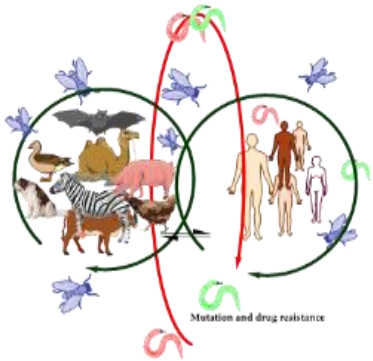
Environmental impact of Pharmaceuticals

Rolf-Alexander Düring
Institute of Soil Science and Soil Conservation
Justus Liebig University Gießen



cost
EUROPEAN COOPERATION IN SCIENCE & TECHNOLOGY

One Health drugs against parasitic vector borne diseases in Europe and beyond - OneHealthdrugs

Funded by the European Union

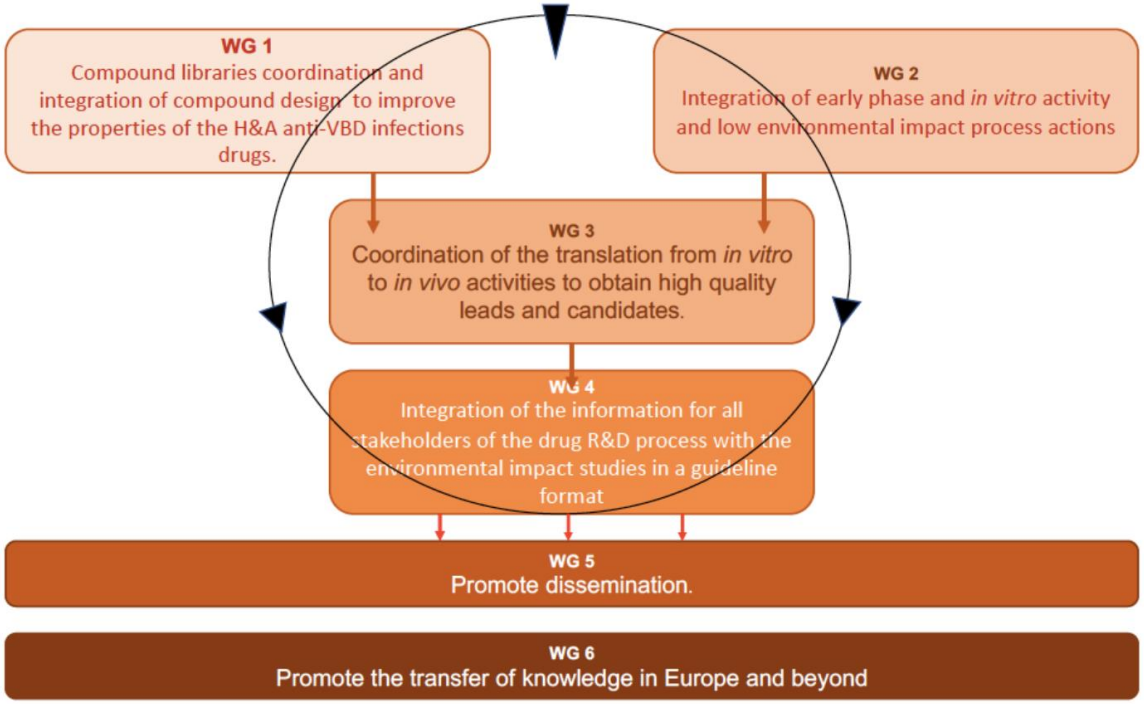
WG4, Workshop 1: Environmental impact of pharmaceuticals and international organizations monitoring
03/04/2023

JLU
NEW PATHS. SINCE 1607

JUSTUS-LIEBIG-UNIVERSITÄT GIESSEN

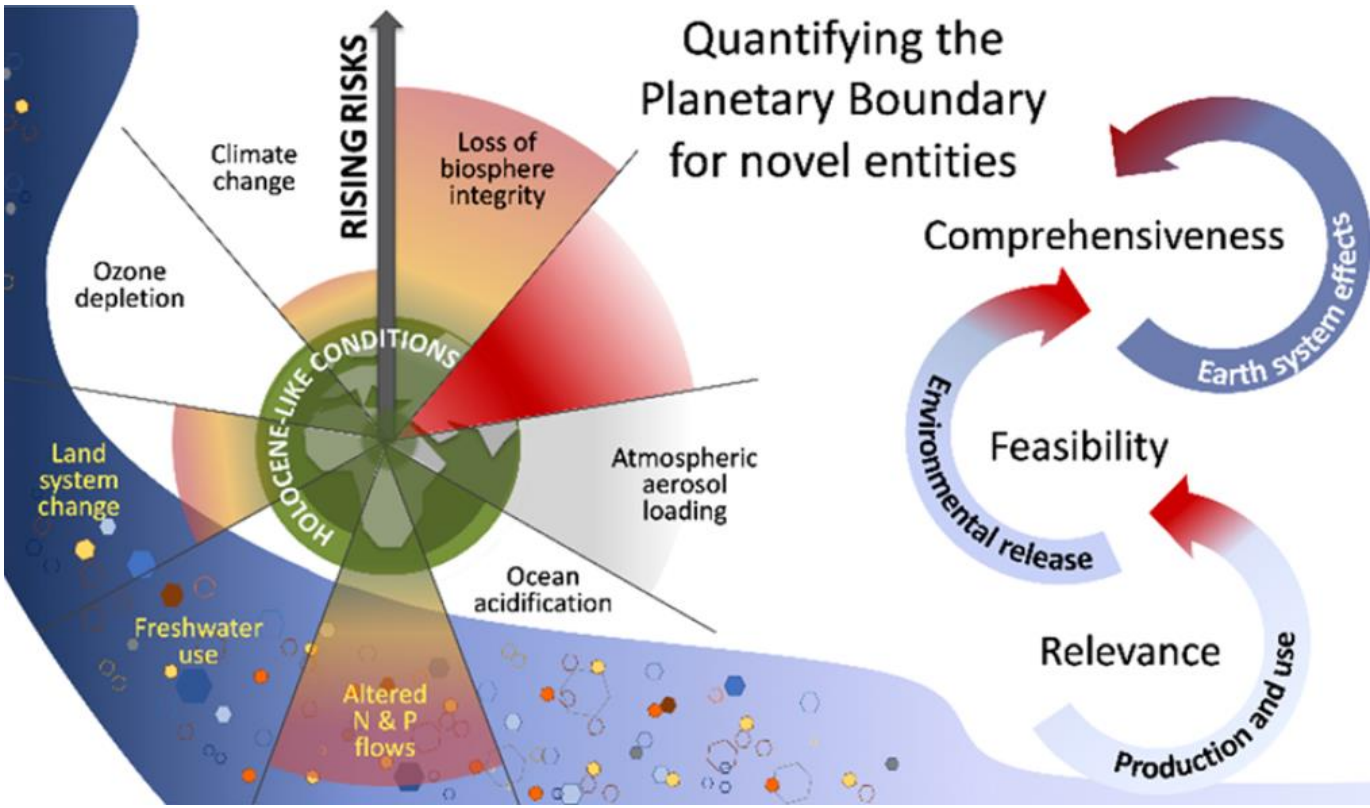
WG4: Integration of R&D Process-Environmental Studies for the Translation in a White Paper

- Drug design in compliance with the overall environmental impact to provide a sharable guideline-like document.
- Assessment of probability of exposure on the basis of substances environmental fate.
- Properly inform drug designers and managers on environmental risks compared to societal benefits.



Are we leaving the Safe Area of the Planetary Boundary for Novel Entities?

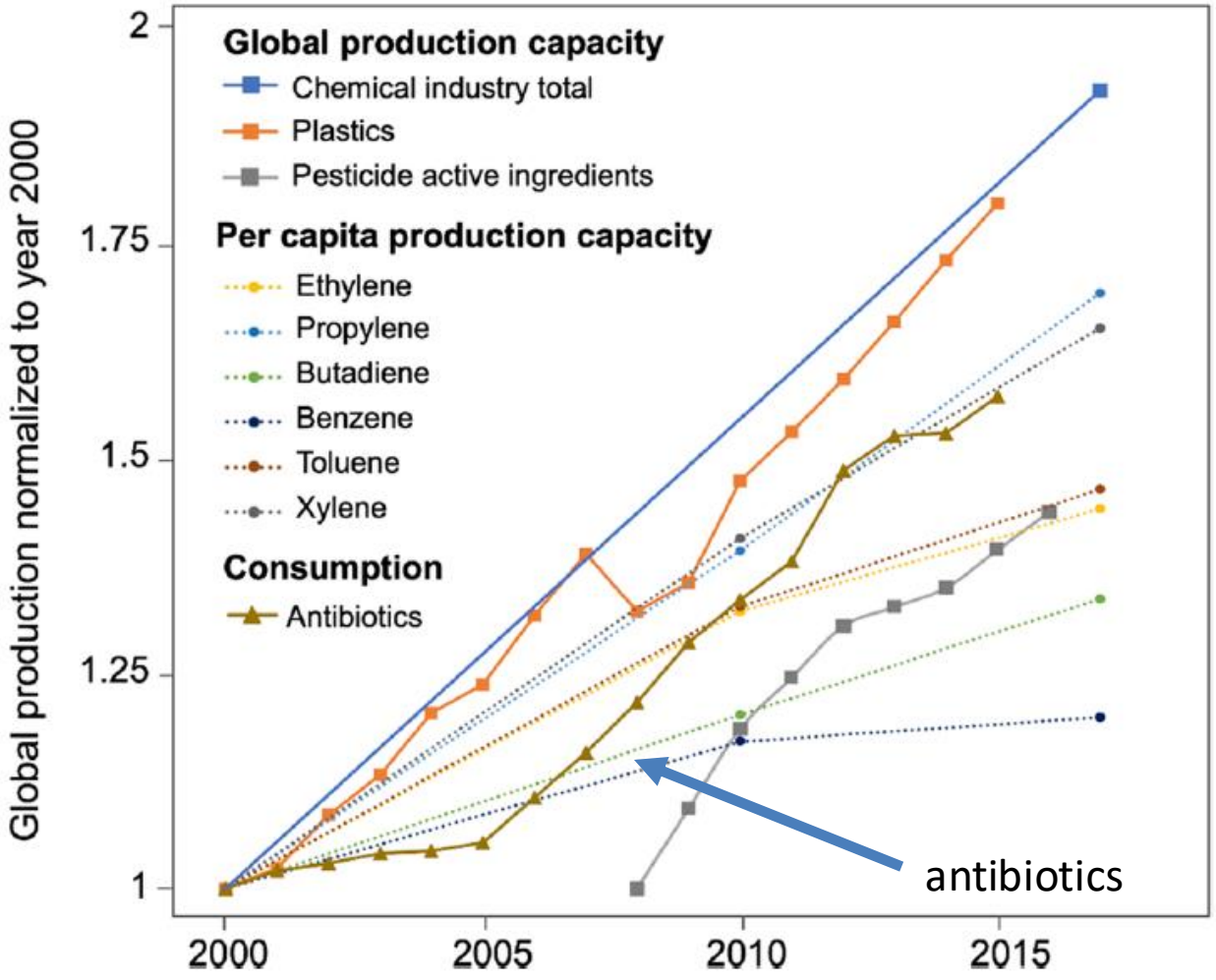
"…the anthropogenic introduction of novel entities to the environment is of concern at the global level when these entities exhibit persistence, mobility across scales with consequent widespread distribution and accumulation in organisms and the environment, and potential negative impacts on vital Earth System processes or subsystems…"



