Dissertation

Exposure and risk assessment of pharmaceuticals in challenging watersheds by enhanced geo-referenced modelling

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June 2021

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Acknowledgements

First of all, I would like to sincerely thank Jörg Klasmeier and Jürgen Berlekamp for their guidance, support, patience, and for the many hours we spent together getting the ideas and milestones behind this work off the ground. In 2016, Jörg asked me to do my PhD under his supervision, having previously written my master's thesis with both of them. So the two have been with me for some time and I can say without exaggeration that without them I would not be where I am today and my life would probably have been completely different. The collaboration with both of them and the associated research group was an educational and above all personally enjoyable affair, during which I learned a lot, not only about research and science. As a PhD student, I am grateful for the high degree of freedom I had in the past years and the many exciting projects and experiences I was allowed to make.

Second, I would like to thank the entire Applied Systems Science research group. Being part of this research group has been a very enriching experience. Thanks to everyone who supported me in many ways, whether they gave me feedback or input for my work, accompanied me or prepared me for conferences, gave me the necessary confidence in my abilities, or were just great colleagues on a personal level.

I have met so many intelligent and personable colleagues over the past few years, some of whom have become friends, and I want to thank you all. I would also like to thank the people behind the scenes who made sure everything went as smoothly as possible for me, especially Elke and Claudia.

Last but definitely not least I would especially like to thank my family and Amelie, who always supported me privately. Thank you for all the uplifting and motivating words and your support in the last years and also the endurance of grumbling and frustration. Without you this work would not have been possible. Of course, this also applies to all my friends who have made sure in the background that I could switch off at the weekend or on vacation and clear my head.

Volker Lämmchen, June 2021

Abstract

For this work the Geo-referenced Regional Exposure Assessment Tool for European Rivers (GREAT-ER) was developed further to support river basin management and the implementation process within the EU Water Framework Directive (WFD). This was achieved through predicting spatially resolved pharmaceutical exposure concentrations in whole watersheds. A major focus of this thesis has been placed on modeling challenging watersheds, whereby challenging can refer to hydrological conditions in a watershed as well as to specific emission patterns that occur within the watersheds. The adapted methodology improves the prediction accuracy in such watersheds with GREAT-ER with respect to pharmaceutical exposures, but can also lead to improved results in other application areas. The possibilities of the latest model version are demonstrated by the extensive inclusion of local and regional conditions. In watersheds with highly variable and seasonally changing hydrological situations, GREAT-ER has been applied satisfactorily for the first time, and additionally, the developed approach can be transferred to equivalent watersheds worldwide.

Comparison with monitoring data confirms that some of the adjustments have resulted in significantly improved model predictions, especially when hydrological and local conditions are specifically addressed. For example, explicit consideration of local drug emissions from hospitals or private medical practices (e.g., for x-ray contrast agents) can improve predictions at the local scale without compromising regional exposure estimates. Pharmaceuticals that have low concentrations and are barely detectable with established analytical methods can be evaluated with model simulations. In addition, current management strategies implemented under the WFD has been replicated and evaluated. These management scenarios simulated with the model allow an a priori evaluation of risk reduction measures. In combination with targeted monitoring approaches, it was shown that the GREAT-ER model can serve as a valuable tool for exposure and risk assessment of pharmaceuticals even in challenging watersheds. This and the useful combination of targeted monitoring and GREAT-ER simulations and the ability of the modeling approach to predict the expected range of spatial surface water concentrations is demonstrated by three selected journal articles.

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Abbreviations

API	Active Pharmaceutical Ingredient
CDF	Cumulative distribution function
CSO	Combined sewage overflow
DEM	Digital elevation model
E1	Estrone
E2	17ß-estradiol
EC	European Commission
EE2	17α-ethinylestradiol
EQS	Environmental Quality Standard
EU	European Union
GREAT-ER	Geography-Referenced Regional Exposure Assessment Tool for European Rivers
ICPR	International Commission for the Protection of the Rhine
Interreg	Interregional; as commonly used abbreviation of the European territorial cooperation (ETC)
JRC	Joint Research Centre
LANUV	Agency for Nature, Environment and Consumer Protection North Rhine-Westphalia
LfU	Bavarian Environmental Protection Office
MEDUWA	MEdicine Unwanted in WAter
MNQ	Mean annual low flow discharge
MQ	Mean annual discharge
NLWKN	Lower Saxony State Office for Water Economy, Coastal and Environmental Protection
PhD	Doctor of Philosophy (degree)
Q50	Median annual discharge
SDG	Sustainable Development Goals
SSD	Species sensitive distribution
STP	Sewage treatment plant
UN	United Nations
UNICEF	United Nations Children's Emergency Fund (founded as: *United Nations International Children's Emergency Fund*)
WFD	Water Framework Directive
WRRL	Wasserrahmenrichtlinie
WWTP	Wastewater treatment plant

1. Introduction

Water constitutes an essential resource for all living organisms including humans. Without access to clean water agriculture, stockbreeding, fishing, industrial activity or permanent settlements are barely possible. Approximately three percent of the earth's water is fresh water, of which only a small part is accessible to humans to serve as drinking water. Access to clean water was recognized as a human right by the United Nations General Assembly in 2010 (UN, 2010). Nevertheless, 2.2 billion people worldwide do not have regular access to clean water and around 785 million people do not even have a basic supply with drinking water (UNICEF, 2019). This fact was also taken into account in the UN-2030 Agenda (UN, 2015), which is meant to be an action plan for people, planet and prosperity. It includes 17 sustainable development goals (SDG) and 169 global targets. SDG 6 of the Agenda addresses "the availability and sustainable management of water and sanitation for all."

The importance of water as a resource is also recognized in Europe and is embedded in the European Water Framework Directive (EC, 2000). The European Water Framework Directive (WFD) constitutes a legal framework that imposes the protection of common water resources on European states. Among other things, this directive calls for establishing the good chemical status of European surface waters. To achieve this goal, exposure and risk assessment of micropollutants, including pharmaceuticals, followed by development and implementation of reduction measures for critical compounds is necessary (Allan et al., 2006; Kümmerer et al., 2019). Currently, the WFD lists 45 priority substances in Annex X of the directive and sets environmental quality standards (EQS) for each of these substances. It is important to note that the list prioritizes but does not claim to be exhaustive. Therefore, protecting surface water, as well as groundwater, from these substances, but also from hundreds and thousands of other undesirable and potentially harmful chemical contaminants, is vital.

Recently it has been checked whether EU directives like the WFD are fit for their purpose by examining their performance (EC, 2019). The WFD was checked aside the Environmental Quality Standards Directive, the Groundwater Directive, and the Floods Directive (EC, 2019). While this fitness checks state that in Germany, the implementation of the WFD has led to an improvement of the state of numerous waters as well as to an

increased knowledge of pollutant loads and water quality, it adds that most of Germany's water bodies will not achieve the given 2027 targets (Vermeulen et al., 2019). The process, which started back in 2000, is therefore far from being completed successfully (Maia, 2017), and the question remains which mitigation measures can make a meaningful contribution to achieving the goals that have been set.

A prerequisite for the definition and implementation of mitigation measures is the knowledge of exposure concentrations of chemicals in the aqueous environment. This has led to large monitoring efforts for so-called emerging contaminants such as pharmaceuticals (Richardson, 2009; Gogoi et al., 2018). To focus these efforts on potentially harmful substances, the EU established a watch list in 2015 (EC, 2015) whose purpose it is to enforce the collection of concentration data for those emerging pollutants for which available monitoring data are considered insufficient. The first watch list included diclofenac, three hormones (estrone (E1), 17β-estradiol (E2), and ethinylestradiol (EE2)), and three macrolide antibiotics (erythromycin, clarithromycin, azithromycin). The list is regularly reviewed in order to respond to new information acquisition and to avoid monitoring of substances for longer than necessary. In the second review of the watch list conducted by the Joint Research Centre (JRC) of the EU, it was concluded that diclofenac could be removed. The updated list should instead include the two antibiotics amoxicillin and ciprofloxacin among thirteen other substances (Loos et al., 2018) and the most recent recommendation (Cortes et al., 2020) was to remove all but three substances (the just added amoxicillin and ciprofloxacin and the insecticide metaflumizone) from the list as there has been a sufficient amount of monitoring data gathered in the last years for all other substances.

In recent years, therefore, great efforts have been made, and thus numerous papers have been published to demonstrate the ubiquitous presence of such pharmaceutically active substances in surface waters around the world (e.g. Kümmerer, 2009; Fatta-Kassinos et al., 2011; Boxhall et al., 2012; Ebele et al., 2017). Monitoring data from these studies, but also from numerous other publications, show not only a vast spectrum of substances detectable in water bodies but also a great variability in concentrations of micropollutants in surface water over time and space.

However, it seems obvious that permanent basin-wide monitoring of thousands of contaminants is impossible due to the limited resources in terms of money and time required for sampling, laboratory work and data evaluation. Furthermore, analytical data should always be interpreted in relation to the environmental conditions during sampling, e.g. the values of key parameters such as the river flow (Puckridge et al., 1998). Even if sampling sites have been selected with local conditions in mind, the spatial and temporal variability of monitoring results often cannot be explained satisfactorily by (repeated) grab sampling as this work will demonstrate. The selection of monitoring sites is usually based on local conditions, but not always on objective considerations. On the one hand, immission-based monitoring has been (and partly still is) the standard criterion for a long time, i.e. monitoring sites are being placed directly downstream of known dischargers (e.g. in Lower Saxony; Hensen et al., 2015; Jaeger et al., 2017) as these sites are relatively easy to plan, but often result in sampling with insufficient mixing in the wastewater plume (Vandenberg et al., 2005; Sonthiphand et al., 2013). On the other hand, accessibility of the potential monitoring site is one of the top criteria when planning monitoring campaigns. These points may result in unsatisfactory compromises with respect to the informative value of the monitoring data.

Temporal variability caused above all by the variation of river flow in surface waters over time, is another dimension that has been rather neglected in monitoring campaigns (Bandyopadhyay & Horowitz, 2006). In the Bavarian part of the Danube basin, which will be part of this work, the distances between official WFD monitoring sites and the nearest gauging stations range from a few meters up to 50 km. On average the distance is 9.5km so that often one or more tributaries discharge between the monitoring site and the nearest available site with flow recordings. Due to the well-known influence of discharge variability on substance concentrations (Kasprzyk-Hordern et al., 2008; Madureira et al., 2010; Burns et al., 2018) this hinders diligent evaluation of the data in terms of substance loads. To circumvent this problem, the approach of establishing a conservative marker to cancel out the effect of varying river flow has not been fully successful in finding an appropriate marker substance (Buerge et al., 2004, Cantwell et al., 2017). One the basis of this research one can claim that the general problem of insufficient accounting for temporal variability in monitoring programs has not really changed in recent years and data from random

samples at arbitrary locations are of limited use. Passive samplers that would adjust for differences in discharge (Vrana et al., 2005) are still rarely used as an alternative according to the publications considered in the course of this work. Instead, evaluation of the spatial concentration distribution would require time-consuming and costly monitoring of longitudinal profiles along a whole river preferably more than once a year. Thus, such efforts are restricted to occasionally performed special monitoring campaigns. Samples taken at the same time along a river are occasionally targeted for spatial interpretation, and repeated individual measurements at selected sites are intended to capture temporal variability as best they can (e.g. Baker & Kasprzyk-Hordern, 2013), but all of these approaches can never completely capture the described variabilities.

Consequently, the question arises as to how in-depth surveillance of water quality and reliable risk assessment can be ensured despite these omnipresent obstacles. In the last two decades geo-referenced simulation models have proven numerous times that they can be of great help for exposure and risk assessment. Models such as GREAT-ER (Geo-referenced Regional Exposure Assessment Tool for European Rivers; Hüffmeyer et al., 2009; Kehrein et al., 2015, Lämmchen et al., 2021a), substance flow models set up for Switzerland (Ort et al., 2009; Kuroda et al., 2016) and the Netherlands (Coppens et al., 2015) or the LF2000-WQX water quality model (Price et al., 2010) have been established as valuable support tools for watershed-based risk assessment and the research presented in this thesis contributes to different aspects of this very complex topic.

