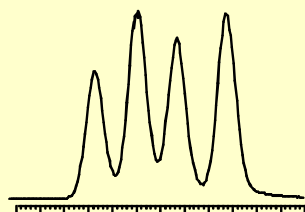
Ion 257



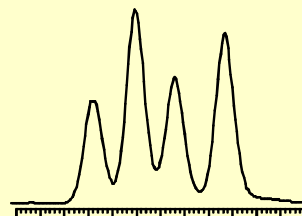
Tench



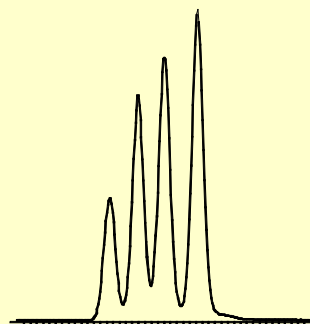
Mussel



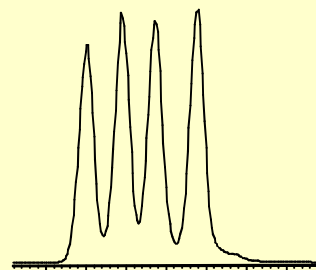
Rudd



Eel

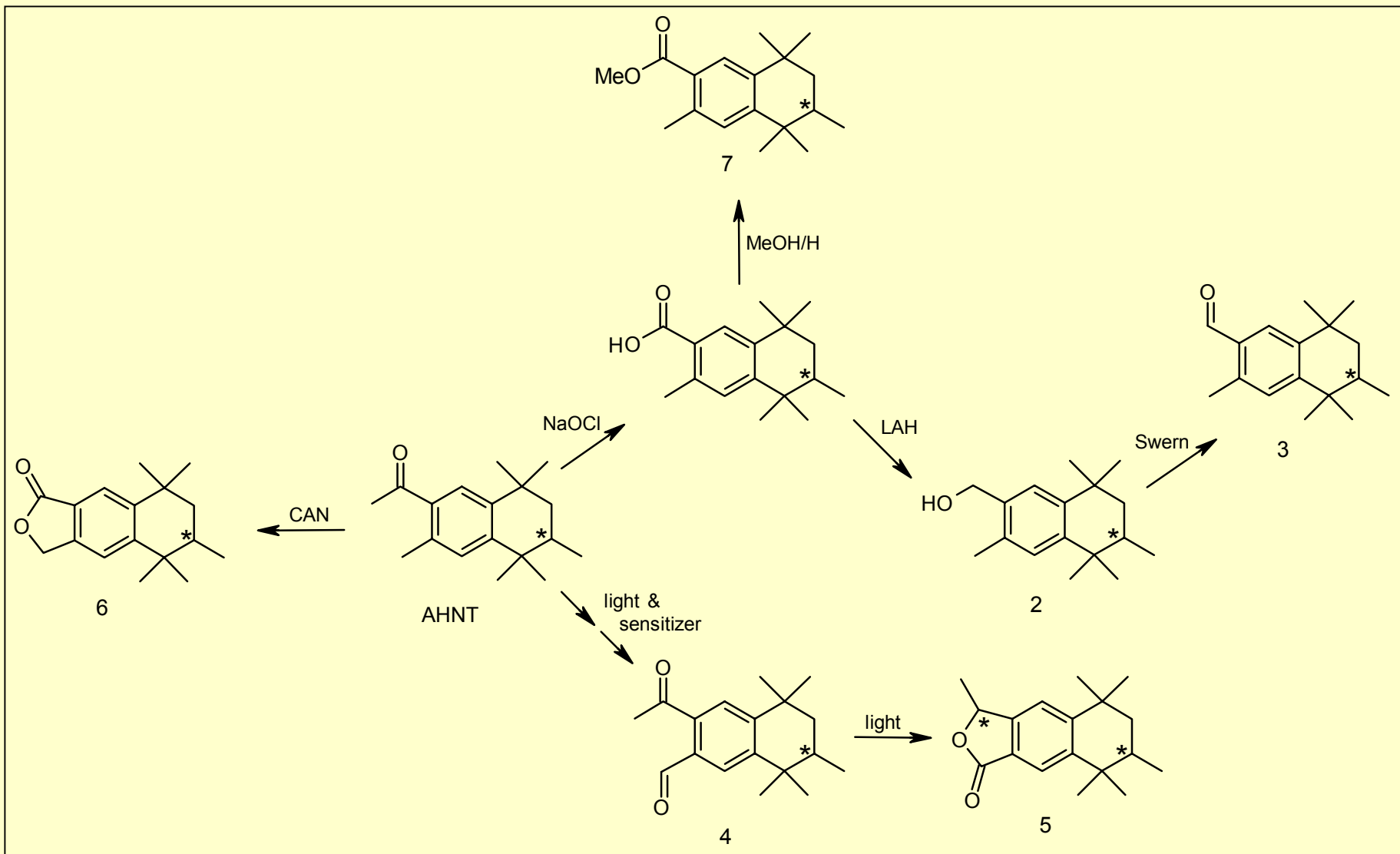


Crucian carp

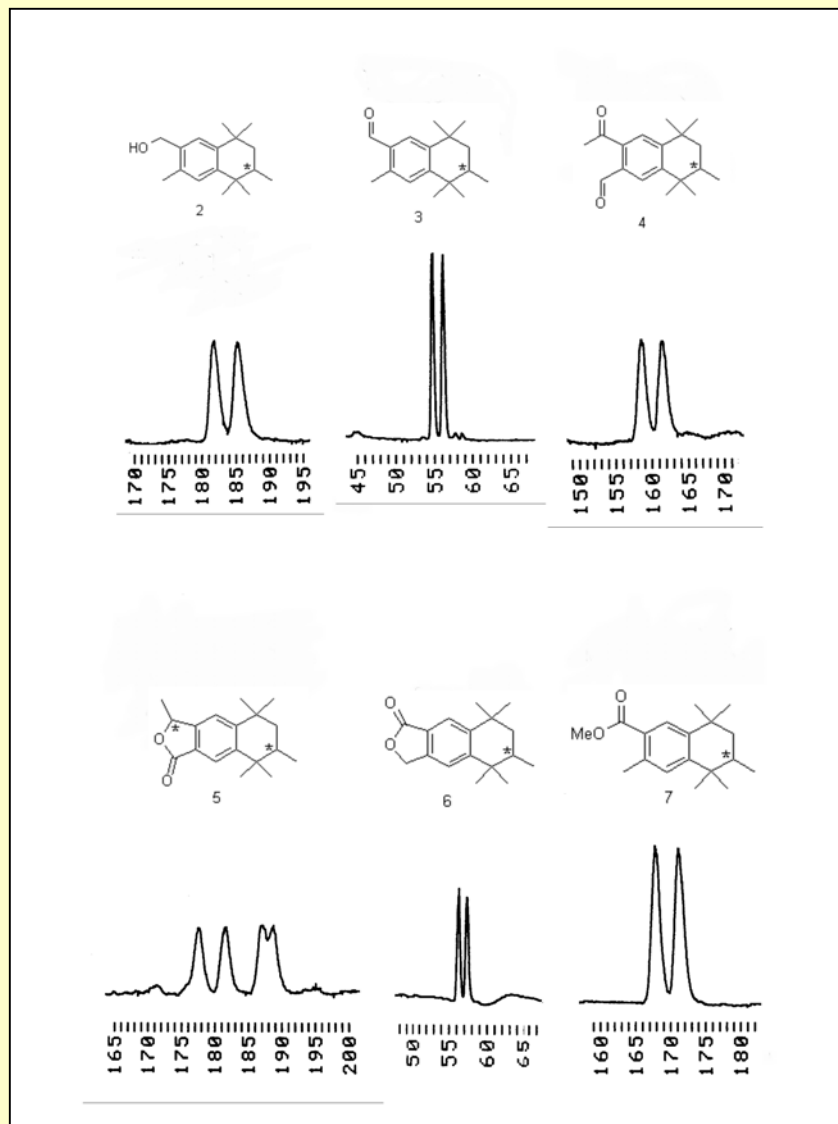


SPMD

Preparation of transformation products of AHTN (Tonalide®) that were found in environmental samples



**Enantioselective separation of the transformation products of AHTN (standards)
using a 6-*O*-*tert*-butyl-dimethylsilyl-2,3-di-*O*- β -cd/OV 1701 1:1 column, 25 m**

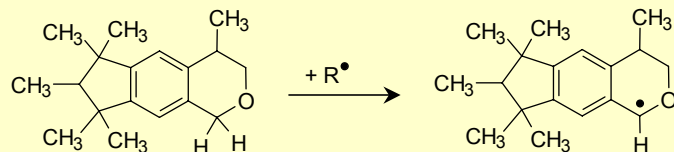


Conclusions

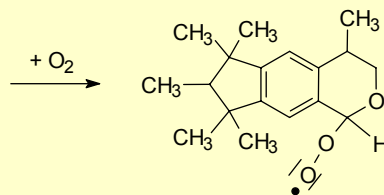
- 1.) A risk assessment with regard to PCPPs in the environment has to take into account their transformation pathways and thus to include the transformation products**
- 2.) The respective transformation processes can be revealed and discriminated by enantioselective chromatography**
- 3.) PCPPs are ubiquitously distributed in all environmental compartments**
- 4.) PCPPs often represent the most prominent environmental pollutants**

Proposed formation route for HHCB-lactone in the aquatic environment

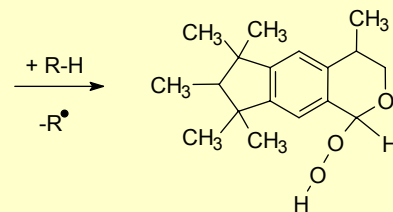
1. HHCB activation (radical formation):