(Persson et al., 2022)

Relative Growth in the Production of Certain Chemicals

- Polymer "plastic" as the most visible form of chemical pollution: total mass of plastic exceeds that of all living mammals
- 2.4% of it enters the environment every year

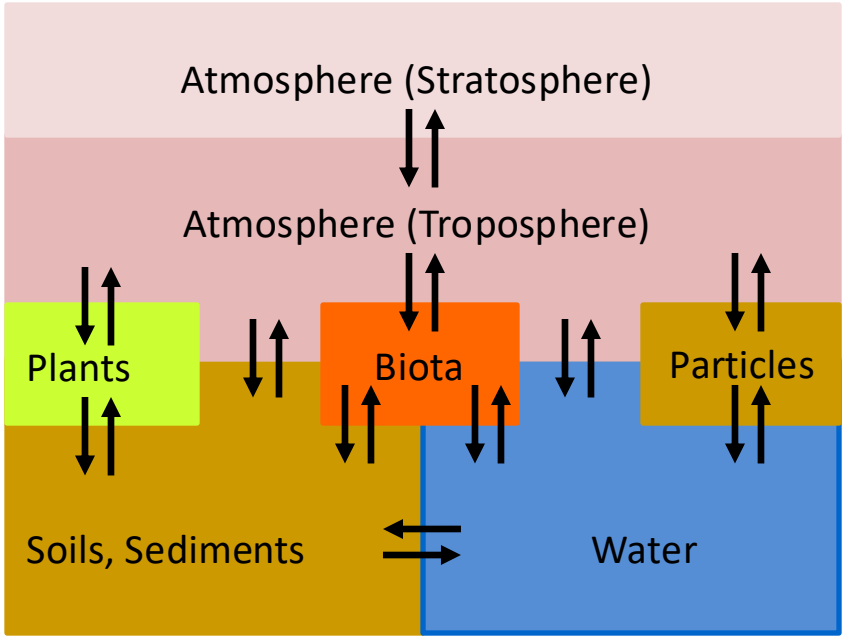


(Persson et al., 2022)

Environmental Impact: What is it all about?

what does the environment do to the substance?

Environmental Chemistry:
Partitioning, transformation, exposure




nature International weekly journal of science

Diclofenac residues as the cause of vulture population decline in Pakistan

Oaks et al. (2004)

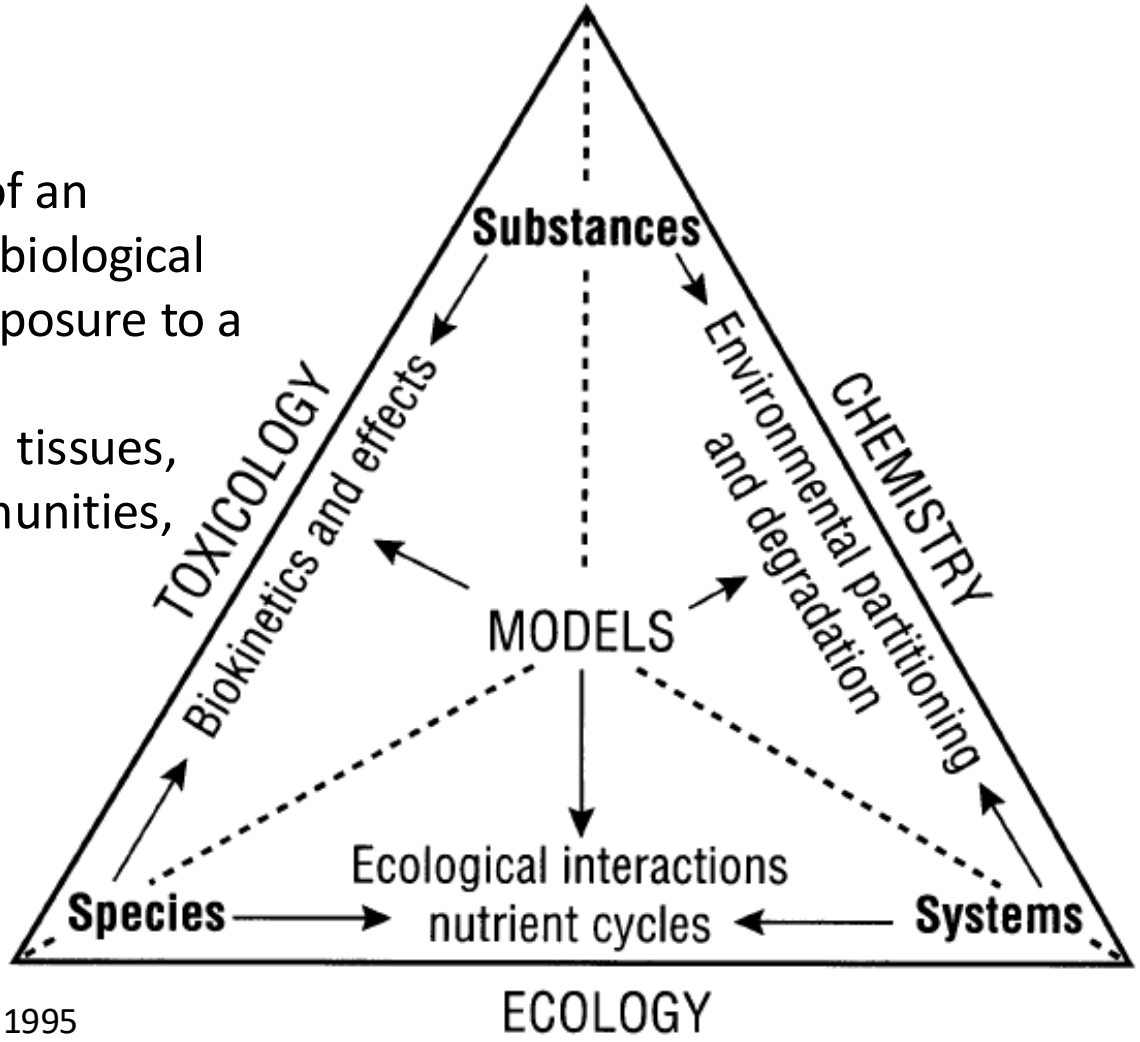
what does the substance do to the environment?

(Eco)toxicology:
Effects on non-target organisms

Ecotoxicology: “Study of the three S's”

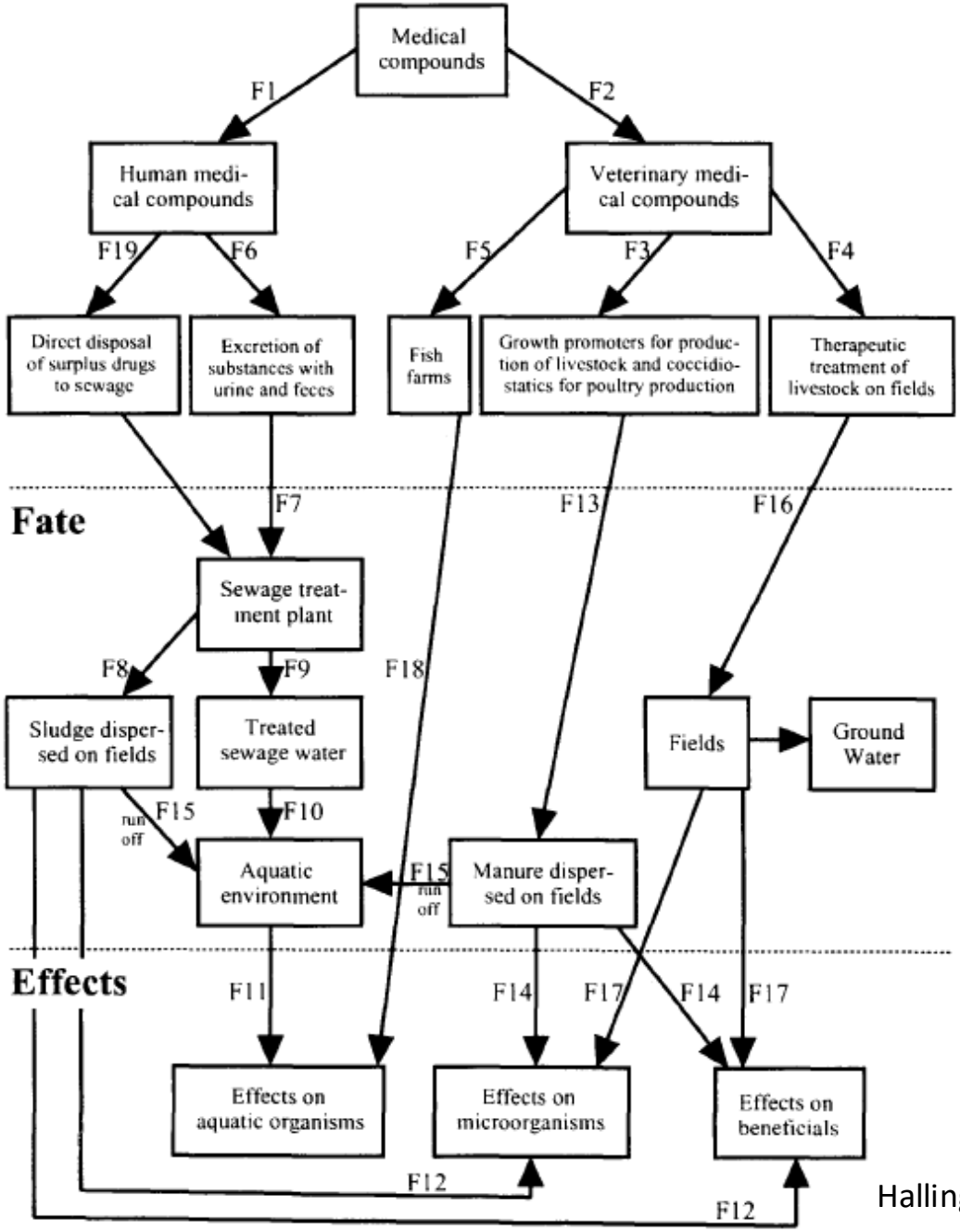
Toxic Effects of **S**ubstances on Nonhuman **S**pecies in Complex **S**ystems

- Changes in state or dynamics of an organism, or at other levels of biological organization, resulting from exposure to a chemical
- From subcellular/cellular level, tissues, individuals, populations, communities, ecosystems, and landscapes