The already mentioned WFD indirectly supports these approaches by strongly advocating the watershed-based approach (EC, 2000). In the WFD, ‘river basin’ means “the area of land from which all surface run-off flows through a sequence of streams, rivers and, possibly, lakes into the sea at a single river mouth, estuary or delta” (art 2(13)). In terms of the WFD, it is therefore necessary to move towards a transboundary, catchment-related risk assessment. As especially the WFD strongly influences national and regional water policy practices within the EU member states (Jager et al., 2016), the approaches suggested there are decisive for the implementation of measures in Europe.

Especially with the GREAT-ER model, this approach has always been followed (Feijtel et al., 1998). GREAT-ER predicts spatially resolved exposure concentrations for down-the-drain chemicals (Kehrein et al., 2015; Lämmchen et al., 2021a) and always operates on the catchment level. Simulation results can be used to easily identify river sites where elevated concentrations, e.g. above a defined target value (e.g. EQS), are expected. This information can support targeted selection of sampling sites and compliment the interpretation of monitoring data in terms of plausibility. Additionally, simulations of management scenarios for selected reduction measures and a priori evaluation of their effectiveness can be very helpful for water managers (Lämmchen et al., 2021a). The exact mode of operation and the advantages of this method will be explained sufficiently within the scope of this work.

In the year 2016, the well-established GREAT-ER model (Koormann et al., 2006; Alder et al., 2010; Aldekoa et al., 2013) was adopted as version 4.0 (Kehrein et al., 2015). In the course of this PhD research, the model was successively developed further, offering use for novel fields of application in numerous new watersheds. The publications integrated in this cumulative thesis show the main achievements of this work over the past years. The basic application of the model and its further development can be separated into three elementary phases, each represented by one of the papers. In all of these three phases, further model improvements were made which increase the overall quality of model predictions. This work therefore contributes to more valid, robust, and meaningful model predictions and targets weaknesses in existing modeling approaches.

Regarding extended geo-referenced modelling, emphasis was placed on modelling the corresponding watersheds with particular accuracy in order to be able to specifically address local conditions (influence of special hospital departments, high number of very small wastewater treatment plants, special dynamics of the hydrology), through the integration of a large amount of additional (spatial) data for each watershed. The results of this effort show the optimization potential that was feasible in the existing model and the improvements developed since 2016 in terms of pharmaceutical modeling. At the same time, these conditions also made the considered watersheds a challenge to model.

Although the term 'challenging' watersheds[1] does not have a fixed scientific definition, it is used in scientific papers whenever a straightforward creation of a water balance is not feasible, but external factors have to be taken into account. These external factors range from irregular rainfall distributions (i.e., drought and flood periods; Shakirah et al., 2016), additional water input e.g., from cloud water (Strauch et al., 2017) or meltwater (Rahman et al., 2013), to highly variable flow rates (Kronholm & Capel, 2014) that make dealing with the respective study areas infinitely more challenging. In addition, the term 'challenging' is also used to some extent in connection with the pollution of surface waters and the management of water resources (e.g. Geissen et al., 2015), which also applies here. The rough framework of this term is thus used in this work and expanded to include anthropogenic influences that result in the need to specifically analyze and model shifting emission patterns and changes in hydrology (Lämmchen et al., 2021b).

The first article applies the newest model version 4.1 in three different German watersheds and is dedicated to how strongly local influence factors may impact the regional level and how this can be investigated with the model. This part also focuses on modifications and refinements that can be made in the adaptation of already existing simulation runs. The second article examines the adaptations necessary for applying the model in regions with difficult hydrological situations due to strong anthropogenic influence. Here, adjustments and improvements that are made in the preliminary stages (raw data handling) of the actual modeling are especially addressed. The final article then deals with the contributions that the most current GREAT-ER version can make to risk assessment. The main aim here is to gain new insights from simulation results by means of new and expanded approaches to risk assessment.

First of all, the model and the associated model approach are presented in detail, as well as an overview of previous work with the GREAT-ER model in recent years, before examine the three aspects mentioned and the corresponding articles.

[1] When referring to watersheds later in this thesis and the attached articles, the words catchment, basin and watershed are used synoymously

2. GREAT-ER model software

As has been described, the model system GREAT-ER was originally developed for environmental exposure and risk assessment of down-the-drain chemicals in rivers. The core of the system is an emission and fate model that represents the input pathways and fate of chemicals in surface waters (Feijtel et al., 1998; Schowanek &Webb et al., 2002; Kehrein et al., 2015). The model system uses a spatially explicit approach to simulate chemical loads of surface waters. For this purpose, the surface water network is represented by means of two-dimensional geometries that are subdivided into subsections of a maximum length of two kilometers. The sections are attributed with a number of parameters such as river flow, length and flow velocity, which are a required parameter in the simulation routines. The hydrological parameters of river flow and flow velocity are estimated in advance by a hydrological pre-processing routine. Flow is derived from the surface-effective precipitation (surface runoff), which usually exist in form of grid data and can be implemented from available data sources or established rainfall-runoff models. Sub-catchments for all river segments are derived from a digital elevation model (DEM). For each sub-catchment, the total runoff for different hydrological conditions can be estimated by weighted averaging of the grid data on effective precipitation. The slope extracted from the DEM is then used to allocate runoff to the next downstream segment. These values are added up along the flow path to give cumulated runoff (discharge) for each hydrological condition in each segment and calibrated against available data from gauging stations. Flow velocity is estimated mathematically by the model from discharge using the methodology described in Round et al. (1998).

The model allows simulating the input of substances into the water body by point and non-point sources. Typical point sources include wastewater treatment plants that receive untreated wastewater from households, industry or hospitals. Emission sources are provided in the model system with their geographic location and additional attributes, that contain e.g. information about the kind of wastewater treatment, the number of connected inhabitants, the number of hospital beds and other attributes, which are taken into account as simulation parameters by the model. The emitted loads are transported downstream in the water network considering decreases by degradation or other loss processes and dilution. The model calculates both a substance load and a substance concentration for each water body section.

GREAT-ER's model equations calculate emission and waterbody loads assuming steady-state flow and mass conservation. The approach assumes a practically constant input of the substances to be simulated over time and the calculated loads and concentrations therefore each reflect the average load over the course of a year. Furthermore, the mass in the system remains constant during transport, unless it is explicitly changed by emissions or loss processes. Consideration of temporally variable input events or the dynamic change of input parameters is not possible without further ado, as will be discussed in more detail in article 1 of this thesis. The model calculates deterministically with given input parameters, but can be used to estimate the load variability by varying the parameters. For this purpose, a Monte Carlo simulation routine (Raychaudhuri, 2008) is used. Input parameters can be defined as stochastic quantities, e.g., to estimate the natural variability of discharge or uncertainty of chemical inputs. This is addressed in more detail in article 1 as well as in article 2. The Monte Carlo simulation iterates the deterministic model with changing input parameters to obtain an approximation for the unknown distribution of calculated concentrations. Specific sub-models can be used to simulate input pathways and loss processes in the water body, e.g., describing the elimination of the substance amount during wastewater treatment in sewage treatment plants. Another sub-model is for example the hospital sub-model that is introduced in article 1. The fate in the water body is represented by an aggregated first-order degradation rate, which takes into account different loss processes of varying complexity as required (e.g. photolysis, biodegradation, etc.).

The current version of the most important model equations is attached in the appendix of this work. Even if most of the equations have not changed since version 4.0, they are attached to the end of this work for the sake of completeness as a current status was previously last shown in the appendix of Kehrein et al. (2015). Equations that have been changed or added since then are explicitly emphasized in the appendix. The used version 4.1 of the model system is implemented as an extension of the professional geoinformation system ESRI®ArcGIS Desktop 10.5.1. More on the software structure and version history of the model can be found in the appendix as well.

3. Research projects and research areas

This section provides an overview of the different watersheds that have been prepared for application with GREAT-ER over the past four years in research projects with my involvement. The most prominent work was the continuous development of the GREAT-ER database for the Vecht basin, which was the geographic focus of the MEDUWA project[2] funded by the EU INTERREG V program (project number 142118). MEDUWA-Vecht (MEdicine Unwanted in WAter) was a collaboration of 27 Dutch and German companies, universities, hospitals, and private organizations focusing on the transboundary catchment area of the Vecht River. The aim was to develop products and services that reduce emissions of human and veterinary medicines, and as a consequence also the development of multi-resistant microorganisms (especially in water), while supporting the regional economy. One of the most innovative aspects of the MEDUWA project was that it worked simultaneously on several stages of the life cycle of pharmaceuticals. In addition, the project contributes to 7 of the 17 United Nations SGDs (Number 3, 6, 9,11, 12, 14 and 15; UN 2015).

The task of the University of Osnabrück was to develop an easy-to-use tool to identify potential problems caused by contamination with pharmaceuticals in a whole river basin. Furthermore, the effectiveness of reduction measures developed in the project should be evaluated to provide participating companies with results from a priori simulations showing the reduction potential of their products. Together with Geoplex GmbH (Osnabrück), the so-called Watershed Information System (WIS)[3] was developed for this purposes. This is a unique, innovative and user-friendly visualization tool which brings together and manages information about the water quality (in terms of the chemical and biological status) in the entire river basin considering contributions from several sources. All data included was generated during the project by the partners and third parties.
Additionally, results from scenarios on the effects of climate change or special hydrological conditions were included. With all this integrated information, it is possible to simulate and visualize the impact of specific mitigation measures for the entire Vecht basin based on the innovations of project partners. For this purpose, the GREAT-ER model version 4.1

[2] https://www.meduwa.uni-osnabrueck.de
[3] https://meduwa.geoplex.de

(Lämmchen et al., 2021a) was used to simulate the fate of 15 selected pharmaceutical compounds serving as reference for different active pharmaceutical ingredients (APIs) of which eight are incorporated in article 3 (Duarte et al., 2021). Reference scenarios and mitigation scenarios were simulated and compared with each other and the results were integrated and visualized in the WIS. The WIS is well suited to accompany communication and decision-making processes in the field of surface water quality management and constitutes an innovative tool in the context of science communication. This extensive project had a significant influence on this dissertation and two out of three articles therefor deal with the catchment area of the Vecht. Even though no direct project results are presented in the context of this thesis, the corresponding articles resulted from the necessity to deal with certain problems, needs and further developments that arose during the project in terms of model application and that were specifically targeted.

Other watersheds covered during my PhD include the German river basins of Ruhr, Lippe, Danube and Main as well as the whole river system of Luxembourg. These catchments or sub-catchments contained therein (e.g. Naab or Lenne) were investigated as part of projects that have been carried out in recent years in cooperation with state agencies and water boards, e.g. for the Lippeverband[4]. Large parts of this work were summarized in the form of official reports being no scientific publication in the strict sense. With kind permission of the state agencies, monitoring data gathered in these project could be used for the case studies included in the corresponding article. All cooperative projects not only included catchment setup, but also investigating specific aspects and respective improvement of the model tool. For example, the annual mean river flow (Q50), including a customized calibration routine against gauging data, was added as a new hydrological model parameter during a project effort.

All catchments that have been processed in the time of this dissertation (2016-2021) can be seen on the following map (Fig. 1).