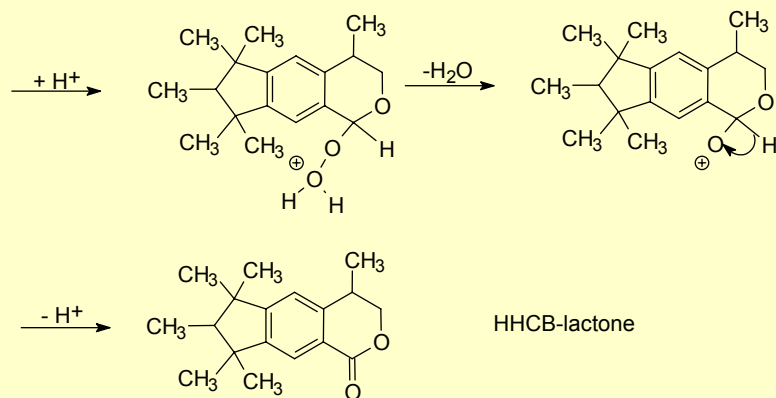
2. Addition of molecular oxygen:

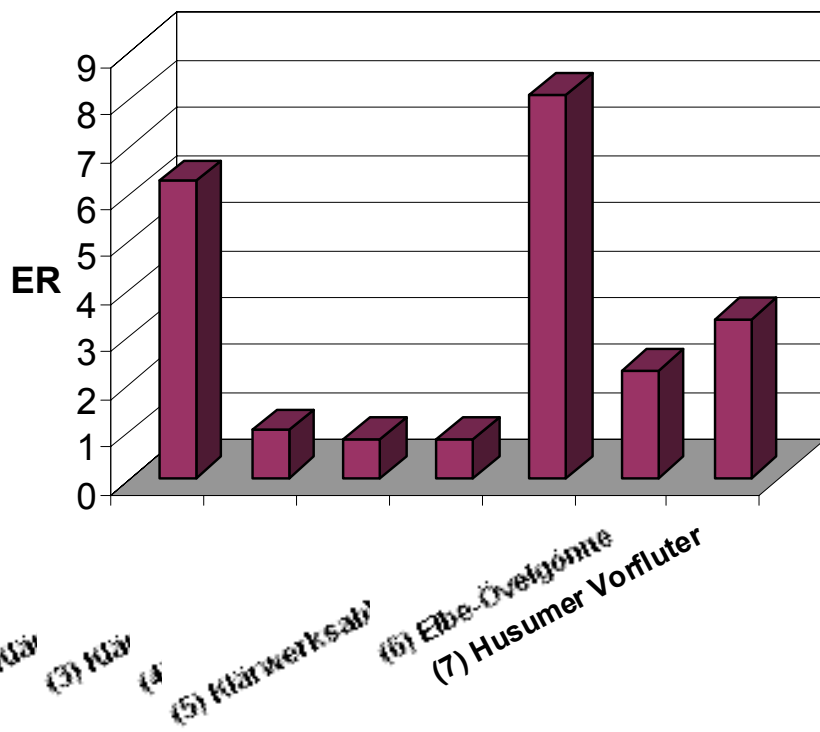


3. Formation of peroxides:

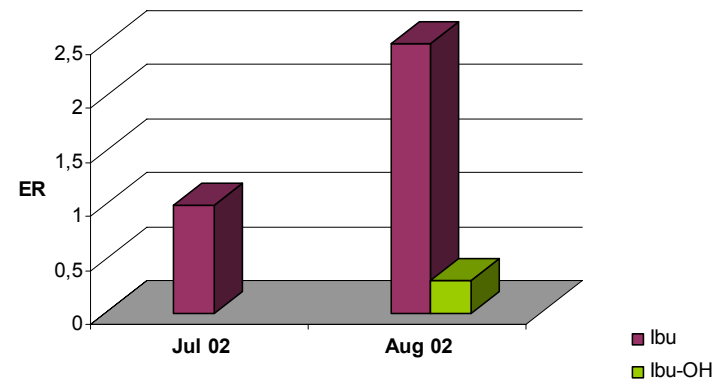


4. Protonation and removal of the water molecule:

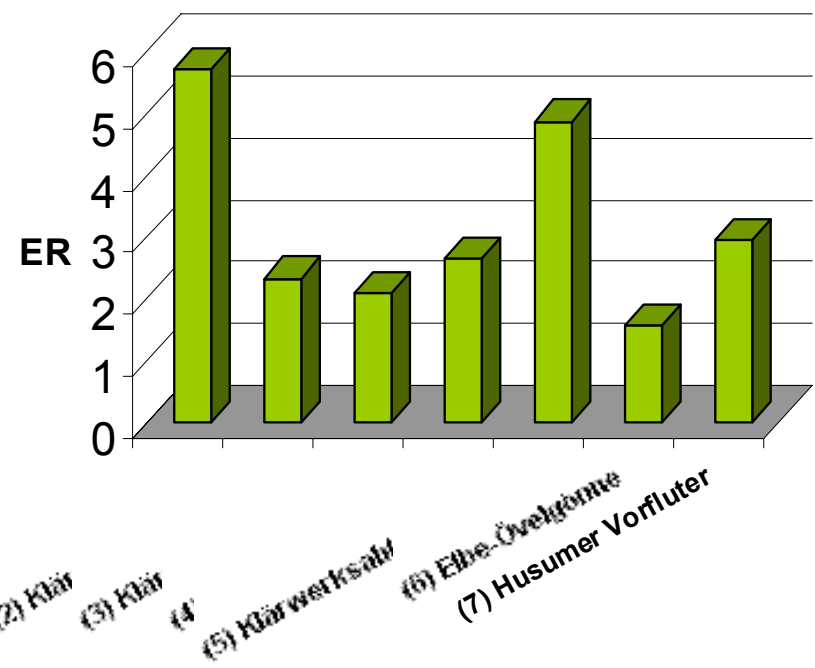