Van Leeuwen, 1995

Occurrence, Fate, and Effects of Pharmaceutical Substances in the Environment



different exposure routes of veterinary and human medicinal substances

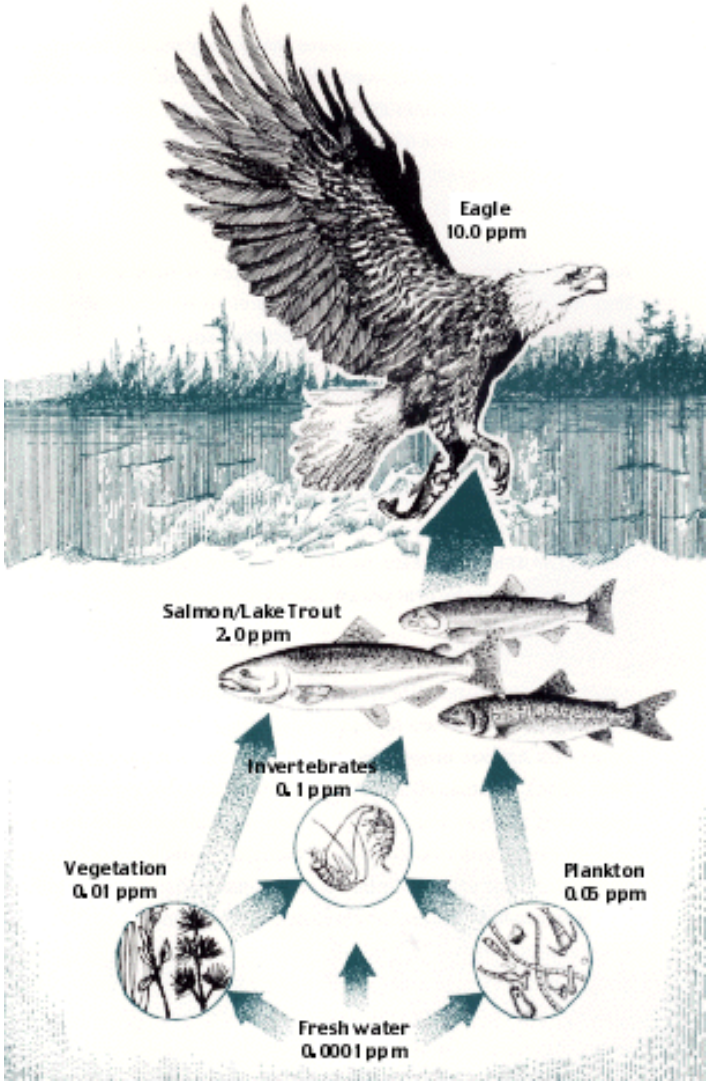
Halling- Sørensen et al., 1997

Partitioning:

K_{OW}, Indicator for Bioaccumulation

	$\log K_{OW}$
Benzene	2.13
Trichlorobenzene	4.05
Pentachlorophenol	5.01
PAHs	3.35 – 6.6
PCBs	~5 - ~7

$$K_{OW} = \frac{C_{oct}}{C_w}$$



Parasiticide Ivermectin:

Range of $\log K_{OW}$
3.2 (– 5.8) in the literature

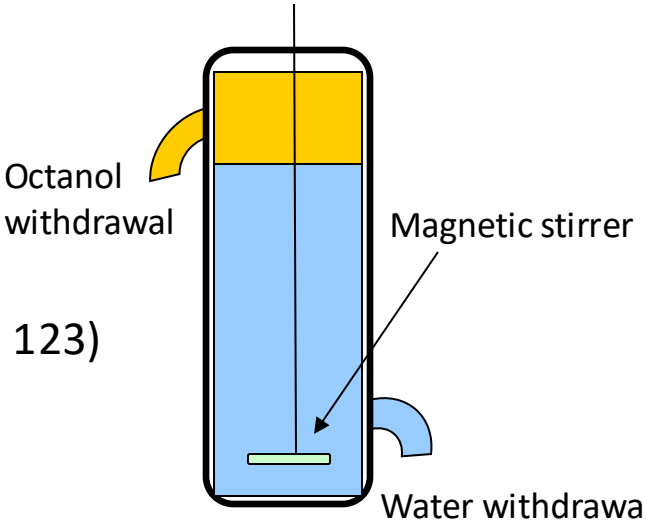
Bioaccumulation?

Gaps in databases need to be filled!

Octanol-Water Partition Coefficient

Different Methods and Different Results

- Shaking method (OECD TG 107) with artifacts due to water droplets in octanol phase; up to $\log K_{OW}$ 4



- Slow stirring method (OECD TG 123) up to $\log K_{OW}$ 8

Correction of $\log K_{OW}$ for ivermectin:
from 3.2 to 5.6

(Römbke et al., 2019)

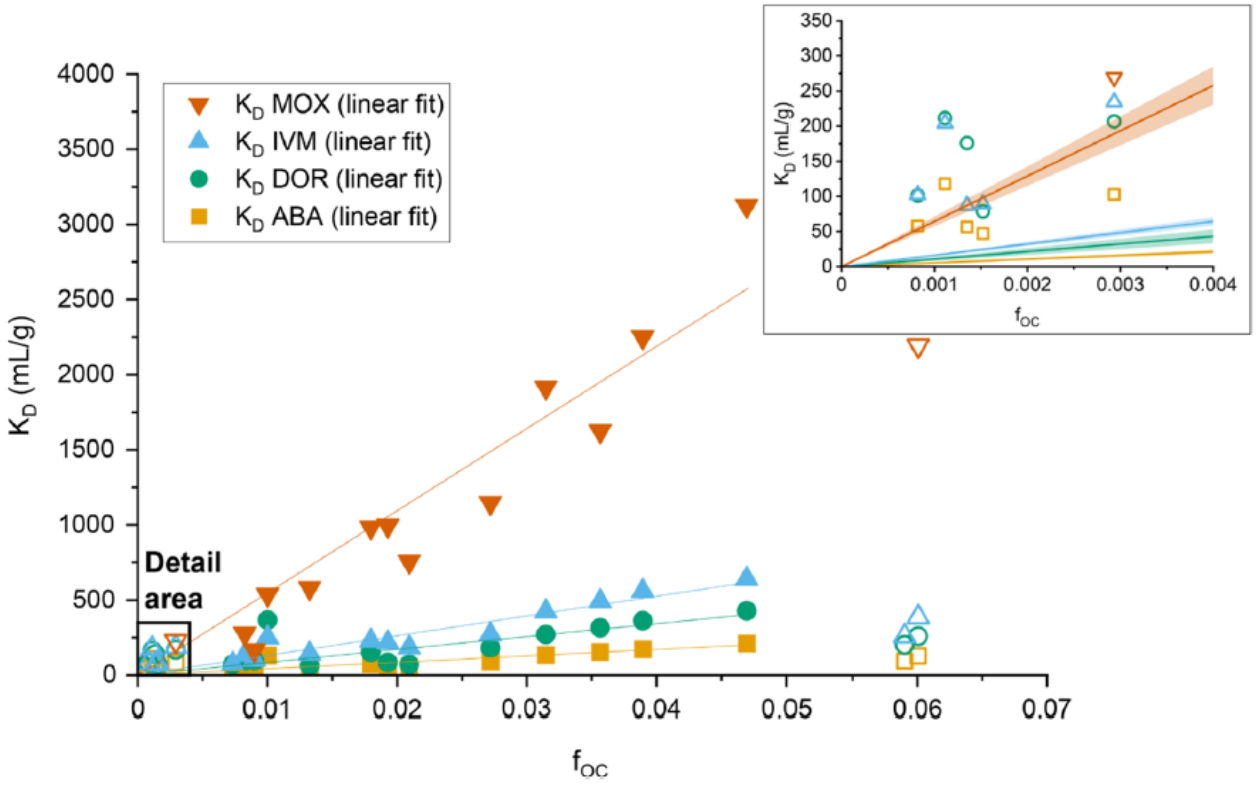
Sorption in Soils and Sediments

Indicator for mobility in the Environment

$$K_D = \frac{C_s(eq)}{C_{aq}(eq)}$$

$$K_{OC} = \frac{K_D}{f_{OC}}$$

K_{OC} is important for the classification of mobile substance as so-called „PMT“-substances



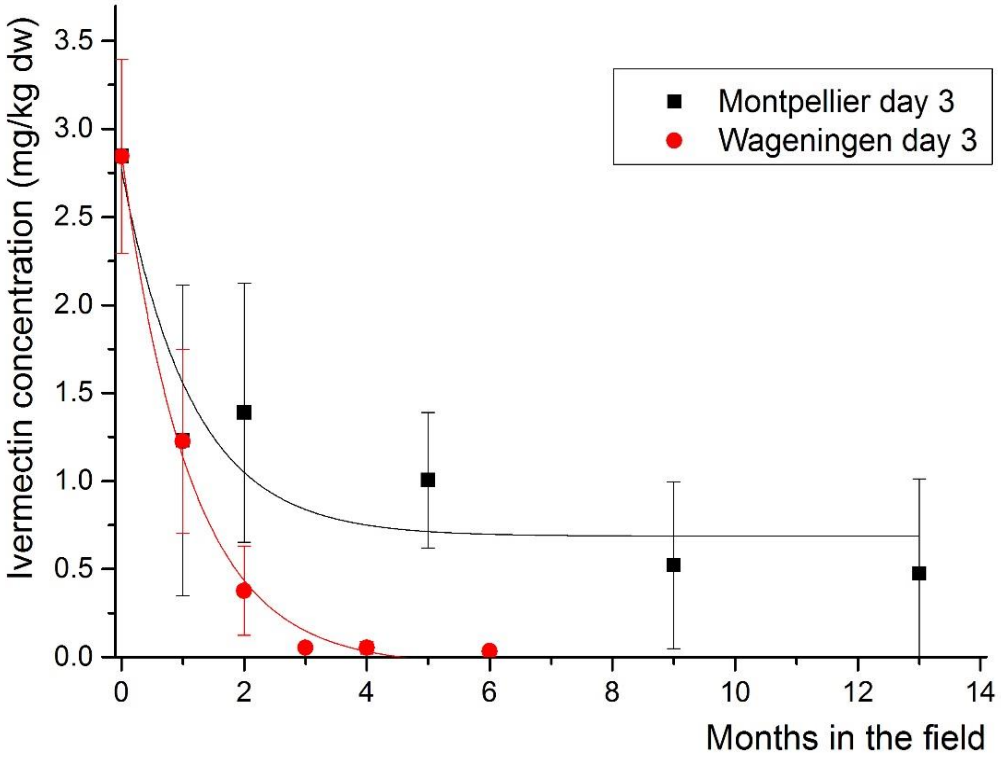
(Heinrich et al., 2021)

Transformation: Dissappearence, ”Loss“ of Ivermectin

Possible sub processes

- degradation?
- volatilization?
- leaching to surface and subsurface water?
- irreversible fixation to soil?
- Transformation to non detectable compounds?

„…differences in ivermectin dissipation in cattle dung among sites, with 50% dissipation times of up to 32 d and 90% dissipation times >396 d.”