[4] https://www.wiwmbh.de/wiw/web.nsf/id/pa_hvalbedhyv.html

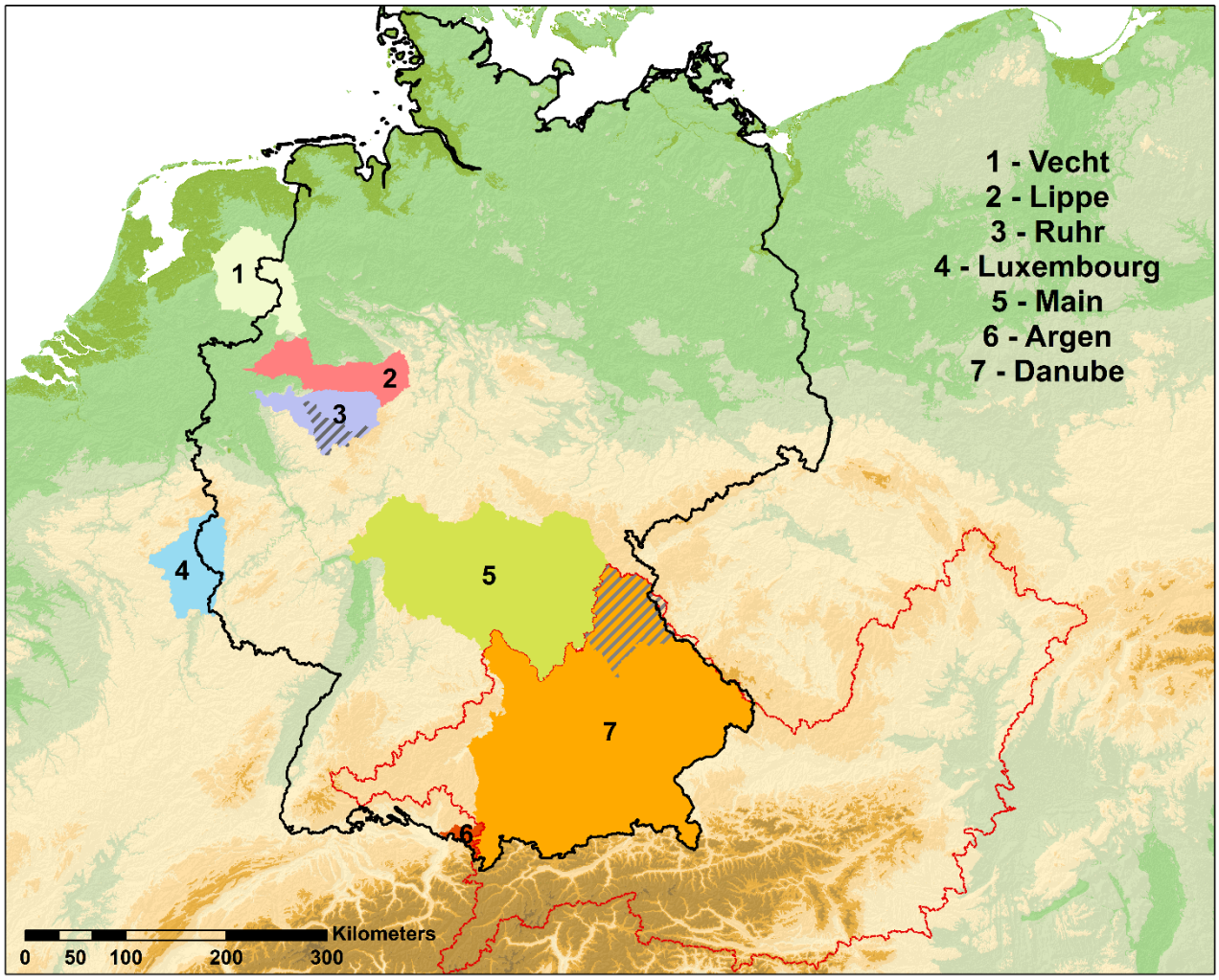

Figure 1: Catchments processed in time of the dissertation (2016-2021). Outlined in red the project area of the Danube which also covered Austria and parts of Baden-Württemberg, the Czech Republic, Hungary and Slovakia, while only the orange area within Bavaria was actually presented in the project report. Cross-hatched in grey are the catchments of Naab and Lenne which are part of article 1. These catchments are part of the Danube and Ruhr catchments area and have been clipped out of these bigger databases and then these sub-basins were examined more closely. The Luxembourg catchment area is a little bigger than the national borders as some rivers are crossing the border (e.g. the Sauer/Sur) and these sub-catchments are included as well.

4. Geo-referenced simulation of pharmaceuticals in whole watersheds: application of GREAT-ER 4.1 in Germany - Article 1

Published as:

Lämmchen V, Niebaum G, Berlekamp J, Klasmeier J, 2021. Geo-referenced simulation of pharmaceuticals in whole watersheds: application of GREAT-ER 4.1 in Germany. Environ. Sci. Pollut. Res. (28), 21926–21935. https://doi.org/10.1007/s11356-020-12189-7

The first research article related to this thesis presents new features of the GREAT-ER model by application to selected pharmaceuticals in three German catchments. As explained, starting point of this thesis was GREAT-ER version 4.0 (Kehrein et al., 2015) which was then further developed to version 4.1 under joint conceptualization of the entire working group. While the actual program coding was mostly implemented by other PhD students, the focus of this publication is on the application of the novelties conceived. More about this topic can be found in the appendix of the thesis and a detailed listing of the exact contributions of each author to this article can be found in the authors contributions section included at the end of the article.

The article itself describes the highlights of version 4.1 such as the explicit inclusion of hospital emissions in the simulation routine by the new hospital (sub)model and an actual management scenario. In addition, a probabilistic simulation was performed at the beginning to evaluate the model performance. Each of these elements was exemplary described in specific case studies in specifically selected watersheds to best demonstrate the functionality, effects and impact of the new features.

For the probabilistic simulation, the antibiotic clarithromycin was studied in the Main catchment area. This catchment was selected, because evaluation of the probabilistic simulation routine requires monitoring data over a longer period for comparison which could be applied from a previous monitoring campaign of the Bavarian Environmental Protection Office (LfU) between 2010 and 2017 in the respective area. At the same time, the issue of antibiotic resistance gained urgency in recent years (e.g. MacGowan & Macnaughton, 2017; Aslam et al., 2018). Recent research indicates that the environment is

an important component in the transmission of resistant bacteria and in the emergence of resistant pathogens (Bengtsson-Palme et al., 2017) and entire antibiotics groups as macrolides for example are at risk of being rendered ineffective by the development of this resistances (Chironna et al., 2011; Schroeder & Stephens, 2016). Among the substances for which sufficient monitoring data for model evaluation were available therefore the macrolide antibiotic clarithromycin was selected, which also has been placed on the EU Watch List (EC, 2015) and is widely used in Germany (Baumann et al., 2015).

The Lenne River catchment area was selected for demonstration of the benefit of the hospital sub-model. Here, a monitoring station operated by the Ruhrverband directly downstream of the hospital housing the only radiological department in the catchment area was important for evaluation of the model. Such a situation was supposed to strongly affect the regional distribution of X-ray contrast media, which are more or less exclusively applied in radiological treatments (Weissbrodt et al., 2009). The hospital sub-model allows for representation uneven consumption patterns by attributing specific consumption figures to individual hospitals based on available information on the department structure. Compared to the standard scenario, in which total consumption in hospitals is simulated as evenly distributed via a general proxy, the consumption for the individual hospital could be adjusted to the real situation while the values were accordingly reduced for all other hospitals. The case study clearly illustrates the extent to which model results that were already well evaluated regionally can be adjusted to better represent local conditions. This finding was well supported by the comparison of model simulations with monitoring data.

In order to show the state-of-the-art applicability of the model, a real existing measurement strategy was implemented in the last case study. In general, there are several ways to achieve the improvements called for in the WFD. One of the existing strategies in Germany is the closure of very small wastewater treatment plants (defined as ‘Kleinkläranlagen’ with less than 2,000 connected inhabitants), which exist especially in rural areas (UM, 2008). Their wastewater is then rerouted to larger centralized plants (UM, 2017; SMUV, 2018). These larger plants can be operated with less money and upgraded for better removal efficiency more easily if the necessity is identified at a stage. This approach has been translated in a GREAT-ER simulation scenario within the Naab catchment. The Naab is a

tributary of the Danube River characterized by a large number of small wastewater treatment plants. It is therefore best suited to simulate the implementation of such a strategy a priori. Ethinylestradiol, the active ingredient contained in the contraceptive pill, was selected as exemplary substance due to several reasons: The substance is widely used for comprehensible reasons and is therefore present almost ubiquitous in surface waters all over the world (Hannah et al., 2009). At the same time, the concentrations of the substance in surface waters are mostly so low (pg/L range; Kuch & Ballschmiter, 2001; Sumpter & Jobling, 2013) that quantification and detection with current analytical techniques is very difficult if not impossible (Loos et al., 2018). The substance has also been shown to cause some environmental effects of concern (Laureson et al., 2014) and has been placed on the EU Watch List. This situation is almost predestined for the GREAT-ER model to support possible future decision-making. In this case, the model can help to better understand the overall situation through simulation and can then be used primarily to evaluate the impact of any measures that could not be evaluated with pure sampling alone.

Geo-referenced simulation of pharmaceuticals in whole watersheds: application of GREAT-ER 4.1 in Germany

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Received: 14 August 2020 / Accepted: 21 December 2020 / Published: 07 January 2021

Abstract

The geo-referenced regional exposure assessment tool for European rivers (GREAT-ER) is designed to support river basin management or the implementation process within the EU Water Framework Directive by predicting spatially resolved exposure concentrations in whole watersheds. The usefulness of the complimentary application of targeted monitoring and GREAT-ER simulations is demonstrated with case studies for three pharmaceuticals in selected German watersheds. Comparison with monitoring data corroborates the capability of the probabilistic model approach to predict the expected range of spatial surface water concentrations. Explicit consideration of local pharmaceutical emissions from hospitals or private doctor's offices (e.g., for X-ray contrast agents) can improve predictions on the local scale without compromising regional exposure assessment. Pharmaceuticals exhibiting low concentrations hardly detectable with established analytical methods (e.g., EE2) can be evaluated with model simulations. Management scenarios allow for a priori assessment of risk reduction measures. In combination with targeted monitoring approaches, the GREAT-ER model can serve as valuable support tool for exposure and risk assessment of pharmaceuticals in whole watersheds.

Keywords

Geo-referenced modeling, Environmental fate, Pharmaceuticals, Exposure assessment, River basin management, GREAT-ER model

Introduction

A major problem for humankind is access to clean and readily available drinking water. Therefore, protection of groundwater and surface water against unwanted and potentially harmful chemical contaminants is important. The European Water Framework Directive

(WFD) constitutes a legal framework that imposes the protection of common water resources on European states (EU 2000). The call of the directive among other things is the good chemical status of European surface waters. To achieve this goal, exposure and risk assessment of micropollutants, including pharmaceuticals, followed by development and implementation of reduction measures for critical compounds is necessary. Currently, the WFD lists 45 priority substances in Annex X of the directive and sets environmental quality standards for each of these substances. A prerequisite for the definition and implementation of mitigation measures is knowledge of the exposure concentrations of chemicals in the aqueous environment. This has led to large monitoring efforts for so-called emerging contaminants such as pharmaceuticals. To focus these efforts on potentially harmful substances, a watch list was established in 2015 whose purpose is to enforce collection of concentration data for those emerging pollutants for which available monitoring data are considered insufficient. The first watch list included diclofenac, three hormones (estrone (E1), 17β-estradiol (E2), and ethinylestradiol (EE2)), and three macrolide antibiotics (erythromycin, clarithromycin, azithromycin). The list is regularly reviewed in order to respond to new information and to avoid monitoring of substances for longer than necessary. In a recent review conducted by the Joint Research Centre (JRC) of the EU, it was concluded that diclofenac could be removed and the updated list should instead include the two antibiotics amoxicillin and ciprofloxacin among thirteen other substances (Loos et al., 2018).