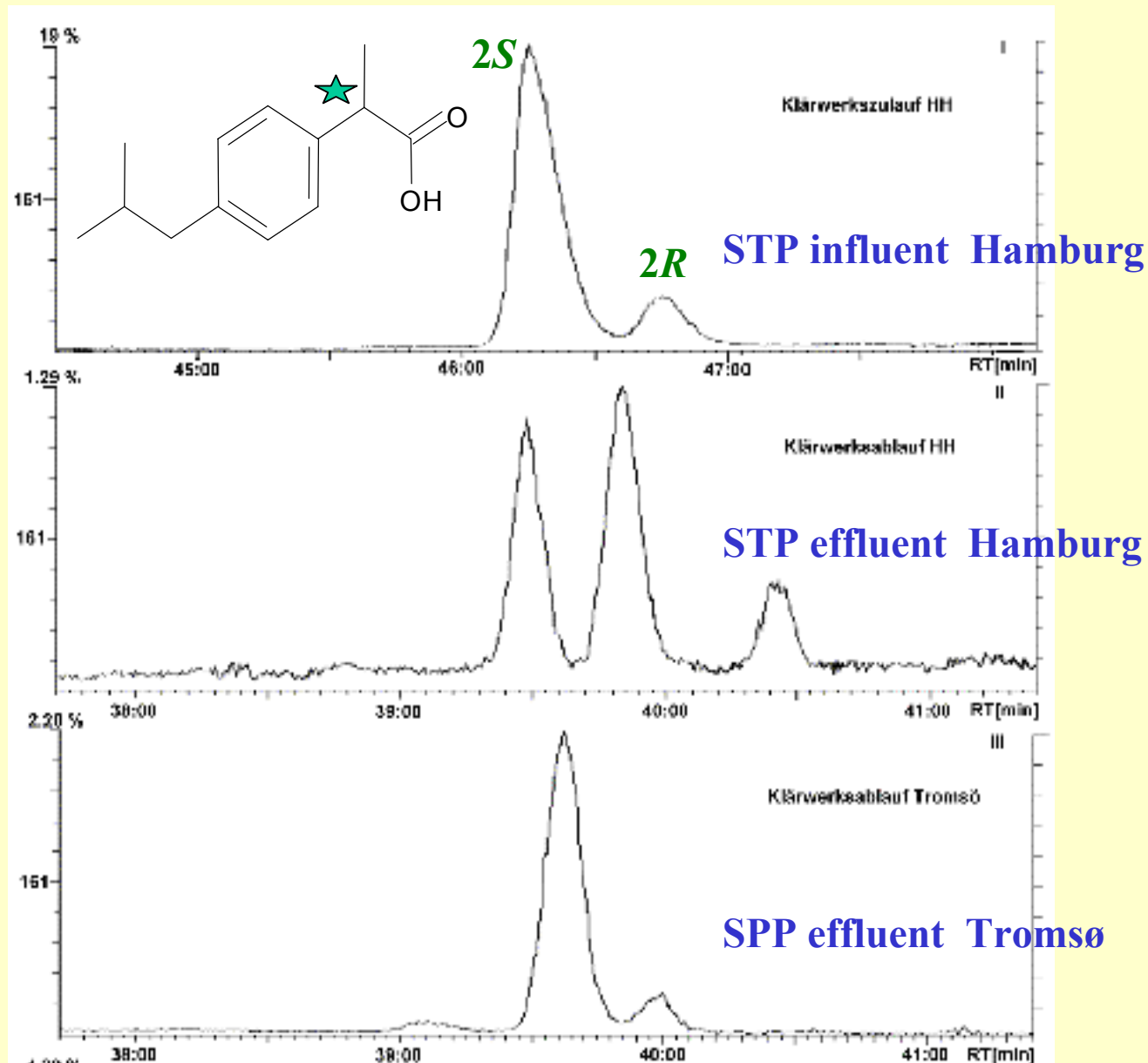
ER Ibuprofen



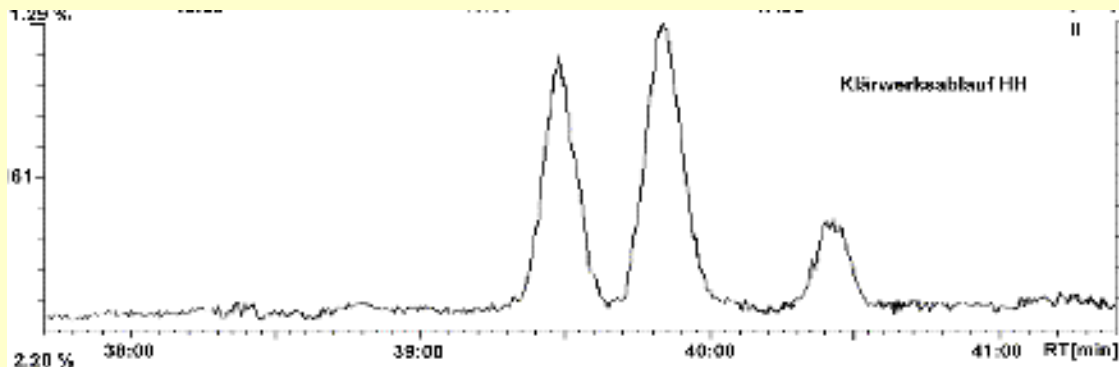
ER Ibu-OH



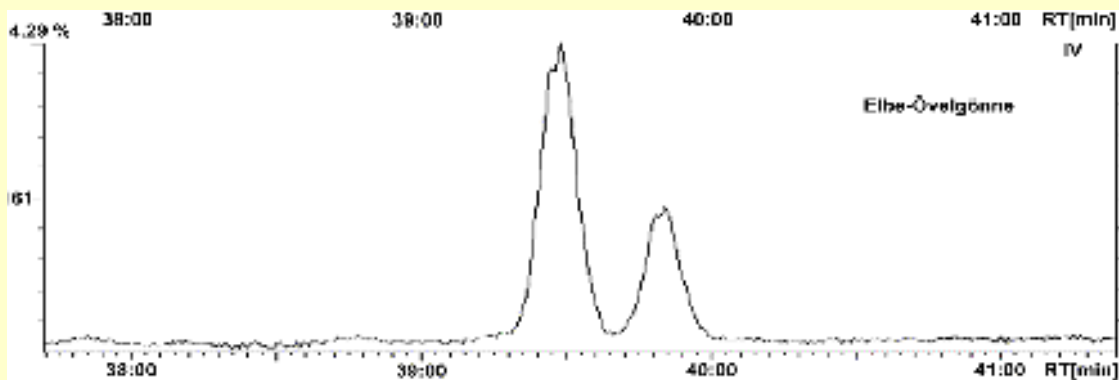
Separated enantiomers of Ibuprofen in sample extracts STP in- and effluent in Hamburg and effluent in Tromsø