Wohde et al., 2016

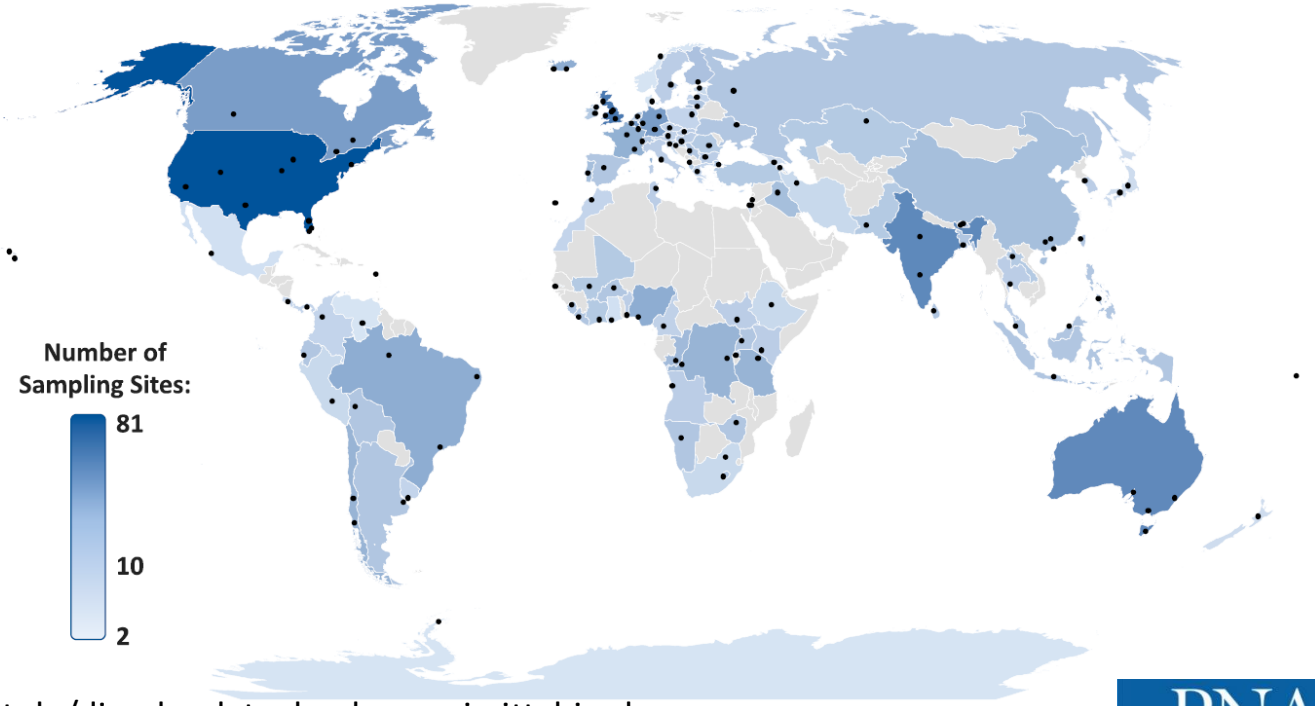
Occurrence and Exposure

Pharmaceutical residues occur globally in the environment

(UBA, 2023)

Pharmaceutical pollution of the world's rivers

"…a global-scale study of API pollution in 258 of the world's rivers, representing the environmental influence of 471.4 million people across 137 geographic regions. Samples were obtained from 1,052 locations in 104 countries (representing all continents and 36 countries not previously studied for API contamination) and analyzed for 61 APIs…"



Databases:

PHARMS-UBA

https://www.umweltbundesamt.de/die-uba-datenbank-arzneimittel-in-der

IPCHEM-Portal

https://ipchem.jrc.ec.europa.eu/

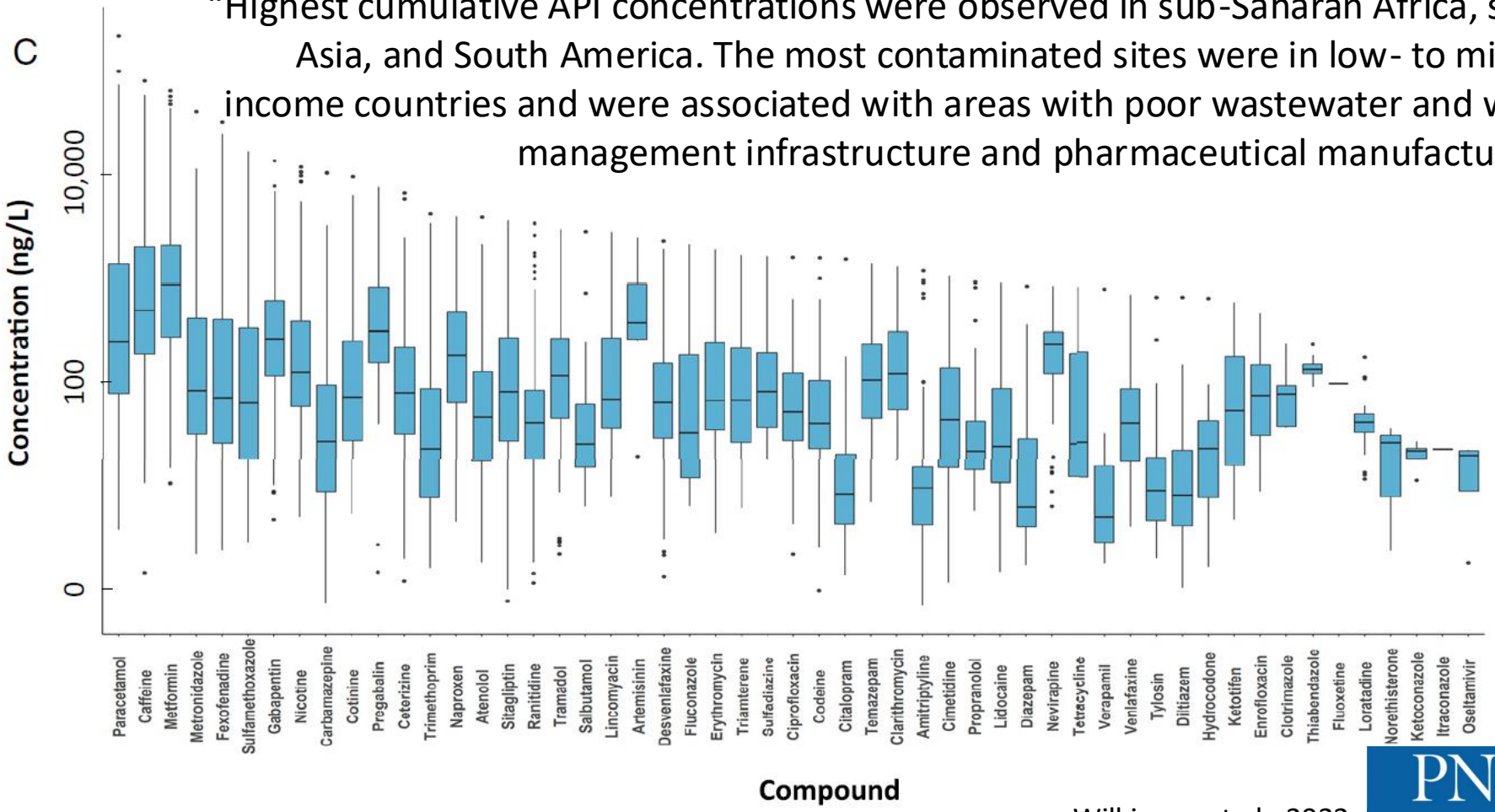
Wilkinson et al., 2022

PNAS
Proceedings of the National Academy of Sciences of the United States of America

Gießen, 03/04/2023

Pharmaceutical pollution of the world's rivers

"Highest cumulative API concentrations were observed in sub-Saharan Africa, south Asia, and South America. The most contaminated sites were in low- to middle-income countries and were associated with areas with poor wastewater and waste management infrastructure and pharmaceutical manufacturing."



Wilkinson et al., 2022

PNAS
Proceedings of the National Academy of Sciences of the United States of America

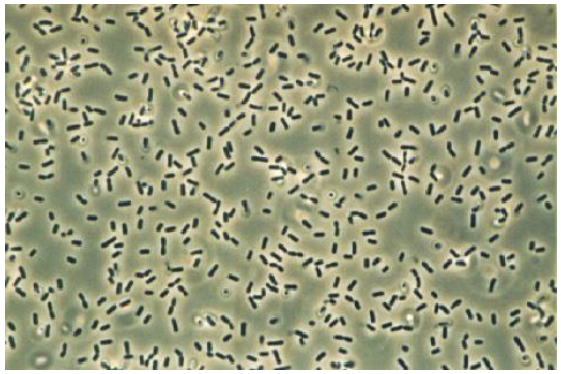
APIs and metabolites/transformation products in environmental compartments

Number of	Global		European Union	
Year	**2021**	**Change to 2015**	**2021**	**Change to 2015**
detected substances	**992**	**+221**	**749**	**+153**
in WWTP[1] effluent/sewage/reclaimed water	771	+ 158	591	+117
in surface water/bank filtrate/groundwater/drinking and tap water	703	+ 175	483	+99
in manure/dung/sediment from aquaculture/SPM/biosolids/sludge	337	+192	250	+166
in sediment/soil/SPM	295	+111	227	+95

Source: UBA Pharms Database version 2 (2015) & version 3 (2021)

Gildemeister et al., 2022

Effects on Non-Target Organisms:
Test Methods



- Inhibition of respiration of bacteria (Effect concentration, EC)
- Inhibition of reproduction of algae (Effect concentration, EC)
- Survival of crustacean (daphnie)
- Survival of fish (lethal dose, lethal concentration, LD/LC)

Studies on deputy organisms, acute toxicity in mostly single-species tests, standardized in OECD Guidelines

OECD
BETTER POLICIES FOR BETTER LIVES

Effects of pharmaceuticals on non-target organisms

Non-target organisms	Effect in Lab trial	Active substance
water fleas	low toxic effect	Sulfadimethoxin, Sulfamethoxazol, Sulfadimidin, Trimethoprim
	strong toxic effect	Closantel, Cypermethrin, Deltamethrin, Doramectin, Eprinomectin, Fenbendazol, Flubendazol
chironomidae	strong toxic effect	Deltamethrin
fish	strong toxic effect	Altrenogest, Closantel, Cypermethrin, Deltamethrin, Eprinomectin, Ivermectin
Earth worms	moderate toxic effect	Closantel, Cypermethrin, Deltamethrin, Eprinomectin, Ivermectin
Dung organisms	moderate toxic effect	Closantel
	strong toxic effect	Cypermethrin, Deltamethrin, Doramectin, Eprinomectin, Ivermectin
soil organisms	decreased phosphatase activity	Doxyzyklin
	change of bacterial community	Lincomycin, Sulfadiazin
water plants	low growth inhibition	Trimethoprim
	strong growth inhibition	Florfenicol
crops	moderate germination inhibition	Sulfamethoxazol
	strong germination inhibition	Florfenicol
	moderate germination inhibition	Enrofloxacin, Sulfadiazin
	strong germination inhibition	Enrofloxacin, Florfenicol
cyano bacteria	low growth inhibition	Trimethoprim
	moderate growth inhibition	Amoxicillin/Penicillin Säure, Tetrazyklin
	strong growth inhibition	Enrofloxacin, Erythromycin, Oxytetrazyklin
green algae	no growth inhibition	Amoxicillin/Penicillin Säure
	moderate growth inhibition	Enrofloxacin, Ivermectin, Tetrazyklin
	strong growth inhibition	Erythromycin