In the last years, numerous papers have been published demonstrating the ubiquitous presence of pharmaceutically active substances in surface waters all over the world (e.g., Ivešić et al., 2017; Chiffre et al., 2016; Nebot et al., 2015). The monitoring data show a large variability of micropollutants' surface water concentrations in time and space. Consequently, each data point should always be interpreted in relation to environmental conditions during sampling, e.g., values of key parameters such as river flow. However, it is obvious that permanent basin-wide monitoring of thousands of possible contaminants is virtually impossible. Moreover, even if selection of sampling sites has been done considering local circumstances, spatial variability of the monitoring results can often not be satisfyingly explained. At this point, geo-referenced simulation models can be of great help for exposure and risk assessment such as the GREAT-ER model (Kehrein et al., 2015). Other prominent examples are substance flow models set up for Switzerland (Ort et al.,

2009; Kuroda et al., 2016) and the Netherlands (Coppens et al., 2015) or the LF2000-WQX water quality model (Price et al., 2010).

The well-established model GREAT-ER (Geo-referenced Regional Exposure Assessment Tool for European Rivers) predicts spatially resolved exposure concentrations for down-the-drain chemicals (Kehrein et al., 2015; Aldekoa et al., 2013; Alder et al., 2010; Koormann et al., 2006; Feijtel et al., 1998). Simulation results can be used to easily identify river sites where elevated concentrations, e.g., above a defined target value (PNEC or EQS), are expected. This information can support targeted selection of sampling sites and compliment the interpretation of monitoring data in terms of plausibility. Additionally, simulations of management scenarios for selected reduction measures and a priori evaluation of their effectiveness can be very helpful for water managers.

The objective of this paper is to illustrate the capabilities and limitations of GREAT-ER 4.1 using meaningful case studies for selected pharmaceuticals in three different German catchments. In particular, we demonstrate (1) the usefulness of the probabilistic model approach to consider natural variability of river flow that is reflected by the temporal variability of measured concentrations at selected sites, (2) the explicit consideration of hospital wastewater emissions important for pharmaceuticals predominantly emitted at the location of treatment, (3) basin-wide exposure assessment for substances with low PEC and EQS values, and (4) the informative value of management scenario simulations.

The GREAT-ER 4.1 model software

How the model works

The GREAT-ER model calculates spatially explicit steadystate concentrations of down-the-drain chemicals in surface waters of entire catchment areas considering point and non-point emissions from different sources assuming more or less constant emissions over time (Kehrein et al., 2015; Hüffmeyer et al., 2009). In general, wastewater from households, hospitals, and industry as well as runoff from agricultural areas can be taken into account as emission sources. Household emissions are treated according to the place of residence using an average per capita consumption value. In GREAT-ER 4.1, a hospital sub-model to investigate the local effect of hospital wastewater on the concentrations of selected medicinal agents has been adopted. The number of total patients (or beds) in hospitals has

been suggested as appropriate proxy for respective emissions from a single hospital (Kuroda et al., 2016). Therefore, GREAT-ER 4.1 requires a per patient consumption value in this case.

The model uses mass balance equations that track the chemicals along the emission pathways into surface water including removal in wastewater treatment plants (WWTPs). Sedimentation, volatilization, and degradation by photolysis, hydrolysis, or biological processes are considered as pseudofirst-order in-stream loss processes. Mass conservation applies to each segment, so that the mass flow at the beginning corresponds to the mass flow at the end, unless it has been changed by diffuse emissions or loss processes. In the model, the river network is represented as a hydrological geometric network which is subdivided into segments (edges) of maximum length of 2000 m. Nodes are set at all confluences, point emission sites, and other points of interest (e.g., gauges, monitoring sites, weirs). Emission loads from point sources (mainly WWTPs) are estimated by a series of submodules. The loads are discharged into the receiving river at the respective node and are then transported further downstream in the model. Loads are expressed in terms of mass per unit time and are considered constant over time in order to obey to the steadystate assumption.

The model requires a number of substance-specific input parameters as well as environmental attributes. This encompasses physicochemical data, consumption, and use patterns as well as removal efficiencies during sewage treatment. The latter is modeled as simple percentage removal whose efficiency depends on the specific treatment category (lagoon, constructed wetland, bio filter, or activated sludge). Each river segment possesses a vector of attributes, e.g., flow velocity and river flow, which is used for the calculation of required intermediate parameters such as travel time. Depending on the available information, the user can choose between different complexity modes for the different submodules. A detailed description of the model equations is given in the appendix of Kehrein et al., (2015).

Natural variability of environmental parameters, uncertainty of substance parameters, and temporal fluctuation of consumption patterns can be considered by a probabilistic Monte Carlo approach. As opposed to deterministic model runs, corresponding parameters are not fixed, but defined as probability distributions of random variables. The distributions

represent the expected frequency with which a parameter will take a single value. Probabilistic model runs are performed iteratively with parameter value vectors chosen from the probability distributions. The model calculates concentration distributions for each river segment mapping the expected range of the temporal variability for the selected parameter combinations. The output can be used to calculate any percentile of the respective concentration distribution. Results are primarily presented as color-coded maps or concentration profiles along a selected river course (see Figs. 2 and 4 in the case study section). In addition, a number of options for in-depth analyses of the results are implemented. Another key feature of the GREAT-ER model is the scenario builder. It enables the user to evaluate the effect of defined changes in boundary conditions on the simulated concentrations. Potential scenarios include changes in consumption, technical retrofitting of sewage treatment plants (tertiary/quaternary treatment), or re-routing of wastewater.

How to prepare a GREAT-ER database

The GREAT-ER model core is delivered as Add-In for the commercial software ArcGIS Desktop®. The GREAT-ER philosophy follows the idea of river basin management as laid out in the EU Water Framework Directive. This means that model simulations are performed within whole catchments including all watercourses with perennial flow. All required data for the simulations must be stored in a catchment-specific database. The databases need to have a standardized structure, which is assigned during the so-called pre-processing. Here, raw data are processed to form the topological river network, to connect point sources (WWTP, industry, and hospitals), and to assign other data (gauges, monitoring sites) to the respective river segments.

Over the years, GREAT-ER has become increasingly complex due to new simulation and analyses features to fulfil the needs of different users such as scientists, authorities, (environmental agencies) and industry, and the demand for the tool has continuously increased. However, one of the major obstacles for widespread use of the model was the laborious preparation of the required data set for the catchment under investigation. Preparation of an executable database for a selected river basin demands a number of pre-processing steps, which has so far impeded broad application of the model by different users. This problem has been partly overcome since the freely available model version now

comes along with a semi-automated data processing routine for catchment preparation, several tutorials, and an exemplary dataset of a hypothetical catchment with which users can set up a GREAT-ER database and familiarize themselves with its practical use. This forms a sufficient knowledge base for interested users to generate their own catchment database and proceed with the full version GREAT-ER 4.1.

A prerequisite for GREAT-ER simulations is assignment of realistic flow rates for average conditions (MQ), dry weather (MNQ), and the 50th percentile (Q50) to each river segment. There are numerous hydrological models (e.g., SWAT or NASIM) that can be used to estimate these data independently and import them into the GREAT-ER database. The GREAT-ER pre-processing provides an alternative semiautomated procedure to estimate river flow for each segment from spatially resolved runoff data for the whole catchment. Regardless how the MQ and MNQ values for each segment were estimated, they are calibrated against available gauging data before use. Substance-specific parameters have to be entered manually into the respective fields of the database. Selected attributes in the database (e.g., number of people connected to a treatment plant) can be edited to keep it up-to-date.

Case Study simulations

For the application of the model, three different pharmaceutical compounds in three German river basins of different size (see Fig. 1) have been simulated. The specific characteristics make them suitable to demonstrate some of the main benefits of the new model version for exposure (and risk) assessment. The selected substances were the antibiotic clarithromycin, the X-ray contrast agent iopamidol, and the natural hormone ethinylestradiol (EE2). All simulations were performed applying the implemented Monte Carlo simulation routine with 10,000 model realizations. All substance properties used for the model simulations are given in Table S1 in the SI. The location of the three catchments is shown in Fig. 1; basic characteristics are summarized in Table S2 in the SI.

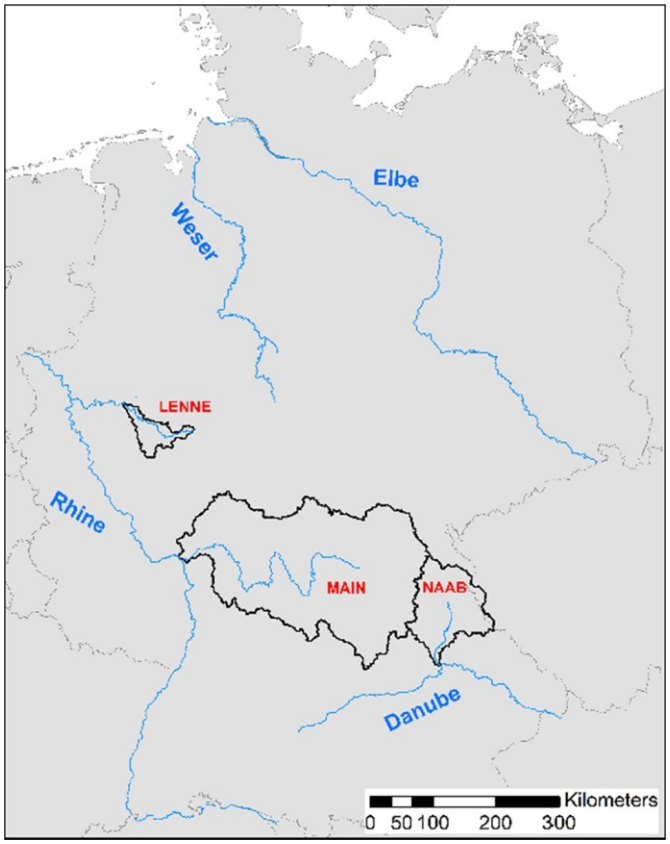

Fig. 1: Location of the three German case study catchments: Main (1), Lenne (2), and Naab (3)

Results and discussion

Simulation for clarithromycin

Figure 2 shows predicted mean environmental concentrations (PEC), in the whole river basin in form of a color-coded map. This provides a quick overview of the spatial distribution of expected concentrations in the whole watershed and allows for easy identification of river segments with elevated concentrations. The environmental quality standard (EQS) of 130 ng/l for clarithromycin defined in the EU Water Framework Directive (WFD) (Carvalho et al., 2015) is only exceeded in a few small creeks with mean concentrations of up to 187 ng/l (red segments marked by circles in Fig. 2).

The EU Commission Directive 2009/90/EC (EU 2009) specifies that an exceedance of EQS is incurred when the mean value of all measurements is above this threshold value. From the simulation results, it can be concluded that the majority of the river network will meet

this regulatory criterion. Nevertheless, due to the large variability of river flows, concentrations may occasionally exceed the EQS at more sites even when mean values are below (Ort et al., 2010a). This can be investigated using the results of the probabilistic simulation. The probability distribution represents the expected variation of concentrations over time due to discharge fluctuations and input parameter uncertainties. Comparison with monitoring data was performed at six sites (locations shown in Fig. 2), for which multiple clarithromycin measurements were available (see Fig. 3). These sites cover a wide range of average river flow in the catchment going from 2 m3/s (site 6) up to more than 200 m3/s (site 1). Figure 3 demonstrates that the range spanned by the 10th and 90th percentile of simulated concentrations (displayed in grey) well represents the temporal variability of the monitoring data points at the six sites. At least 80% of the data points are within the respective probability range.