Ibuprofen: Enantioselective Transformation in STP /in the River Elbe



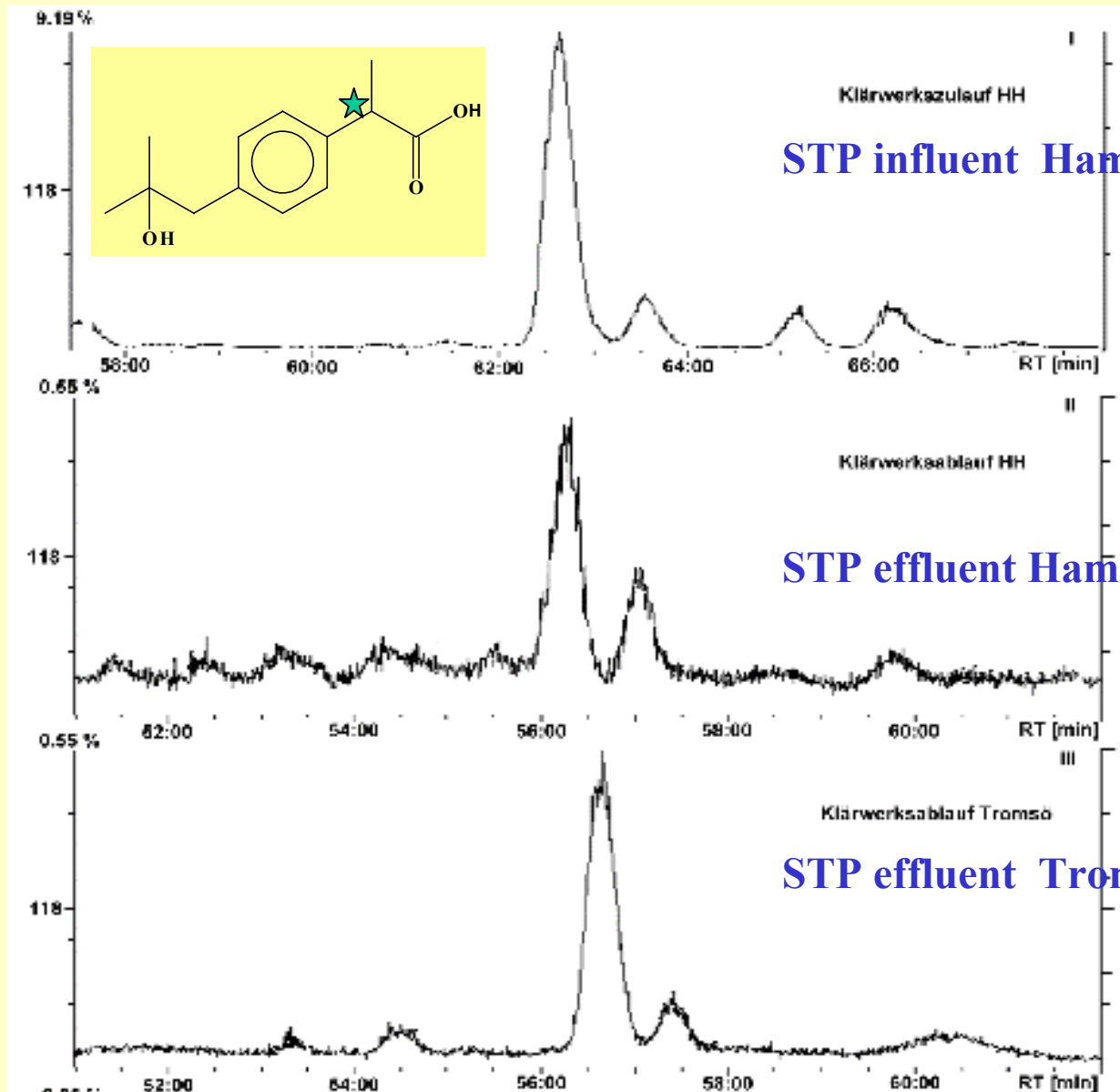
STP Hamburg



River Elbe at HH-Övelgönne

Separated enantiomers of Ibu-OH in sample extracts