Laboratory

Extrapolation

Ecosystem

toxic effect

shift of species composition

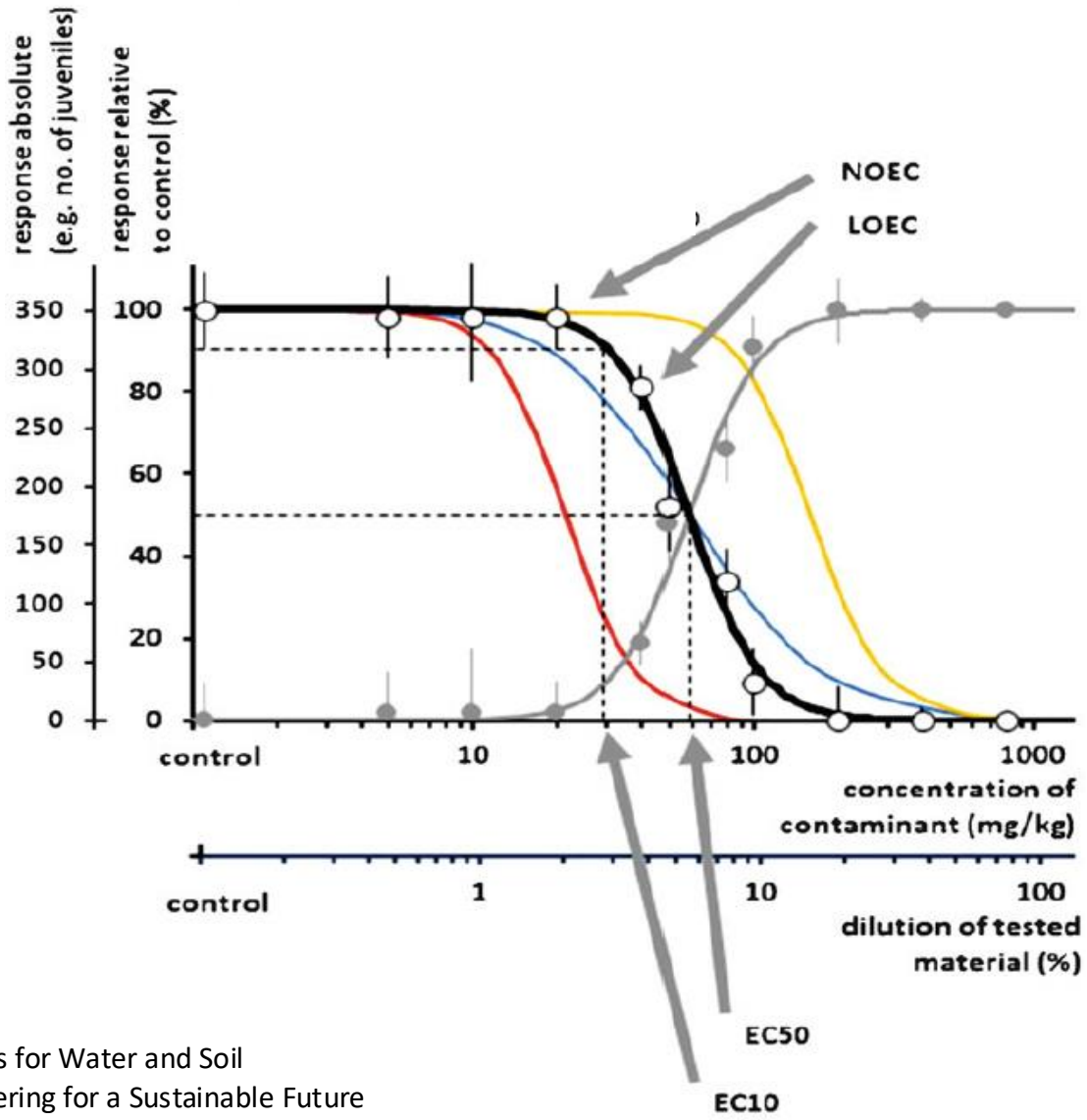
growth inhibition

(UBA, modified, 2017)

Gießen, 03/04/2023

Prospective Assessment: Ecotoxicity of Chemicals

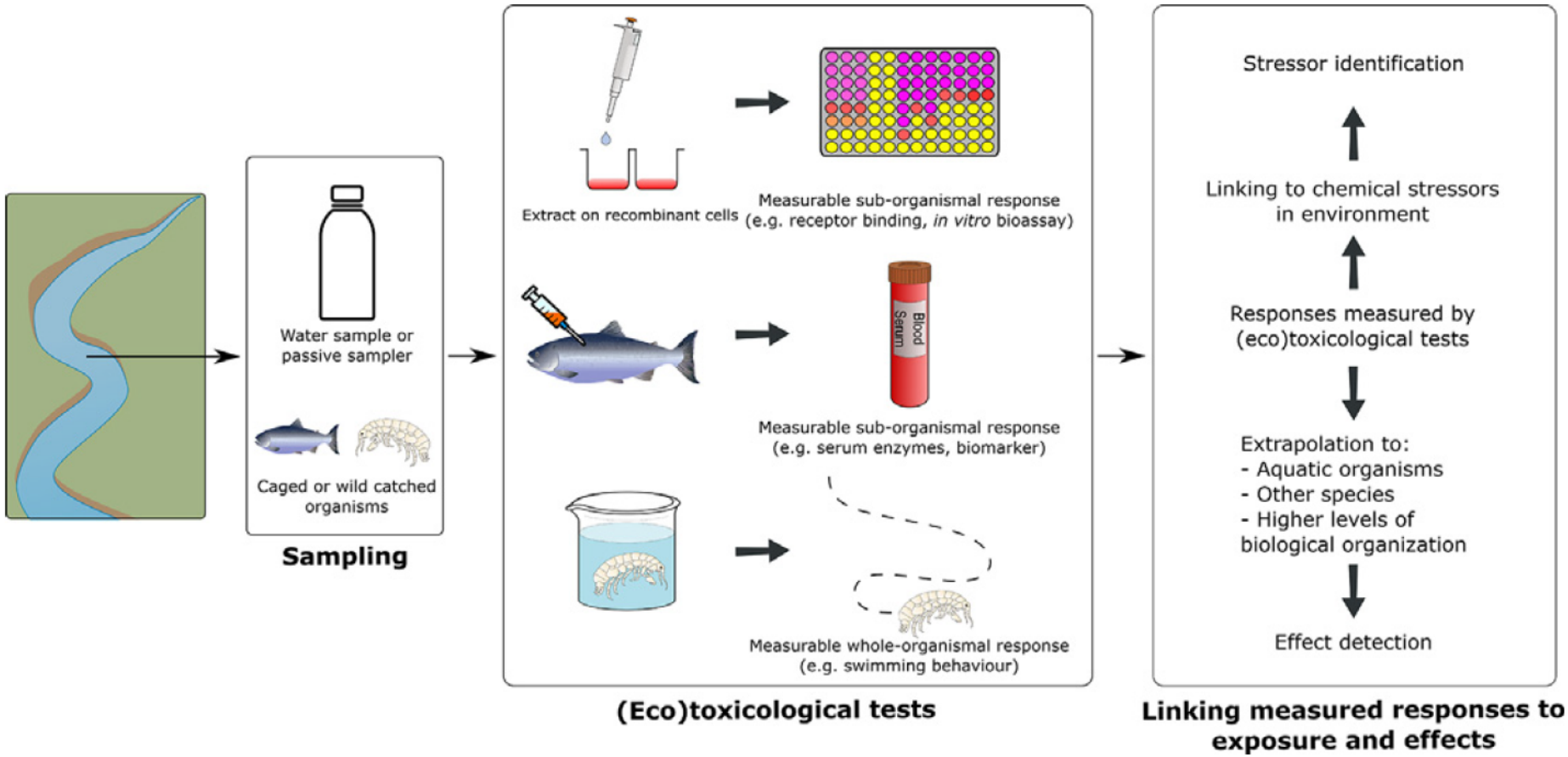
Ecotoxicity parameters (**NOEC, LOEC, EC50, LC50**, etc.) are derived from the modelled concentration–response curve, determined for one single test substance



Adapted from Bláha and Hofman, 2020
in: J. Filip et al. (eds.), Advanced Nano-Bio Technologies for Water and Soil Treatment, Applied Environmental Science and Engineering for a Sustainable Future

Retrospective Assessment:
Ecotoxicology of Contaminated Samples

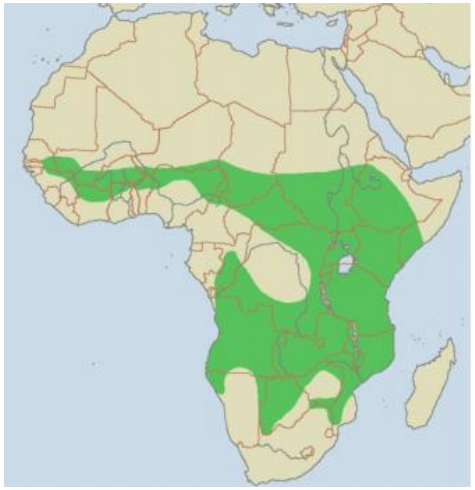
Advanced approach: integration of ecotoxicity tests into monitoring practices



Schuijt et al. (2021)

Environmental Risk Assessment
Based on Exposure and Effect

danger: lion



exposure: low in Europe

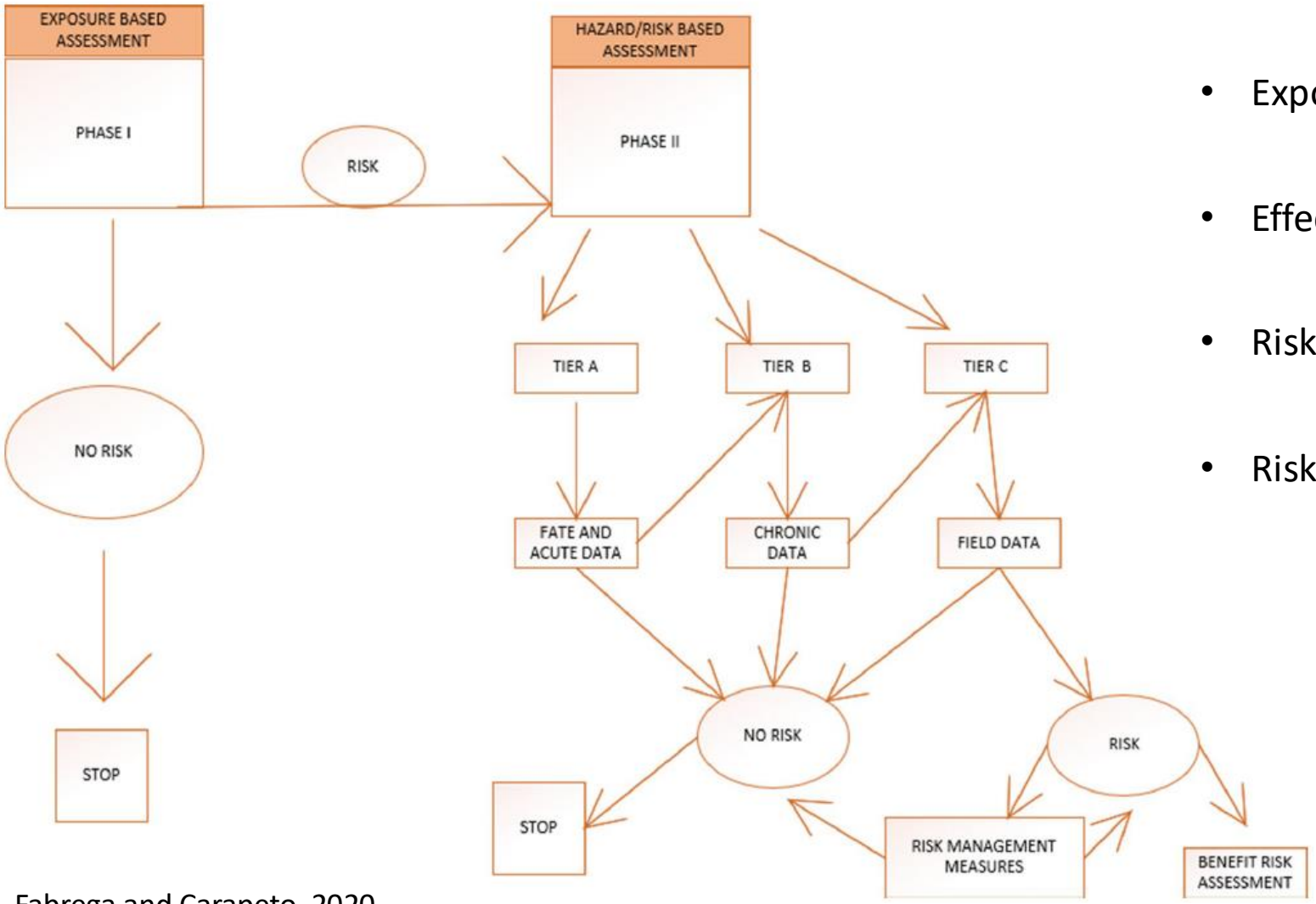
"danger": corresponds to **PNEC**, predicted no effect concentration;
e.g. on the basis of NOEC including a safety factor