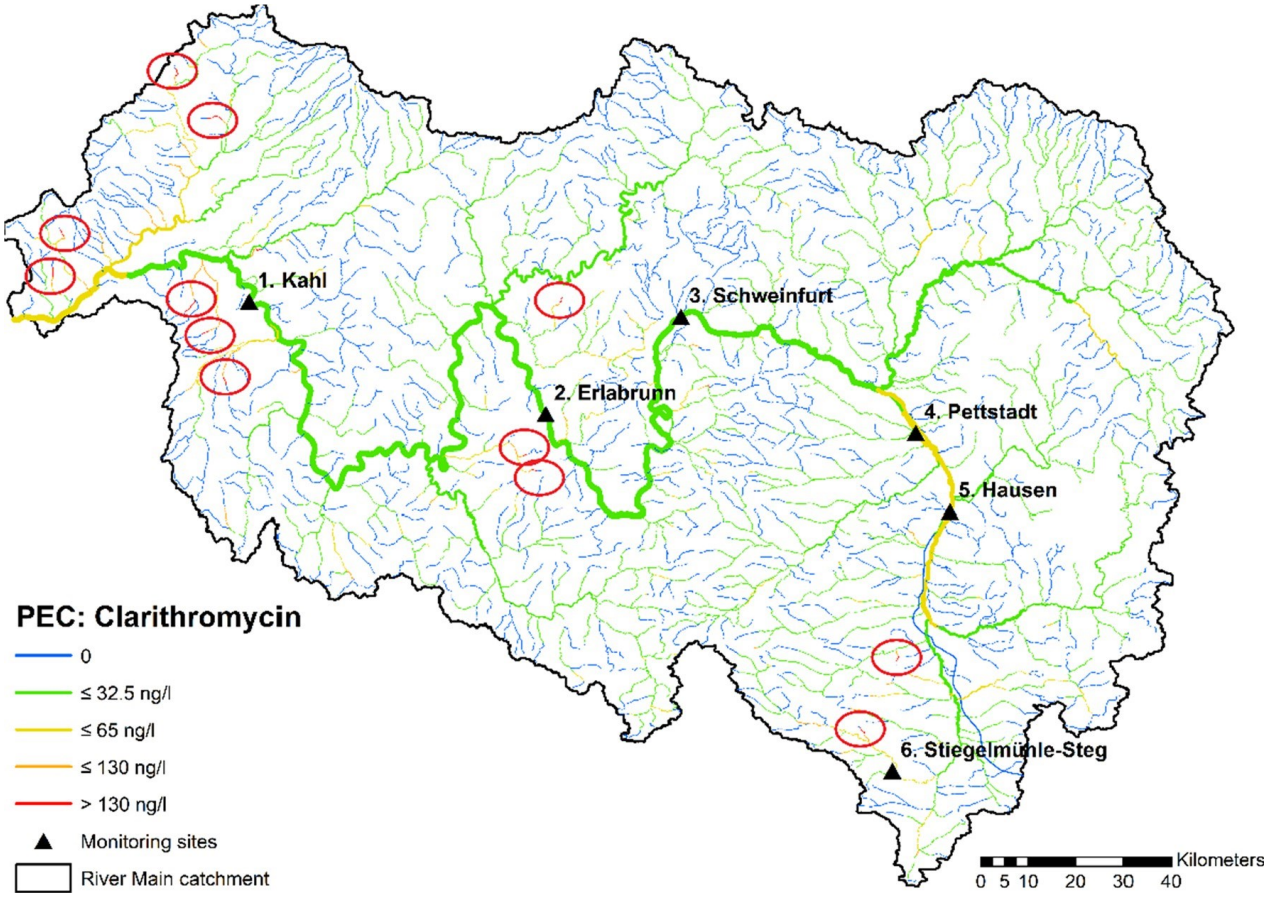

Fig. 2: Color-coded map of average clarithromycin concentrations in the Main catchment predicted by GREAT-ER; hot spots (sites with highest concentrations) are highlighted by red circles; the six monitoring sites are marked as black triangles

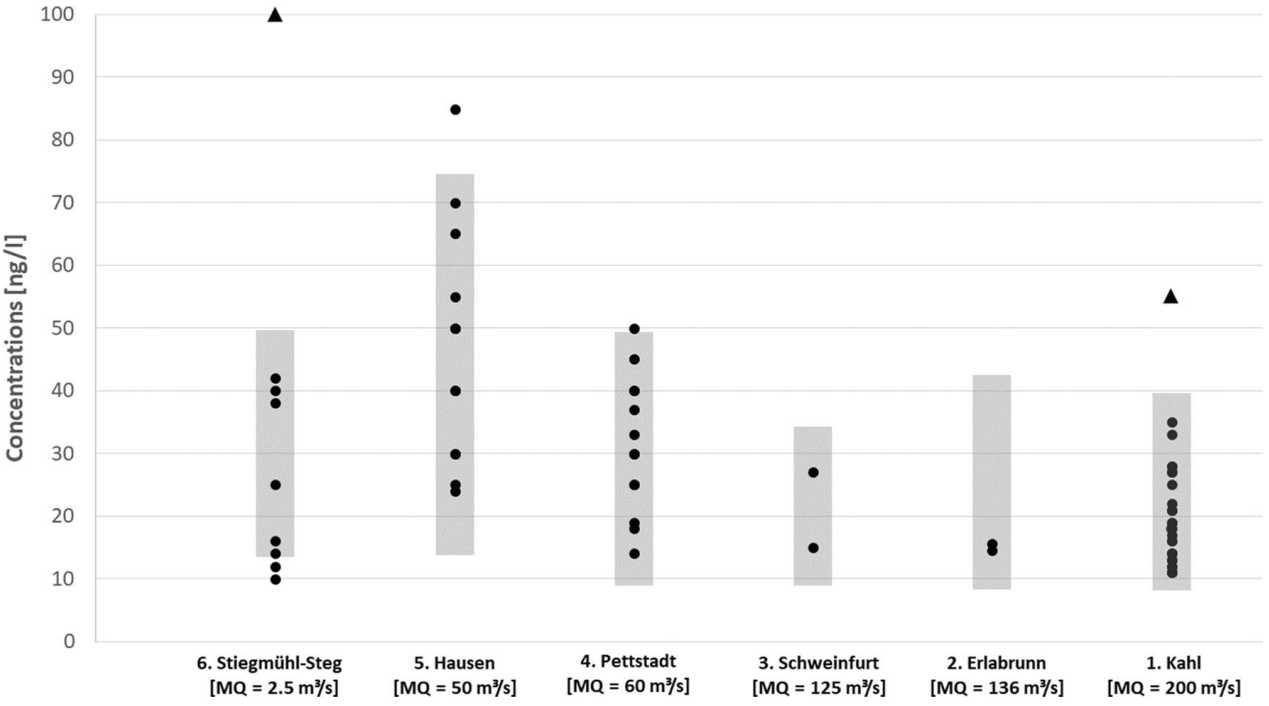

Fig.3: Comparison of clarithromycin measurements taken between 2010 and 2017 at the monitoring sites 1–6; sorted according to MQ; marked in grey the 10th-to-90th percent interval of 10,000 simulations runs. Two outliers according to Dean-Dixon test ($p < 0.01$) are marked with a triangle

On top, the Dean-Dixon test (Dean and Dixon 1951) for small samples (n < 30) identified the two extremely high data points at sites 1 and 6, respectively, as outliers at a significance level of p = 0.01. The high concentration value of 100 ng/l at site 6 (Stiegmühl-Steg) may be explicable by specific temporal emissions due to the occurrence of combined sewage overflow (CSO) events. In the sampling period, intense precipitation in the area was recorded resulting in high flow rates approximately 50% above annual mean flow. It could well be that the water sample was affected by a recent CSO event having introduced large amounts of untreated wastewater. Consequently, emission loads of clarithromycin may have temporally jumped up even overcompensating the dilution effect by the higher flow rate.

Simulation of iopamidol concentrations in the Lenne catchment

X-ray contrast agents such as iopamidol are applied exclusively in hospitals or private doctor's offices for radiology. More than 90% of the applied dosage is excreted via urine within the first 24 h after administration (Duchin et al., 1986). In Switzerland, approximately 50% of X-ray contrast media are administered to stationary inpatients, and

75% of the dosage is already excreted in the urine within 4 h (Weissbrodt et al., 2009). Emissions from stationary treatments will surely enter the wastewater cycle at the location of medicinal treatment. We presume that additionally the first urinary excretion of treated non-stationary patients within the 4 h window will also occur at the treatment site so that 87.5% of the total administered dose was emitted there.

For GREAT-ER model simulations, the iopamidol fraction excreted at the site of medicinal treatment (87.5%) was allocated to the eleven hospitals located in the Lenne catchment proportional to the total number of patients treated in the individual hospital. The resulting emission loads are then routed into the receiving sewage treatment plant, since hospitals are not directly emitting their wastewater into the river basin. The remaining emission fraction from prescriptions to nonstationary patients (12.5%) is still considered by the usual per capita approach according to the place of residence principle. This fraction represents the total iopamidol emission from patients after leaving the hospital or private doctor's office and returning home. Figure 4 shows the result of the probabilistic simulation (n = 10,000) based on these assumptions (standard scenario).

The simulation results were compared with monitoring data for iopamidol at six locations (M1–M6) provided by the State Agency for Nature, Environment and Consumer Protection, North Rhine-Westphalia for the period from 2009 to 2015. Five sites are located along the Lenne River, while another one (M6) is in a small tributary, which enters the Lenne between M1 and M2.

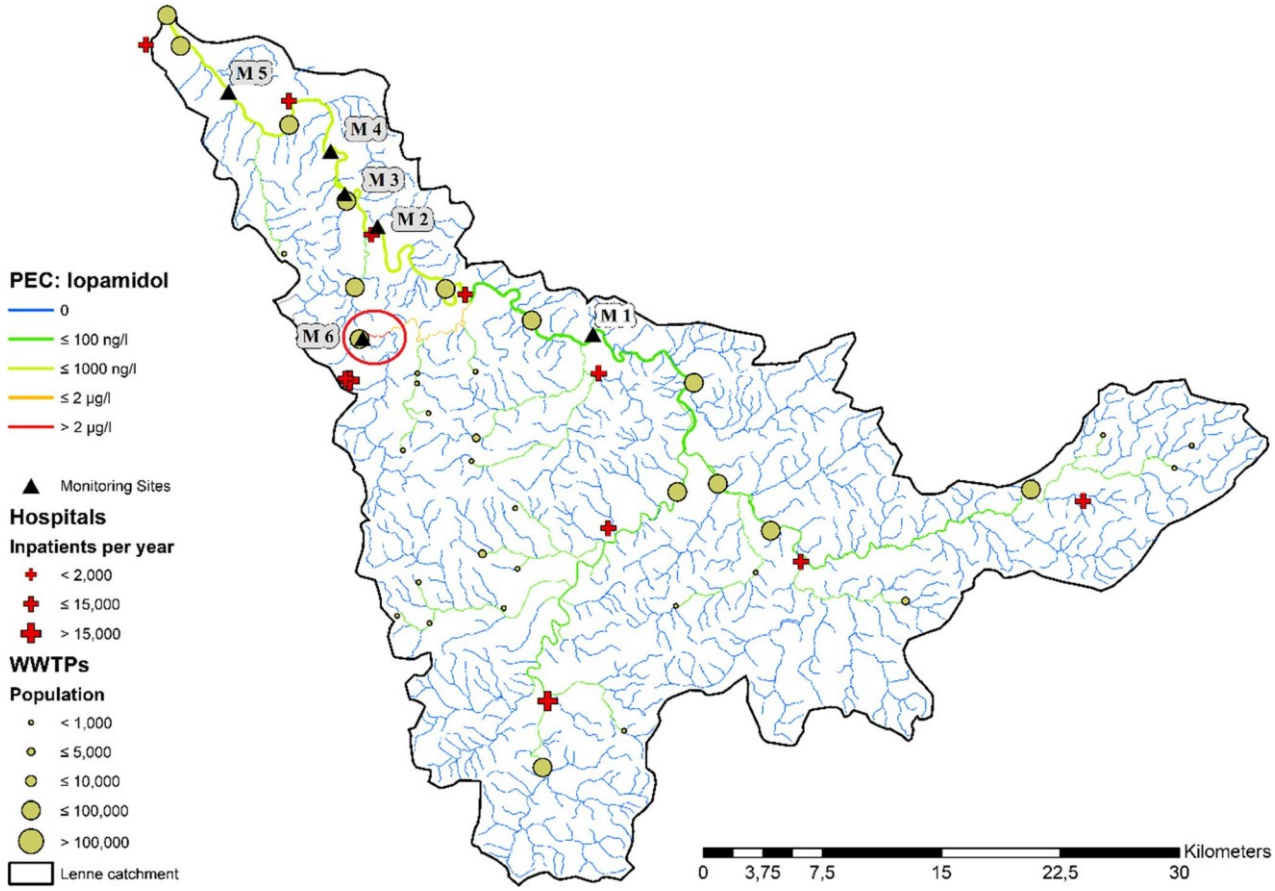

Fig. 4: Color-coded map of the simulation results of a GREAT-ER model run (n = 10,000) for iopamidol in the Lenne catchment. The six monitoring sites (black triangles) are numbered from M1 to M6

This site had been sampled on purpose to check the possible influence of the nearby hospital. Figure 5 (left) shows that the underlying model assumption of evenly distributed per patient consumption in hospitals (standard scenario) does not well reflect the overall situation of iopamidol concentrations in the Lenne basin. It turned out that the standard scenario underestimates the concentrations measured at M6, while data points at M1 were overestimated (see Fig. 5). At M6, even the 90th percentile of the simulation (31 µg/l) is below the four data points (46–110 µg/l) indicating stronger local influence of the nearby hospital. Further downstream (M2–M5), however, the results of the standard scenario simulation agree well with monitoring data.