STP in- and effluent in Hamburg and effluent in Tromsø



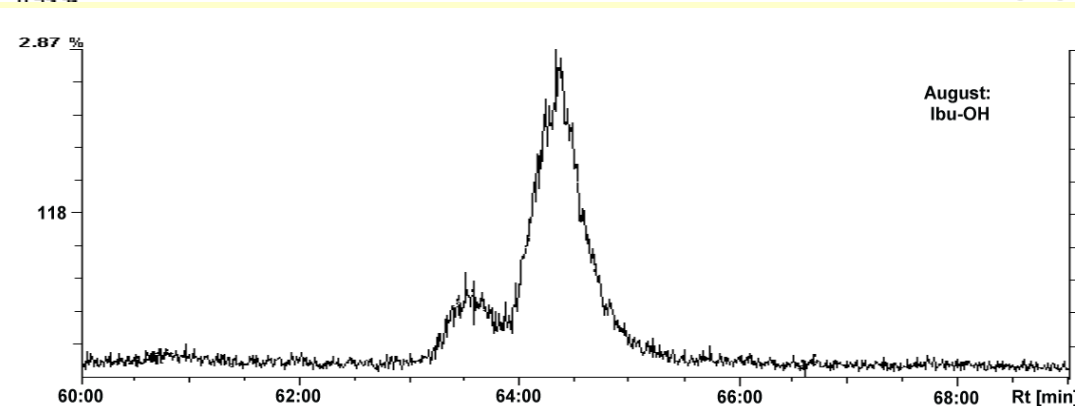
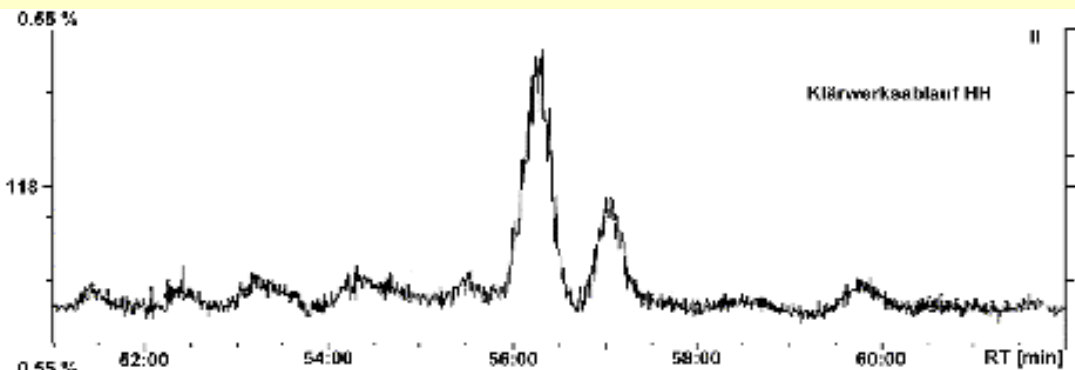
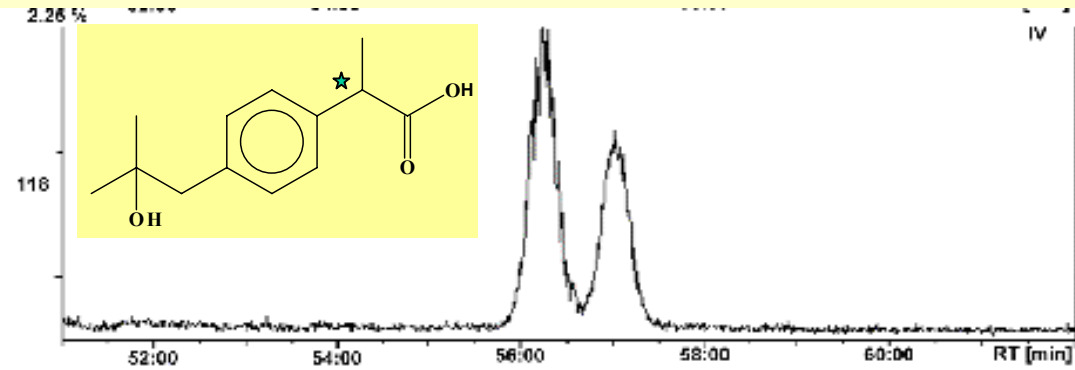
IBU-OH:

Enantioselective transformation in STP /in the environment

River Elbe HH-Övelgönne

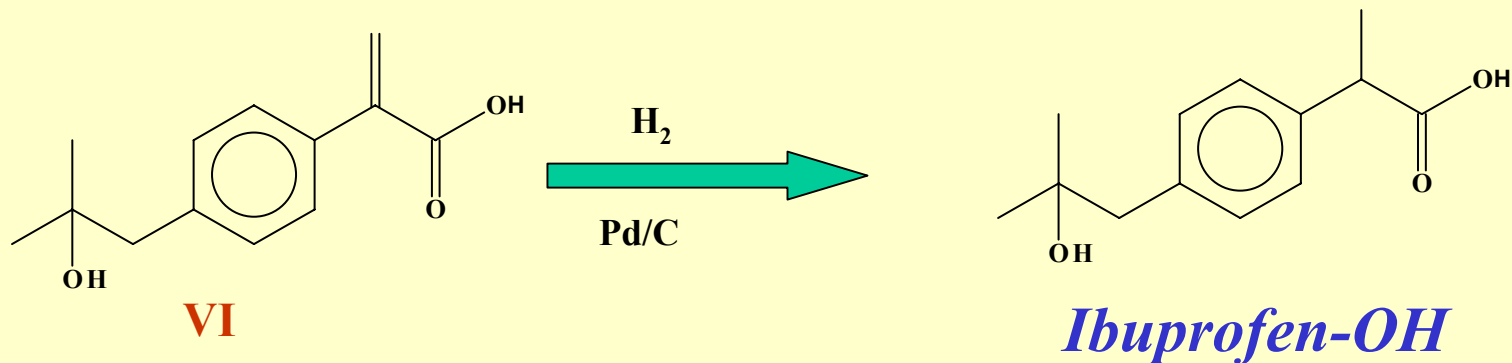
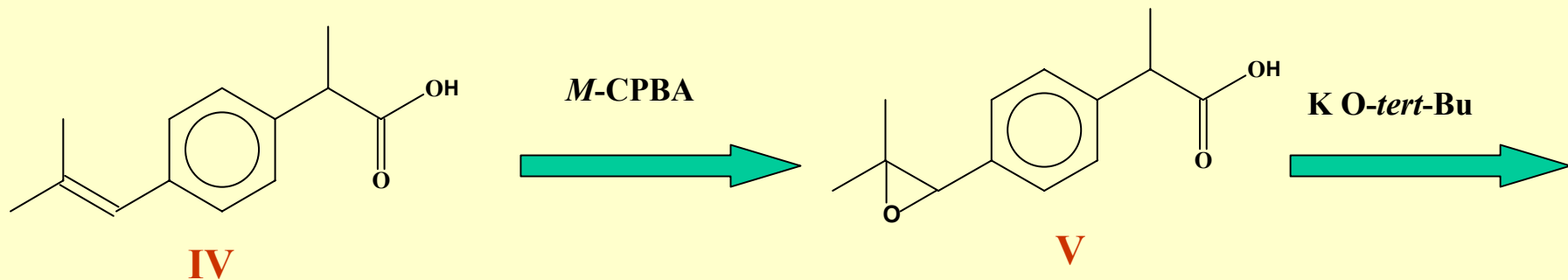
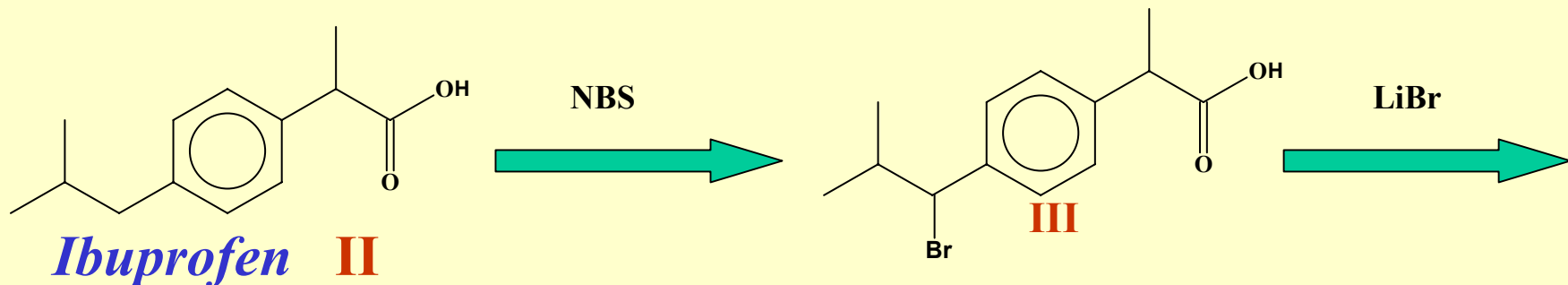
STP effluent Hamburg