"probability of exposure": corresponds to **PEC**, predicted environmental concentration; sometimes "MEC" is used instead

Environmental risk as a result of intrinsic hazard of a compound and probability for exposure

The aim is: $\frac{PEC}{PNEC} < 1$

Framework for the Environmental Risk Assessment for Veterinary Medicinal Products in the EU

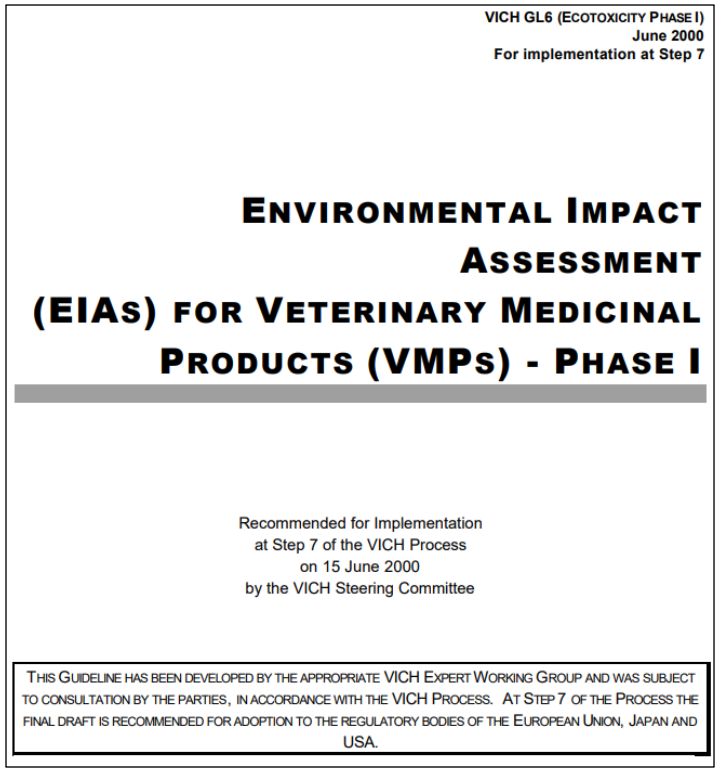


- Exposure
- Effects
- Risk Assessment
- Risk Management

Fabrega and Carapeto, 2020

Environmental Risk Assessment (ERA)
International Governance

- ERA principles for veterinary pharmaceuticals are defined in an international framework (VICH)
- Two basic guidelines: VICH GL 6 & VICH GL 38
- Step-wise approach: Phase I and Phase II ERA

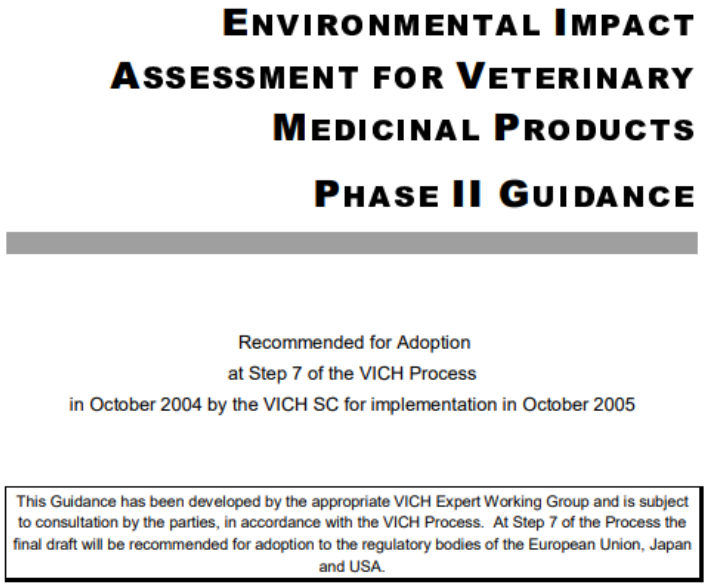


VICH GL6 (ECOTOXICITY PHASE I)
June 2000
For implementation at Step 7

ENVIRONMENTAL IMPACT ASSESSMENT (EIAS) FOR VETERINARY MEDICINAL PRODUCTS (VMPS) - PHASE I

Recommended for Implementation
at Step 7 of the VICH Process
on 15 June 2000
by the VICH Steering Committee

THIS GUIDELINE HAS BEEN DEVELOPED BY THE APPROPRIATE VICH EXPERT WORKING GROUP AND WAS SUBJECT TO CONSULTATION BY THE PARTIES, IN ACCORDANCE WITH THE VICH PROCESS. AT STEP 7 OF THE PROCESS THE FINAL DRAFT IS RECOMMENDED FOR ADOPTION TO THE REGULATORY BODIES OF THE EUROPEAN UNION, JAPAN AND USA.



ENVIRONMENTAL IMPACT ASSESSMENT FOR VETERINARY MEDICINAL PRODUCTS

PHASE II GUIDANCE

Recommended for Adoption
at Step 7 of the VICH Process
in October 2004 by the VICH SC for implementation in October 2005

This Guidance has been developed by the appropriate VICH Expert Working Group and is subject to consultation by the parties, in accordance with the VICH Process. At Step 7 of the Process the final draft will be recommended for adoption to the regulatory bodies of the European Union, Japan and USA.

Phase I ERA

Determination of **environmental exposure of the medicine** and need for ecotoxicological assessment, **mandatory for all veterinary medicines**.

Based on exposure

- Low exposure → Limited risk
- Individual treatments → Phase I
- Pets → Phase I
- Natural substances → Phase I
- Exposure < 100 µg/kg → Phase I

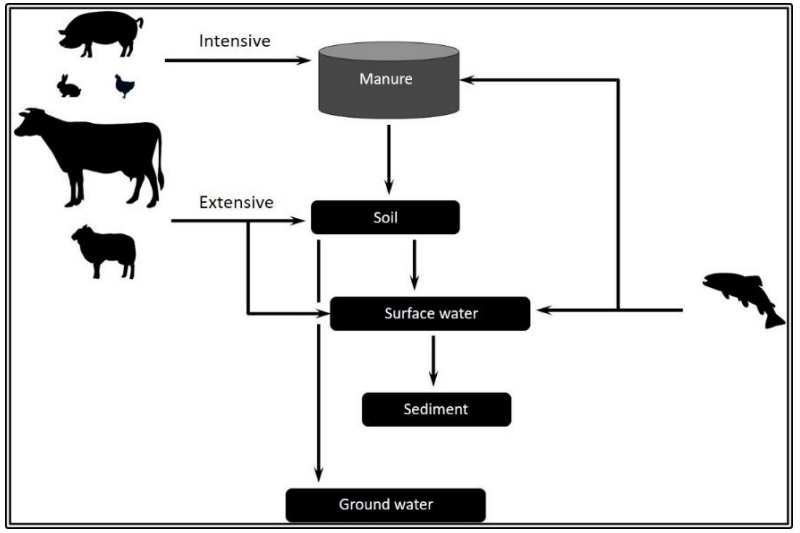
Specific issues:

- Parasiticides → Phase II
- Aquaculture open waters → Phase II
- "However clause"

Relevant for majority of pharmaceutical veterinary medicinal products (> 95%)

Phase II ERA

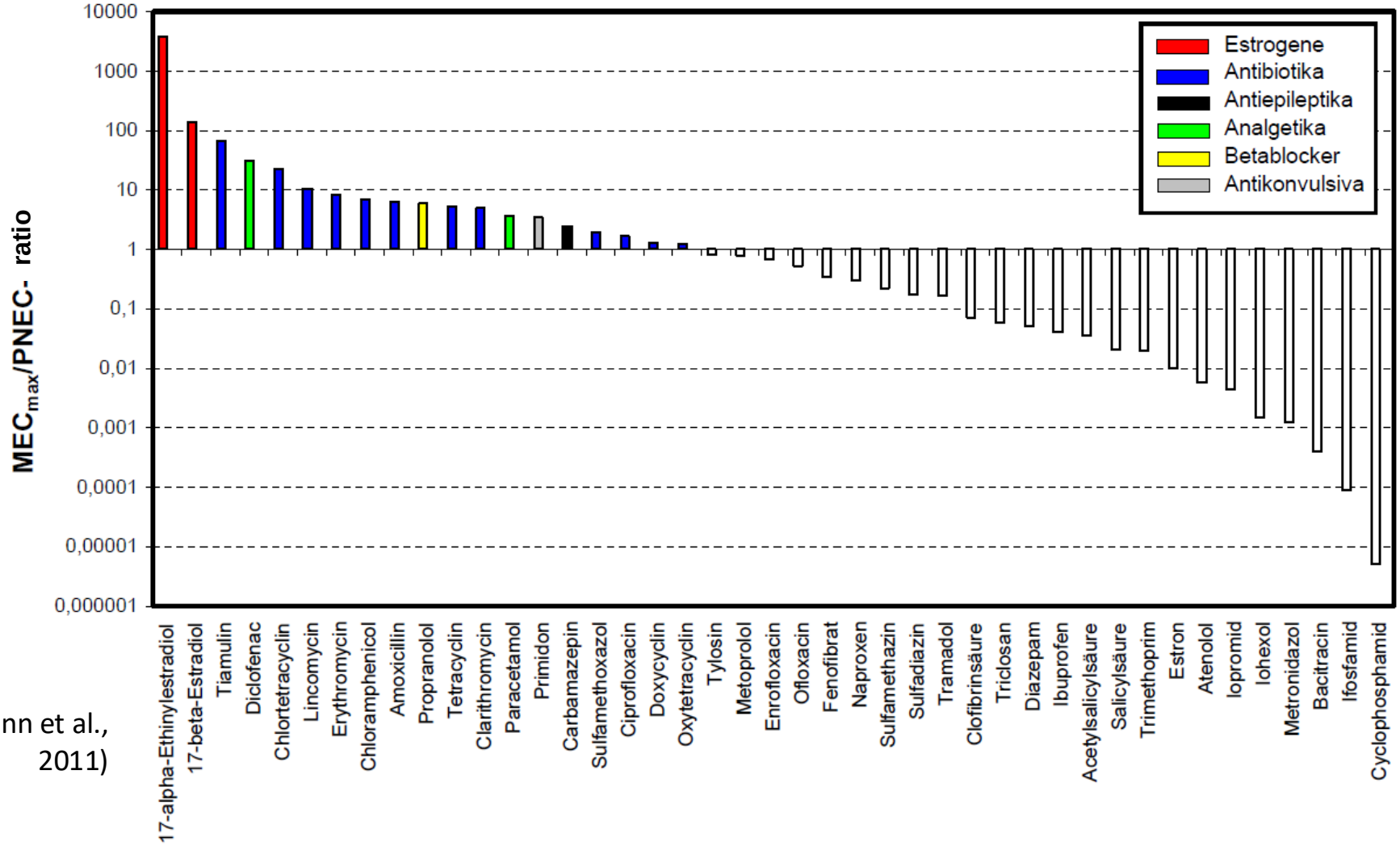
- Problem formulation – Protection goals
  - Protection of ecosystems