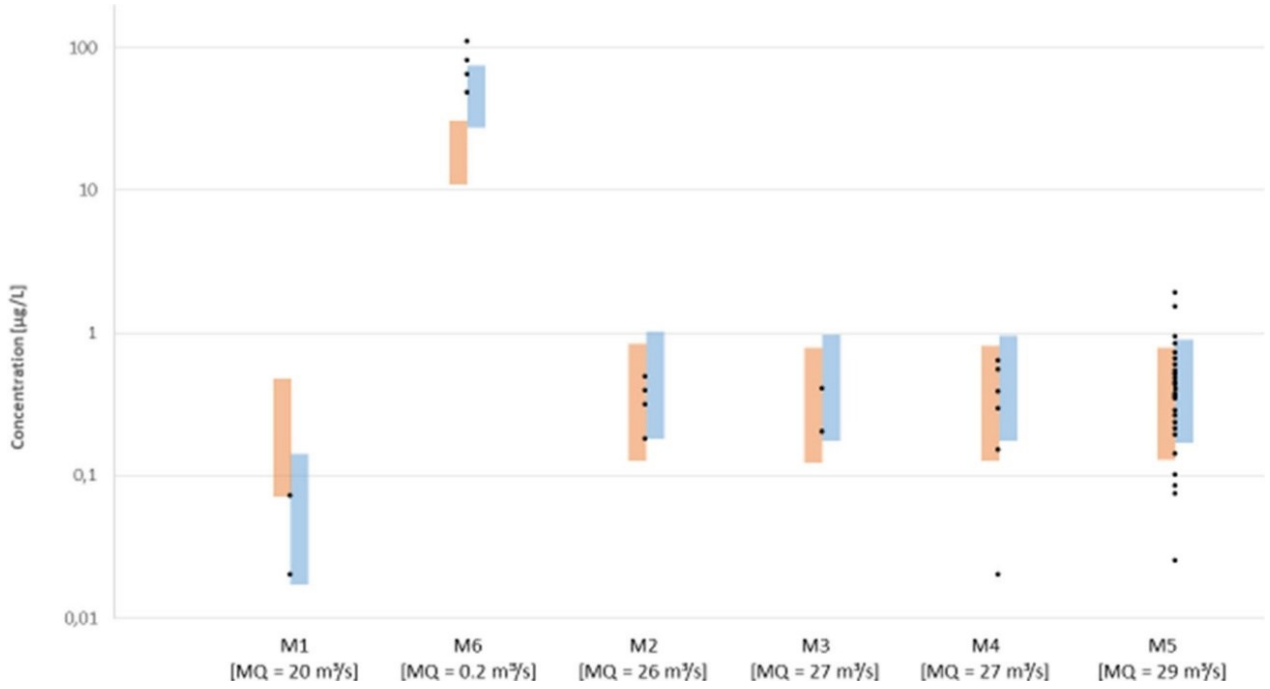

Fig.5: Comparison of the 10th-to-90th percent predicted concentration intervals of two probabilistic simulations (each n = 10,000). On the left (orange): interval for the standard scenario. On the right (blue): simulation with consideration of local hospital consumption patterns. Monitoring sites M1–M6 are arranged according the flow path of the Lenne; M6 is integrated according to the position of the tributary

It has already been shown that for some pharmaceuticals, the size of the hospitals alone could not always explain observed variations in hospital emissions (Kuroda et al., 2016; Kern et al., 2015). Thus, an overall per patient consumption without taking into account the presence or absence of specialized departments as proposed by Ort et al., (2010b) is not generally applicable. For more realistic local emission estimates, specific information such as department structure, stationary patients, and bed or dosage numbers should be considered if available. Since iopamidol is above all administered in specific radiology departments, the total number of patients may not be the best proxy for estimation of individual hospital emissions. Detailed review then revealed that there is only one hospital in the area, for which a radiology department is officially reported. Most likely, this hospital carries out the majority of radiological treatments with contrast agents relative to the total case numbers per year, as none of the other hospitals in the area is specialized in this field. Thus, for a second scenario, iopamidol emissions from hospitals were individually adjusted to increase the degree of realism in the model assumptions: The receiving WWTP of the respective hospital with radiology department was now loaded with an above average

fraction of the iopamidol emissions, while the other hospitals' contributions were decreased accordingly in order to keep the total emission constant. Before the adjustment, iopamidol emissions from hospitals were evenly distributed depending on their size (number of beds and patients). In the adjusted scenario, the single hospital with the radiology department is assumed responsible for 90% of the iopamidol hospital emissions (79% of overall emission). WWTP emissions from diffuse excretion away from the treatment location remained unchanged at 12.5% of total emissions, since reallocation of hospital contributions does not effect this number. Figure 5 shows simulated concentrations of iopamidol for the two scenarios compared to measured data.

The spatial redistribution of iopamidol hospital emissions in the model leads to a much better agreement with monitoring data as compared to the standard scenario at M1 and M6 (see Fig. 5, right), while further downstream (M2–M5), the previous good agreement persists. The model thus allows for consideration of local impacts of hospitals on surface water concentrations for specific pharmaceuticals, while the regional evaluation is only marginally affected. The analysis for iopamidol in the Lenne basin demonstrates that substances predominantly applied in large amounts at hospitals or private doctor's offices experience a shift in their spatial concentration distribution that may locally be dependent on the presence or absence of specific medicinal departments.

Simulation for ethinylestradiol in the Naab catchment

EE2 was chosen as exemplary compound, because it was on the first WFD watch list (2013) and remained part of the second edition (2018). Although extensive monitoring data have been already collected across Europe, the informative value of the data is still low due to the insufficient limit of quantification (LOQ) of the analytical methods. Only half of the responsible countries were able to quantify EE2 concentrations in the range of the EQS or below (Loos et al., 2018). This is where GREAT-ER simulations can be supportive, since for EE2, the model provides the sole possibility to get a comprehensive picture of the expected concentration range in a whole river basin even when concentrations are below the LOQ.

The standard scenario representing the predicted status quo of average EE2 concentrations in the Naab catchment is displayed on the left-hand side of Fig. 6. The map reveals that

EE2 concentrations in most of the river reaches do not exceed the currently proposed EQS of 35 pg/l (Loos et al., 2018). Moreover, only 65 km of the 2077 km flow length in the Naab basin downstream of WWTPs is predicted to exhibit EE2 concentrations detectable with the standard analytical procedures. Thus, comprehensive exposure assessment by monitoring cannot be achieved for EE2.

It is also seen that concentrations are highest in small creeks receiving wastewater from one of the 102 small treatment plants serving less than 1000 inhabitants (marked as small green dots in Fig. 6) with unfavourable dilution ratios. GREAT-ER provides a valuable tool to support authorities in decision-making by a priori simulation of the effect of mitigation measures. Therefore, we investigated the effect of a common strategy in the implementation process of the WFD in Germany, namely, re-routing of wastewater from these small WWTPs to the closest treatment plant with higher capacity (e.g., SMUV 2018; UM 2017). This closest distance boundary condition has been selected to minimize the length of additional sewer pipes for re-routing.

The result of this management scenario is shown in Fig. 6 (right) as relative comparison with the standard scenario. For river reaches displayed in green, PEC values in the action scenario are lower by at least 5% compared to the reference (improvement), while red river parts exhibit higher values (deterioration). Concentration changes of less than ±5% are regarded insignificant and thus marked gray.

In total, lower concentrations are predicted for 655 km flow length (32%) after re-routing, while only 91 km of the river system shows an increase in concentration of more than 5%. 6.1 km is now predicted to be above the EQS where there was no exceedance before, while 38.9 km is now below, resulting in a net relief of 32.8 km in sum. This is a direct consequence of the closest distance boundary condition. In the action scenario, redirection of wastewater does not always occur strictly downstream, because the closest larger treatment plant was sometimes located in another tributary's sub-basin. In this case, water managers would have to evaluate different alternatives to find the best compromise between cost and effect. This case study demonstrates how the GREAT-ER model can support them to do so. In the first step, it provides information about the actual exposure situation (status quo) which allows for deciding whether there is a need for action at all. In the second step, the expected effect of

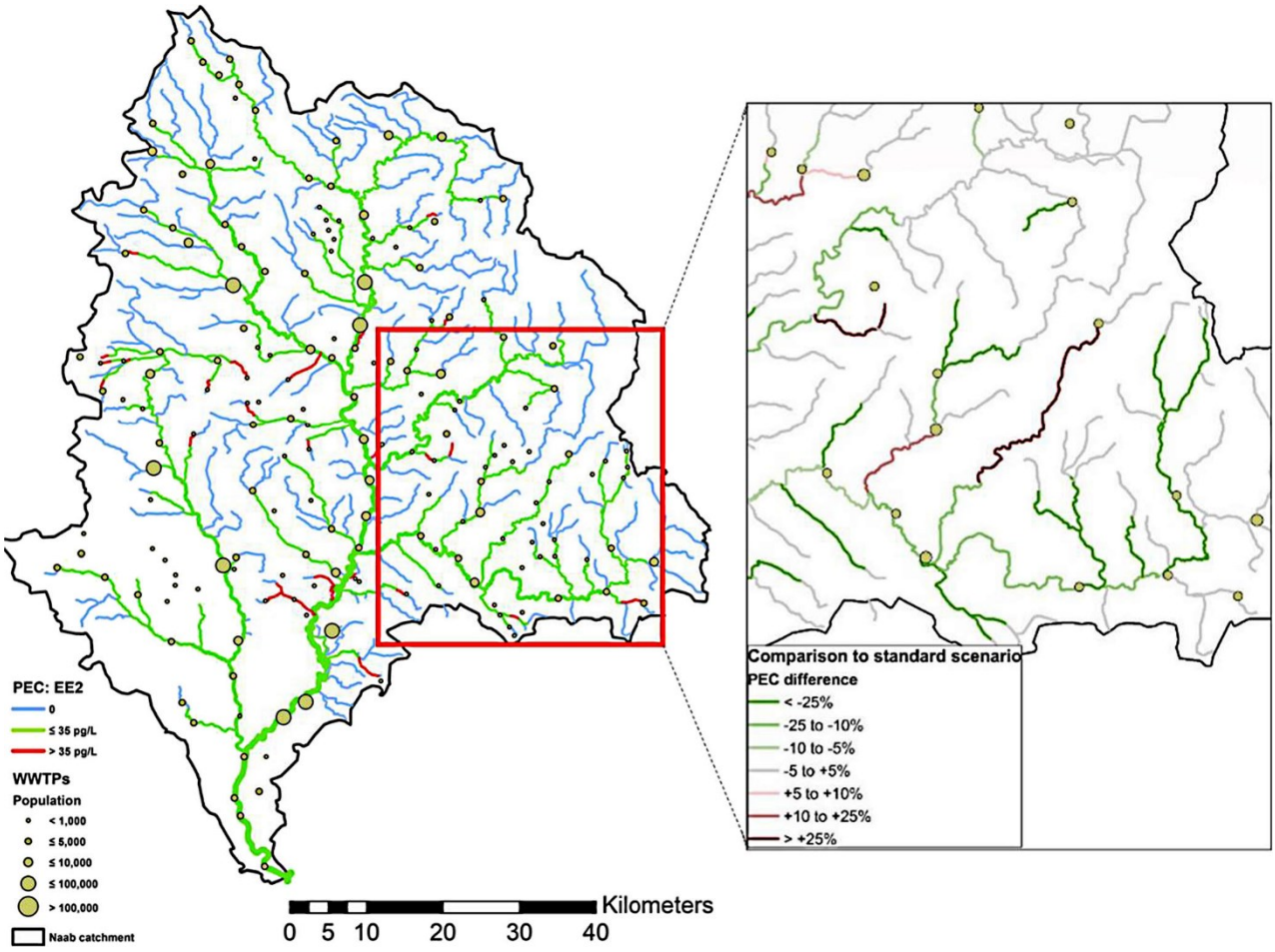

Fig.6: Left panel: PEC/EQS standard scenario. Right panel: relative change in PEC between action scenario and standard scenario for an exemplary area in the Naab catchment

selected measures can be evaluated in order to allow for implementing the most promising strategy taking into account cost-benefit considerations. In the case of EE2, GREAT-ER simulations predict mean concentrations in the Naab basin mostly below the current EQS so that immediate action does not seem to be necessary.