Microbial transformation of
Ibuprofen-OH:
1 µg/L spiked to water of a small
creek (Eiderstedt)

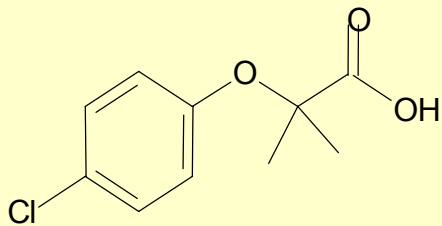


Reference compounds of metabolites not commercially available → have to be synthesised

→ example ibuprofen-OH I

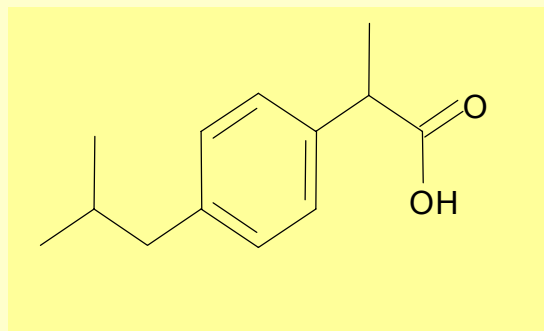


Prominent examples for pharmaceuticals in the aquatic ecosystem



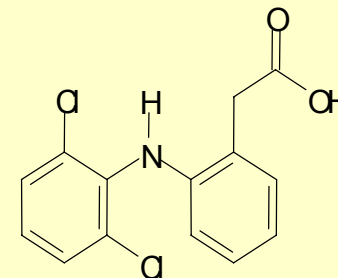
Clofibric acid

*Metabolite of Ethylclofibrate
reduction of plasma
cholesterol and triglyceride*



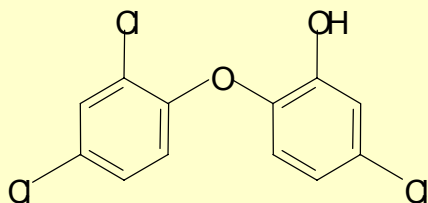
Ibuprofen

*antiphlogistic, analgesic
and antipyretic properties*



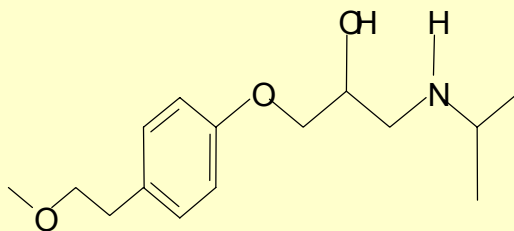
Diclofenac

*antiphlogistic and analgesic
effect*



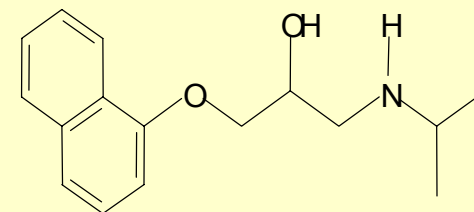
Triclosan

*Antibacterial effect in
soaps, toothpaste etc.*



Metoprolol

adrenergic β -receptor blocker



Propranolol

adrenergic β -receptor blocker