- Risk assessment
  - Exposure calculation (PEC) → Husbandry practices; Physicochemical/fate studies
  - Toxicity determination (PNEC) → Environmental compartments
    - Soil
    - Water
    - Dung
    - Sediment
  - Risk Quotient Approach → RQ = PEC/PNEC → mitigation measures to reduce the risk to an acceptable level?

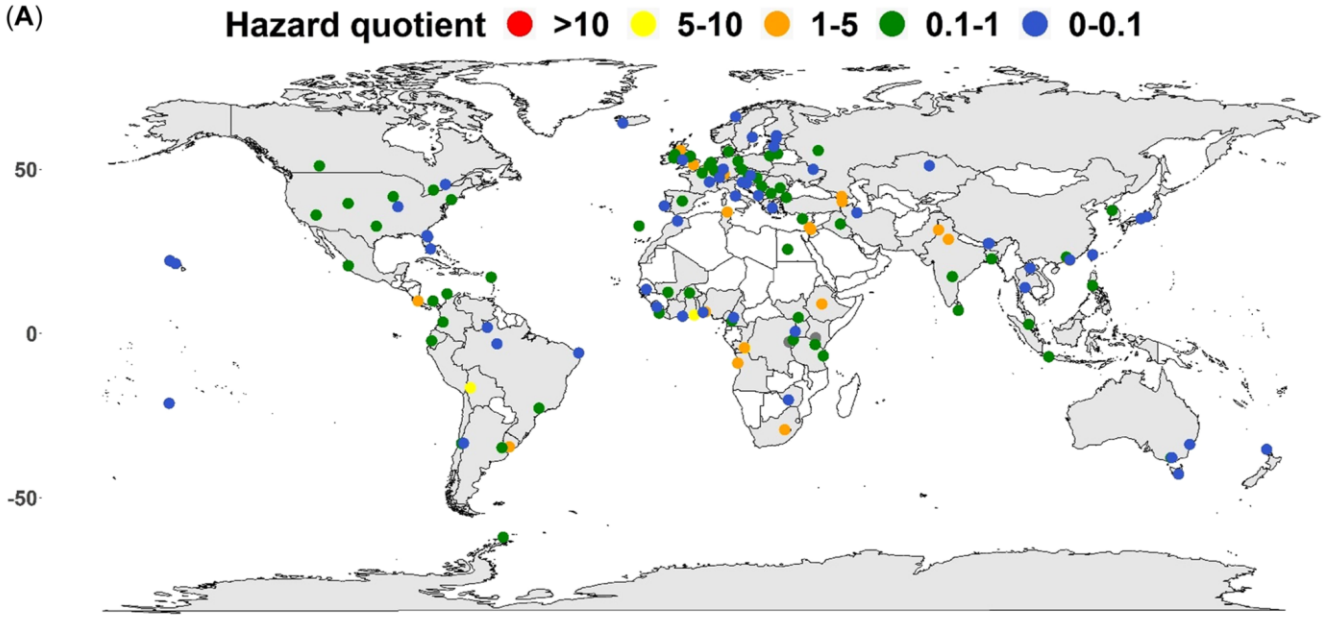
MEC/PNEC-Ratios for Pharmaceuticals

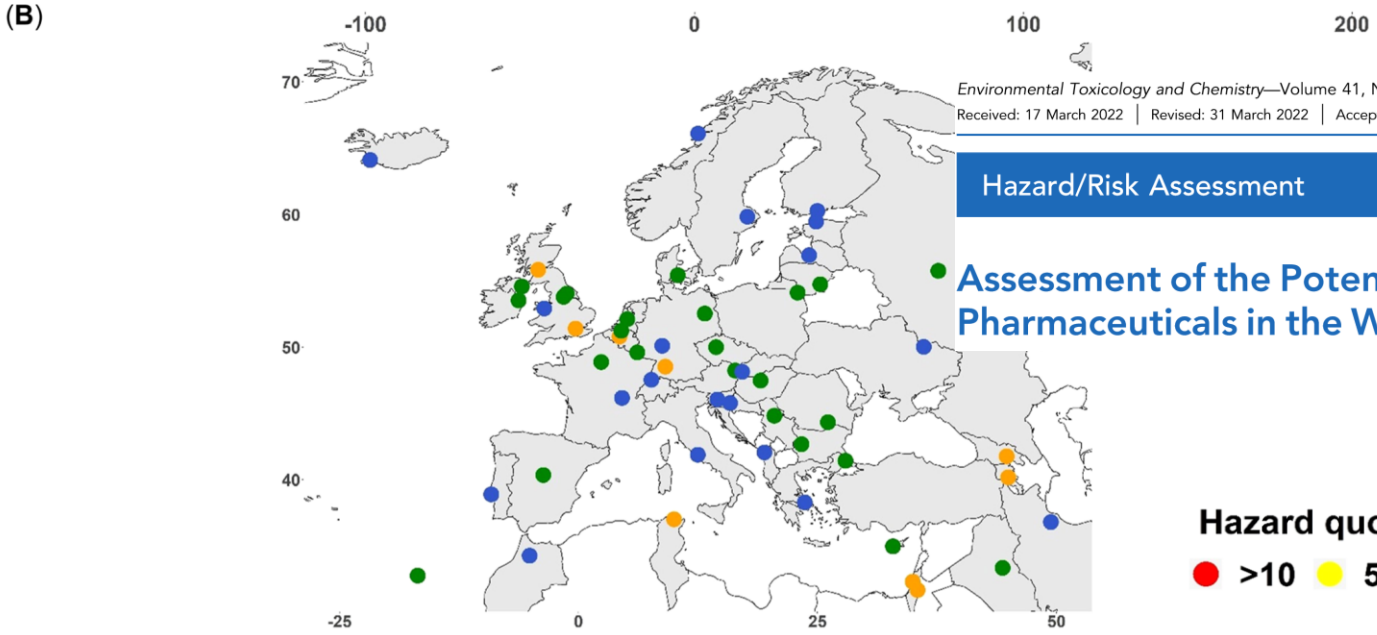
with Good to Sufficient Ecotoxicological Data Base



(Bergmann et al., 2011)

Risk Assessment





Environmental Toxicology and Chemistry—Volume 41, Number 8—pp. 2008–2020, 2022
Received: 17 March 2022 | Revised: 31 March 2022 | Accepted: 26 April 2022

Hazard/Risk Assessment

Assessment of the Potential Ecotoxicological Effects of Pharmaceuticals in the World's Rivers

Hazard quotient

>10 5-10 1-5 0.1-1 0-0.1

Bouzas-Monroy et al., 2022

Little Consideration of APIs in Environmental EU legislation

watchlist:
- diclofenac
- estrone (E1)
- 17-beta-estradiol (E2)
- 17-alpha-ethinylestradiol (EE2)
- three macrolide antibiotics

EU Legislative framework	Year of adoption	Consideration of pesticides[1)]	Consideration of pharmaceuticals	Current EU action
Water Framework Directive (2000/60/EC)	2000	Annex VI, Part A Annex VIII	No	-
Directive on Environmental Quality Standards (Directive 2008/105/EC amended by 2013/39/EU)	2013	Art. 7a, Substances in annex (EQS)	Art 8b Watchlist, Art 8c strategic approach	Review of priority substances[2)], Fulfilling strategic approach pharmaceuticals[39]
Groundwater Directive (2006/118/EC)	2006	Annex I: Groundwater quality standards	No	-
Sewage Sludge Directive	1986	No	No	revision proposed, impact assessment closed
Urban Waste Water Directive	1991	No	No	in revision
Industry Emissions Directive	2010	Annex I: Chemical industry / production	Annex I: Chemical industry / production	draft of revision published in 2022
Classification, labelling & packaging regulation	2008	YES	No	Revision planned
Revised Drinking Water Directive	2020	(17) Recital Annex I Water quality	(7), (17) Recital Art. 13 8. Monitoring Art. 19 3. Evaluation	-
Soil Health Law	Open	Open	Open	Proposal in 2023

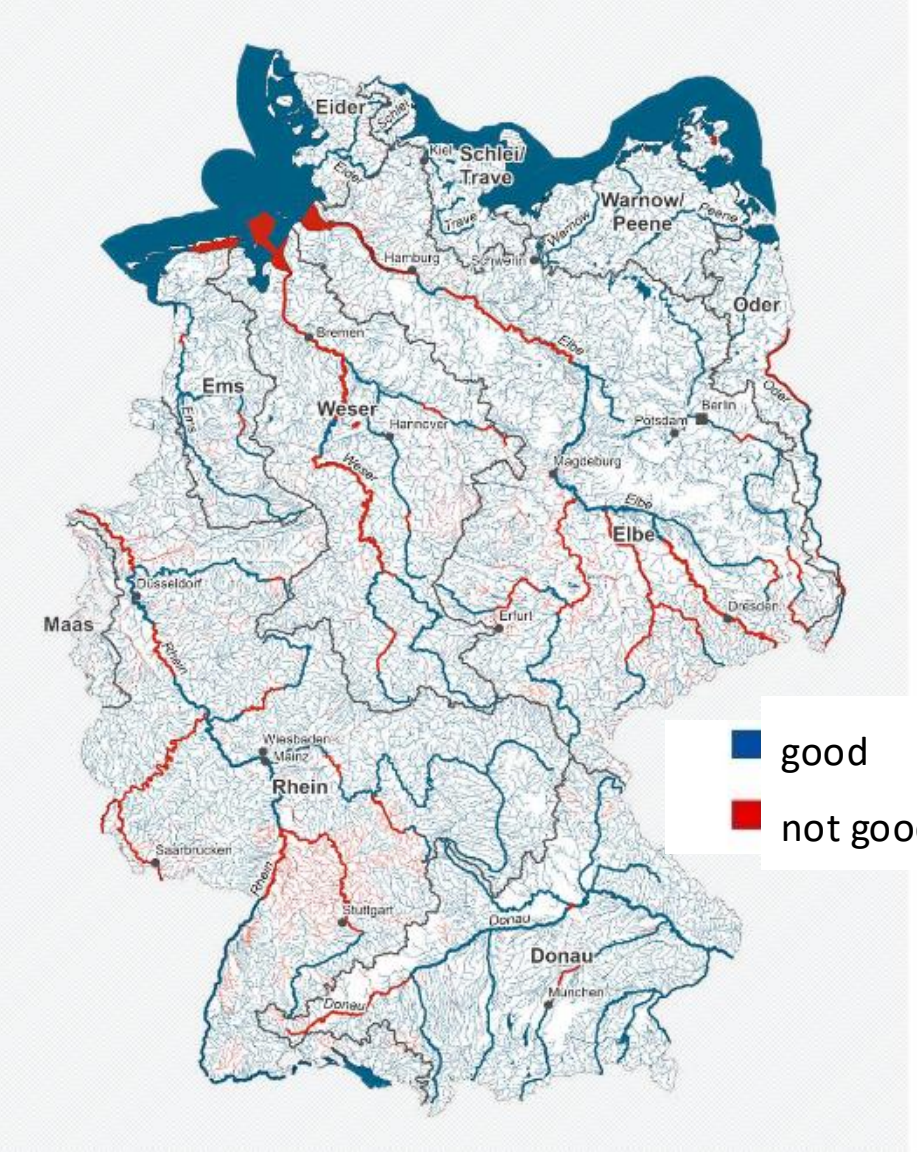
1) regulations on plant protection products and biocides