Conclusions

The geo-referenced steady-state model GREAT-ER simulates the spatial concentration distribution under the assumption of steady state for specific boundary conditions. It was shown that probabilistic simulations considering natural variability of river flow and/or uncertainty of model parameters well predict the expected range of concentrations. We conclude that exposure assessment in river basins should not solely rely on a restricted

number of monitoring data but make use of the complementary GREAT-ER model approach.

However, the general assumption of more or less evenly distributed emission patterns does not hold true for pharmaceuticals administered in large fractions in hospitals or private doctors' offices. While this does not largely affect exposure assessment on the regional scale, local assessment may fail for such compounds if the flow path of hospital wastewaters is not explicitly considered in the model representation. Exposure and risk assessment for micropollutants at low concentrations in the range of the limit of detection constitutes a particular challenge. A prominent example for this dilemma is EE2 due to its low exposure concentrations and the low EQS value proposed. While in such cases monitoring alone is not sufficient for basin-wide exposure assessment, this can be achieved with the support of the GREAT-ER model.

An essential part of the GREAT-ER software is the ability to create and analyse specific action scenarios. These features can be used for a priori assessment of measures on the catchment scale. For example, re-routing of wastewater from decentralized small WWTPs to larger ones has been shown to provide an option for improvement of the water quality in small creeks with unfavourable dilution factors.

This may be all the more important as the EU recently has run so-called "fitness checks," assessing whether EU Directives are fit for purpose by examining their performance. The WFD was checked aside the Environmental Quality Standards Directive, the Groundwater Directive, and the Floods Directive (EU 2019). While this fitness check states that in Germany, the implementation of the WFD has led to an improvement of the state of numerous waters and the knowledge on pollutant loads and water quality could be increased considerably, it adds that most of Germany's water bodies will not achieve the 2027 targets (Vermeulen et al., 2019). We conclude that complimentary use of targeted monitoring and geo-referenced modelling constitutes a promising option to save time and money while completing these tasks.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1007/s11356-020-12189-7 and is also attached in the appendix of this work.

Authors' contributions

VL collected and processed the geo-referenced data, performed the simulations, and evaluated the results against monitoring data. He was also a major contributor in writing the manuscript. GN adopted and improved the GREAT-ER model according to the needs of the study. JB supported processing of the geo-referenced data and generation of the final GREAT-ER databases. JK supervised the whole study and was a major contributor in writing the manuscript. All authors read and approved the final manuscript.

Funding

Open Access funding enabled and organized by Projekt DEAL. This work was partly supported by the Bavarian Environmental Agency (LfU) and the State Agency for Nature, Environment and Consumer Production North Rhine-Westphalia (LANUV).

Data availability

A basic version of the GREAT-ER 4 model along with tutorials is available on registration at: www.usf.uni-osnabrueck.de/en/forschung/applied_systems_science/great_er_project. All external monitoring data analysed during the study are available from the corresponding author on reasonable request.

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5. Spatial modelling of micro-pollutants in a strongly regulated cross-border lowland catchment - Article 2

Accepted as:

Lämmchen V, Klasmeier J, Hernandez-Leal L, Berlekamp J, 2021. Spatial modelling of micro-pollutants in a strongly regulated cross-border lowland catchment. Environ. Process. Manuscript accepted for publication.

In principal, GREATER is applicable in any river catchment as far as the required data are available despite having been developed originally for European rivers. However, the hydrological modelling approach can only be suitable for largely natural flow conditions that can be represented by a steady-state approach. Natural flow conditions mean, for example, that although runoff varies seasonally with periods of high and low precipitation and melt water supply in winter/spring, there are no external interventions in the flow behaviour. If the natural flow and other parameters are influenced anthropogenically (Rahman et al., 2013) or are subject to tidal influences (McCarthy et al., 2007), the previously mentioned steady-state approach of the water system reaches a limit and the model and/or the parameterization must be adapted to represent such situations as realistic as possible. This is also true for consideration of event-driven emissions (e.g. by combined sewer overflows), but in article 2 only the hydrological modelling aspects are discussed.

In general, most hydrological models were originally developed to represent natural streams (e.g., Schowanek & Webb, 2002) and publications that address hydrologically difficult watersheds in the context of solute modelling are rare (e.g., Carluer & Marsily, 2004) or deliberately exclude such hydrologic special cases (e.g., Archundia et al., 2018). Article 2 addresses such special hydrological cases where anthropogenic influences such as channelization of surface waters, operation of pumps and agricultural irrigation affect the original hydrological flow conditions in a way that largely overwrites the natural flow regime in the catchment.

This is exemplified in the catchment of the Vecht, a cross-border river between Germany and the Netherlands characterized by large human interventions especially on the Dutch side. In the Vecht catchment, this human influence has been present for years: As early as 1904, the Nordhorn-Almelo Canal was completed, through which textiles produced in Nordhorn and the surrounding area were shipped to the Netherlands. Even though these times are over, the canalization of the Vecht catchment has increased significantly until today (Lulofs & Coenen, 2007). Additionally, natural river sections have been straightened in the past, so that the Vecht has lost more than 40 km flow length compared to its original course. This leads to higher flow velocities, which has to be compensated by adding additional water, especially in summer, in order to maintain a minimum water level necessary for ecosystem services (navigation, irrigation, tourism; Lulofs & Coenen, 2007).

In this context, water diversion is not an invention of modern times; mills and polders were already used centuries ago to divert or drain water from arable land or settlement areas (Hoeksema, 2007). Today, high-powered pumps, dams and sluices are used to realize these tasks. The nature of the intervention remains the same, but the water volume diverted increases considerably. Additionally, in the Vecht large-scale irrigation of agricultural land and extraction of drinking water is present (Lulofs & Coenen, 2007) and tourism requires year-round navigable canals and tributaries. All of this adds up to a multitude of human interventions that completely disrupt the natural flow regime in the entire watershed.

With these boundary conditions, it was not possible to apply GREATER or similar models in this catchment properly without major adaptations. Since the use of GREATER in the Vecht area was part of the MEDUWA project, it was necessary to find solutions to include representation of the above mentioned influences in the model. The article gives examples of how the problems were addressed. This includes an adapted pre-processing routine and optimized organization of the source data. As the article will show, significant improved results of the later model can be achieved just by processing the raw data differently (better). For example, by selectively cutting stream segments during the GREAT-ER pre-processing routine, it can be achieved that later use of the same data in different databases (and with different flow directions) can be easily implemented.

Article 2 describes how the representation of the human interventions in the Vecht catchment was implemented in practice in the GREAT-ER model approach. Simulation results could be compared with monitoring data collected during the MEDUWA project showing that the adjustments enabled realistic representation of the Vecht catchment. The adapted methodology for the first time allows for decent application of GREAT-ER in anthropogenically modified catchments and opens up its previously limited use to a number of similar rather “unnatural” catchments.

Spatial modelling of micro-pollutants in a strongly regulated cross-border lowland catchment

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Received: 17 March 2021 / Accepted: 11 June 2021

Abstract

Anthropogenically influenced transboundary catchment areas require an appropriately adapted exposure modelling. In such catchments, water management decisions strongly influence and override natural river hydrology. We adapted the existing exposure assessment model GREAT-ER to better represent artificially overprinted hydrological conditions in the simulations. Changes in flow directions and emission routes depending on boundary conditions can be taken into account by the adopted approach. The approach was applied in a case study for the drug metformin in the cross-border catchment of the Vecht (Germany/Netherlands). In the Dutch part, pumps to maintain necessary water levels and minimum flow rates during dry periods lead to a reversal of the (natural) flow directions and as a consequence to additional pollutant input from the Lower Rhine/Ijssel along with a spatial redistribution of emissions in the catchment area. The model results for the pharmaceutical product metformin show plausible concentration patterns that are consistent with both monitoring results and literature findings at mean discharges and the effects of the changed hydrology in times of low natural discharges, namely an increase in polluted river sections under dry conditions due to the pumping activities. The adapted methodology allows for realistic application of the GREAT-ER model in anthropogenically modified catchments. The approach can be used in similar catchments worldwide for more realistic aquatic exposure assessment.

Keywords

spatial modelling, river basin management, cross-border, anthropogenic impact, GREAT-ER model, metformin

Introduction

River basin management in densely populated regions is a difficult and challenging task. Surface waters fulfil numerous, often competing functions. Wiering et al (2010) state that integrative goals of river basin management are characterised by the connection and combination of different aspects of water systems, such as water quality and water quantity. Integrative river basin management also puts forth the need for communication and cooperation between water management and other policy domains such as spatial planning, agriculture, housing or nature conservation. Since river basins not only stretch out over geographical but also administrative borders, they can be taken as unit for cooperation among different regulators and stakeholders. For large rivers in Europe, cross-border work has been common practice for years. For example, the International Commission for the Protection of the Rhine (ICPR) was already founded in 1950. Since the beginning of the new millennium, the Water Framework Directive (WFD, Directive 2000/60/EC) and the European Flood Risk Directive (EFD, Directive on the assessment and management of flood risks; 2007/60/EC) are additionally calling for this cross-border practice. Especially the WFD strongly influences both national and regional water policy practices. In the WFD, river basin means "the area of land from which all surface run-off flows through a sequence of streams, rivers and, possibly, lakes into the sea at a single river mouth, estuary or delta" (art 2(13)). In terms of the WFD, it is therefore necessary to move towards transboundary, catchment-related risk assessment replacing old-fashioned national approaches within country borders (Coppens et al., 2015; Vissers et al., 2017).

The main subjective of the WFD is the good status of European water bodies including the good chemical status of European surface waters (EU, 2000). The directive constitutes a legal framework that imposes the protection of common water resources on European states (Tsakiris, 2015; Zacharias et al., 2020). In this context, the first version of the WFD listed 45 priority substances in annex X of the directive. Exposure and risk assessment of micro-pollutants such as pharmaceuticals and antibiotics followed by development and implementation of reduction measures for critical compounds are necessary to achieve the goals of the WFD (Kallis & Butler, 2001; Allan et al., 2006). A prerequisite for the definition and implementation of mitigation measures is knowledge of the exposure concentrations of these substances in the environment. This has led to large monitoring efforts for so-

called emerging contaminants (Richardson, 2009; Gogoi et al., 2018). Obviously, a permanent, basin-wide and comprehensive monitoring of the 45 priority substances and of thousands of potentially relevant micro-contaminants is impossible for European surface waters. At this point, models can be a valuable aid for exposure and risk assessment, filling knowledge gaps and supporting existing monitoring efforts (Boxhall et al., 2014). The GREAT-ER model (Geo-referenced Exposure Assessment Tool for European Rivers[5]), for example, is a spatially resolved fate model that predicts chemical exposure at river basin level (Kehrein et al., 2015; Lämmchen et al., 2021). It was developed within the framework of the European ecotoxicological risk assessment system (Feijtel et al., 1998) and has been successfully applied to simulate a wide range of pollutants in several river basins all over the world (Hüffmeyer et al., 2009; Alder et al., 2010; Aldekoa et al., 2013; Archundia et al., 2018; Duarte et al., 2021). In this context, modelling of transboundary catchments imposes particular challenges to overcome such as country-specific administrative structures and water management systems (e.g. Watson, 2004; Podimata & Yannopoulos, 2013) or availability of required input data. For modelling of pharmaceuticals, other aspects like differences in consumption patterns and drug regulations have to be taken into account, where a main obstacle to modelling studies of micropollutants in transboundary catchments is the restricted access to detailed national and regional consumption data (Tiedeken et al., 2017).