2) watch list (established in 2015, updates: 2018, 2020, 2022): pharmaceuticals substances included and now proposed as candidates for priority substances

Gildemeister et al., 2022

Water Framework Directive

Chemical Status of Surface Waters (ubiquitous pollutants excluded)

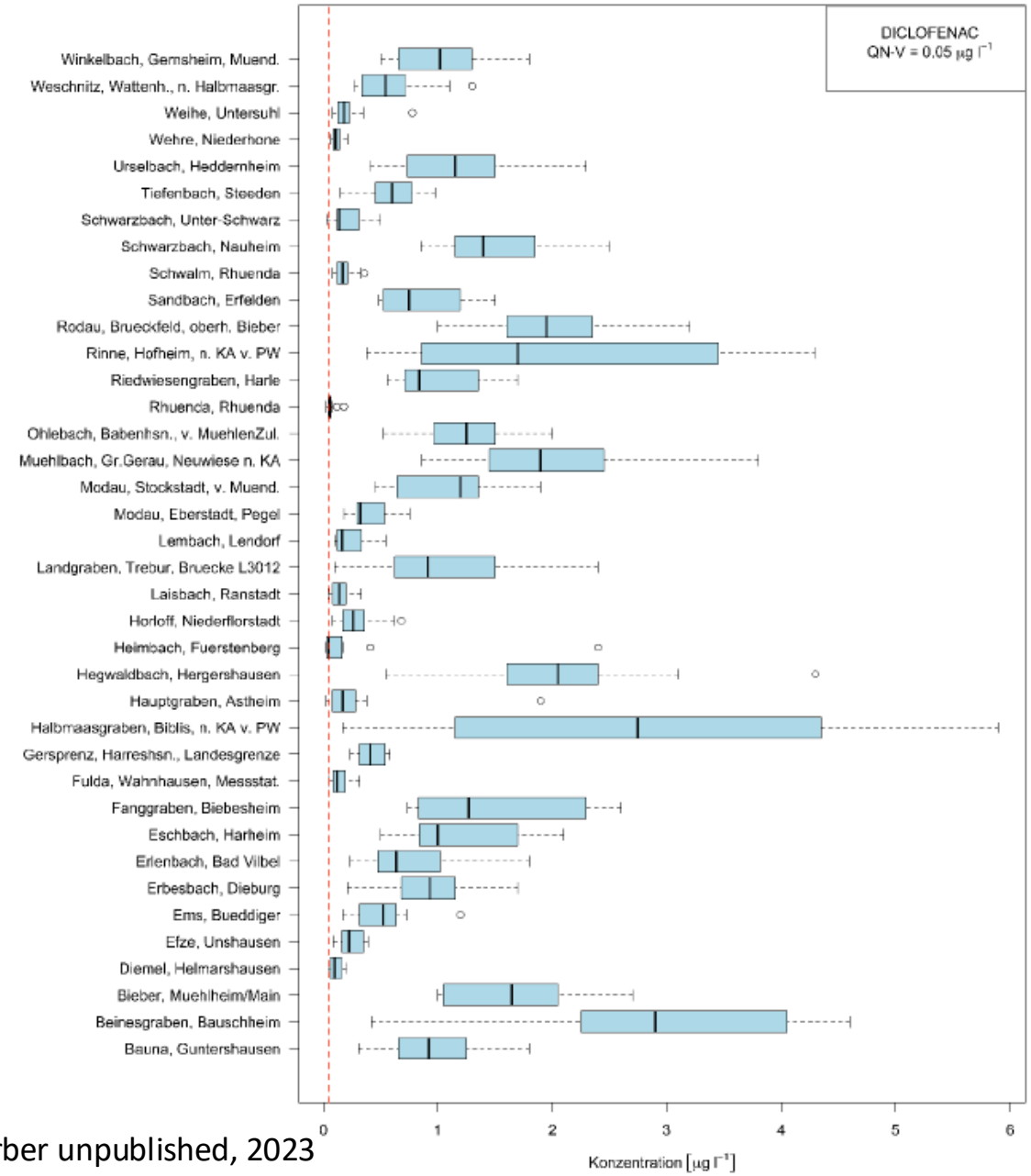


the aim is to bring all rivers, lakes, groundwater and coastal waters into a "good status" by 2027 at the latest.

assessment is based on concentrations in water and biota

Gießen, 03/04/2023

Pharmaceuticals in Running Waters in Hesse, Germany
Diclofenac



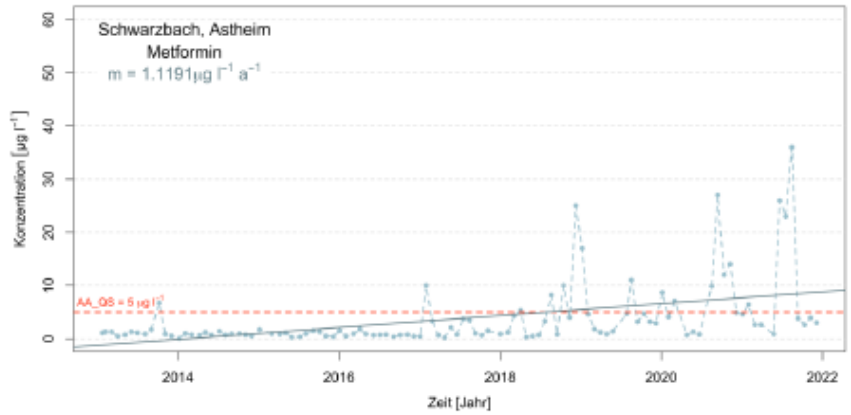
Always above quality limit (quality standard proposal), with increasing tendency!

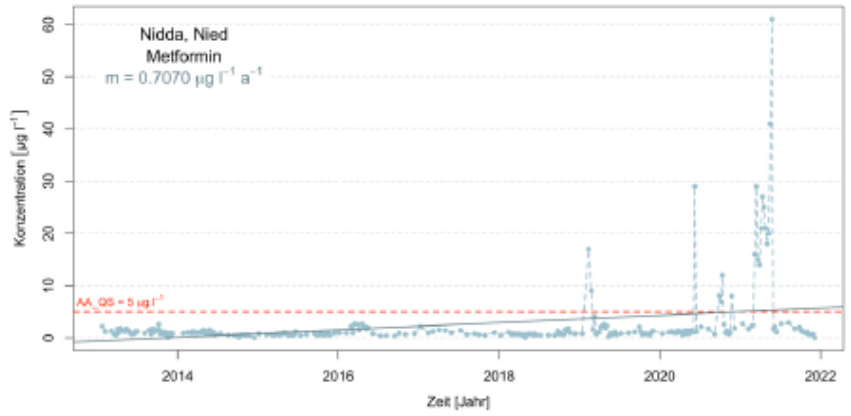
This would mean every river with “not good chemical quality“

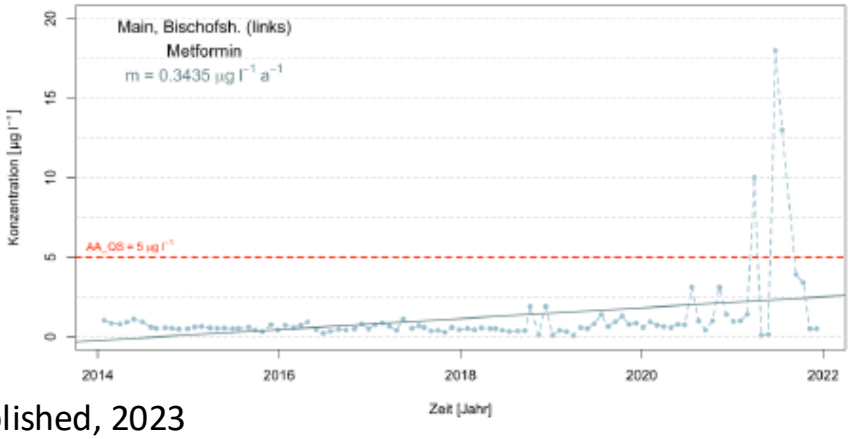
Sperber unpublished, 2023

Gießen, 03/04/2023

Pharmaceuticals in Running Waters in Hesse, Germany
Metformin







Recent strong upward trend (transformation product not considered)!

Sperber unpublished, 2023

Gießen, 03/04/2023

BUND
FRIENDS OF THE EARTH GERMANY

Solutions for Sustainable Management(?) our Basis for Discussion

Drug design

- Publicly accessible collection of data
- Strengthening of ERA with the possibility of refusal of approval
- Research promotion of green pharmacy
- Introduction of an environmental classification system for pharmaceuticals
- Extension of good manufacturing practice to include environmental requirements

Application

- Expansion of preventive and precautionary health care
- Information and training of healthcare professionals
- Prescription requirement for drugs that are particularly hazardous to the environment
- Prohibition of advertising for non-prescription drugs

Downstream measures

- Centralized collection of pharmaceutical residues nationwide via the pharmacies
- Expansion of the 4th purification stage primarily at polluted wastewater treatment plants; separation hot spots (e.g. hospitals) or X-ray contrast media by separate collection and disposal collection and disposal

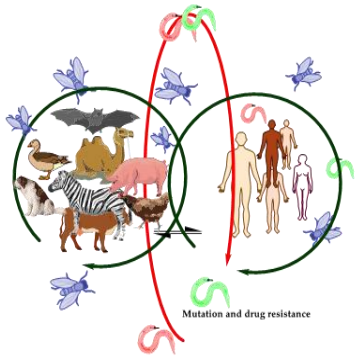
Costs

- According to the polluter pays principle, pharmaceutical manufacturers should contribute to the reduction measures

Gießen, 03/04/2023

Thank you for listening!

cost
EUROPEAN COOPERATION
IN SCIENCE & TECHNOLOGY



Funded by
the European Union

Gießen, 03/04/2023