Exposure models for surface waters always require a realistic representation of the hydrological conditions on the selected spatial and temporal scale. This is especially difficult in anthropogenic regulated river systems, in which numerous canals, sluices, weirs and pumping stations override natural river flow conditions (Gregory, 2006; Lespez et al., 2015). Here, river flow extremes are attenuated and flow dynamics are reduced to prevent from negative consequences such as flooding or drought. Existing hydrological models were mostly developed to represent natural water flow (Schowanek & Webb, 2002) and were thus not designed for consideration of flow regime regulations driven by requirements for shipping, flood control, drainage or irrigation. This is also the case with the standard hydrological representation in the GREAT-ER model (Kehrein et al., 2015).

[5]Program and more details available at: https://tinyurl.com/y8h9y8rq

Chemical exposure in strongly canalized river systems cannot sufficiently be simulated when only natural flow is considered. For example, in large parts of the Dutch canal system distribution of emissions is known to be quite different during summer time compared to the rest of the year (Fiselier et al., 1992; Prinsen & Becker, 2011; Coppens et al., 2015). Many of the challenges faced here also apply for similar catchments for example in Belgium (Verhelst et al., 2018) or in numerous potentially similarly influenced catchments worldwide (Gregory, 2006). To improve the prediction accuracy of aqueous exposure models in general and GREAT-ER in particular, coverage of these aspects must be enabled.

Therefore, the aim of this study was the adaptation of the GREAT-ER 4.1 model environment (Lämmchen et al., 2021) to allow for realistic representation of the hydrological situation in highly anthropogenic regulated cross-border basins. The adapted methodology for the first time opens up the possibility of applying GREAT-ER in strongly anthropogenic modified catchments worldwide. The applicability of the adapted exposure model is demonstrated by a case study for the heavily used pharmaceutical ingredient metformin in the German-Dutch cross-border catchment of the Vecht. By combining more realistic water quantity information with regionalized human consumption data, model simulation results can effectively contribute to integrated cross-border river basin management.

GREAT-ER Model

In principle, the GREAT-ER model consists of three components. The hydrological network, the emission model and the fate model. Here, the focus is on the hydrological parameterization of the river network. A detailed description of the other functions of the model and its application can be found in Kehrein et al. (2015) and Lämmchen et al. (2021).

General hydrological representation

The model's backbone is formed by a GIS-based hydrological network, which is created during a number of pre-processing steps. Hereby, the surface water network is discretized into river segments with a length of less than 2 km. Each segment holds attributes about flow direction, flow velocity, discharge and others, which are used to calculate the

chemical's fate and concentration. To do so, a consistent water balance across the whole river network for three defined flow conditions namely the long-term annual average stream flow (MQ), the long-term annual low flow (MNQ) and the 50-percent-flow-percentile (Q50) is created. The GREAT-ER pre-processing provides a semi-automatic procedure for estimating runoff in each segment. We use grid data for effective precipitation in the entire catchment from available data sources or established rainfall-runoff models. Sub-catchments for all river segments are derived from the digital elevation model (DEM) by Lehner et al. (2008) known as HydroSHEDS.

For each sub-catchment, the total runoff under MQ, MNQ and Q50 conditions is estimated by weighted averaging of the grid data on effective precipitation. The slope extracted from the DEM is then used to allocate runoff to the next downstream segment. These values are added up along the flow path to give cumulated runoff for each hydrological condition in each segment. Local discharge from WWTPs (Wastewater treatment plants) as well as water abstraction (e.g. for drinking water or irrigation) are also explicitly considered in this water balance if quantitative information was available from local water authorities. Actual average daily river flow is usually available from data series of gauging stations covering differently large sub-catchments. Estimated river flow values are compared and calibrated against the available long-term gauging data. The more gauges are available for this purpose; the more accurate the final water balance will be.

This procedure leads to a consistent water balance in the whole catchment for the respective hydrologic situation. Although situations with the same flow condition in the whole catchment at the same time will hardly occur in reality (Fig. S1), this approach forms a standardized, solid basis for spatially distributed exposure assessment.

Emission model

In general, the model distinguishes between domestic and hospital consumption of pharmaceuticals. The load of domestic usage is calculated based on the number of inhabitants connected to a WWTP and a specific compound per-capita consumption rate. This is based on the assumption that the inhabitants connected to a certain WWTP constitute a representative sub-group of the general population with respect to the

prescription frequency of the pharmaceutical. Similarly, the hospital consumption is calculated by considering the number of beds in hospitals that are connected to the WWTP and a specific compound per-bed consumption rate. Since most pharmaceuticals are metabolized after uptake, only a certain percentage is included in the calculations. The final load emitted into the receiving water is reduced based on the removal efficiency of the compound during the treatment process at the WWTP and is then implemented as a point source in the river network. Other loss processes, for example, in-sewer transformation processes are not considered.

In addition, GREAT-ER 4.1 allows for introducing artificial emission points at inlets where substance loads cannot be individually simulated by the model, but must be provided as constant external input. The loads (L) at such inlet points are estimated from monitoring data at the nearest upstream sampling site in the inflowing waterbody, an approach that has already been used elsewhere, e.g. by Coppens et al. (2015).

The general equation for estimation of the average load at the monitoring site L_{moni} is as follows:

$$L_{moni} = \frac{1}{n} \cdot \sum_{i=1}^{n} Q_i \cdot C_i \qquad (1)$$

where n is the number of total measurements, Q_i is the river flow at the time of each measurement, and C_i is the concentration of the substance at measurement i.
In case the monitoring site is located distant from the catchment inlet, it can be necessary to consider the effect of loss processes along the travel distance. For this purpose, loss processes of the individual chemical need to be described by a cumulative pseudo first-order loss rate constant k. The load is then reduced according to the following equation:

$$L_{inlet} = L_{moni} \cdot e^{-k\,t} \qquad (2)$$

with t being the travel time from the monitoring site to the catchment inlet.
The situation is even more complicated when additional emissions occur between the monitoring site and the catchment inlet. In this case, the contributions of the respective

WWTPs are estimated with the usual per-capita approach (Lämmchen et al., 2021). Reduction through loss processes is considered as described above, whereby the individual travel times of the different WWTP load contributions (t_i) are applied.

$$L_{WWTP} = \sum_{i=1}^{n} cap_i \cdot PCC\ (1 - R) \cdot \mathrm{e}^{-k \cdot t_i} \qquad (3)$$

where cap_i is the number of inhabitants treated by $WWTP_i$, PCC is the average per-capita emission rate, R is the (constant) percentage removal of the substance in WWTPs, k is the lumped first-order instream loss rate and t_i is the individual travel time from $WWTP_i$ to the inlet. The total emission at the respective inlet is then calculated from the sum of all relevant terms.

Fate model

After entering the water system, concentrations are calculated by dividing the total load at the beginning of a segment with the river flow defined by the hydrological model. Mass flows are propagated through the network based on flow directions, flow velocities and discharges. Loss processes such as sedimentation, photolysis and biodegradation are taken into account as first-order reduction along the travel distance analogously to equation (2). In principle, natural variability of environmental parameters, uncertainty of substance parameters and temporal fluctuation of consumption patterns could be considered by the probabilistic Monte Carlo routine implemented in GREAT-ER (Lämmchen et al., 2021). However, this routine is not yet applicable to other than natural river flow situations and thus not used in the case study.

Model output

Simulation results provide an overview of the spatial variability of surface water contaminations and can be used to easily identify river sites with increased concentrations above a defined target value (e.g. a given environmental quality standard). GREAT-ER additionally allows the simulation of management scenarios for selected reduction measures and a priori evaluation of their effectiveness. Results are primarily presented as

color-coded maps or concentration profiles along a selected river course (see Fig. 2, Left side).

GREAT-ER finally allows for performing numerous statistical analyses. This includes, for example, sorting all river segments by their concentration in ascending order along with the cumulated flow length resulting in a cumulative distribution function (CDFs) of the concentrations (Fig. 3).

Adaptation of the GREAT-ER structure

GREAT-ER usually represents annual average situations in terms of substance loads and uses a closed water balance for a specific hydrological situation such as MNQ or MQ. The GREAT-ER standard representation is based on the directed river network graph given by the underlying river network. To propagate loads and emissions through the river network system, directional data in form of 'from-to-relationships' must be stored at the nodes in the river system.

In anthropogenically influenced catchments, however, this standard approach cannot always be applied. For example, it may happen that due to water management based pumping activities (e.g. for irrigation purposes) in some parts of the river system the flow directions occasionally change. However, the directed river network is currently represented by a static database structure and thus, such changes cannot be simply managed by flipping the flow directions on a case-by-case procedure. Consequently, two representations of the catchment have been set up representing the different situations of flow directions during days with and without pumping activities in separate databases. One database reflects regular average flow conditions without artificial pumping and the second one represents the periods, where water management instruments partly override natural flow conditions. Each database contains a copy of the basic hydrological network considering respective flow direction changes. Flow rate calibration against data from gauging stations were carried out individually for the two databases. Reference values were calculated individually for both situations, meaning that values representative for the respective scenario were selectively aggregated.

Case Study

To demonstrate the capability of the advanced GREAT-ER approach for realistic resemblance of complex hydrological conditions an exemplary case study for the diabetic drug Metformin in the Vecht catchment has been performed.

Substance information metformin

Metformin (CAS number: 657-24-9) is a highly consumed anti-diabetic, with over 600 million DDD (2g; WHO 2012) prescriptions per year in Germany (Schwabe et al. 2019) and over 100 million DDD in the Netherlands (RIVM 2014). For the simulations, regionalized prescription data (based on sales data on postcode level) from IQVIA (https://www.iqvia.com/) and the Dutch Foundation for Pharmaceutical Statistics (SFK; https://www.sfk.nl/) for the years 2016 to 2018 were used as input. This results in an average per-capita consumption of 13.6 g/a in Germany and 19.8 g/a in the Netherlands, of which approximately 70% of this administered dose is excreted from the human body as parent drug, mainly via urine, entering the wastewater pathway (Moffart et al. 2011). The hospital consumption figures were obtained from several cooperating hospitals in the study area. From these figures, a national or regional per-patient consumption was calculated and assigned to the German (0.26 kg/(bed*a)) and the Dutch hospitals (0.18 kg/(bed*a)), respectively. Even though the individual administration rate in hospitals is significantly higher than in the general population, the overall contribution of hospitals to total emission is almost negligible (3.3 %). The detailed simulation parameters can be found in Table 1.

Table 1: Simulation parameters used for metformin simulations

		Metformin	References
Phys. chem. properties	Unit		
Molar mass	g/mol	129.2	Straub et al. 2019
log Kow		-2.48	Straub et al. 2019
Water solubility	mg/ml	100	Ching-Ling et al. 2004
pKa		11.3	Scheurer et al. 2012
WWTP removal			
Lagoon	%	90	Auvinen et al. 2017
Wetland	%	90	Auvinen et al. 2017
Biofilm	%	97.5	Osterhuis et al. 2013
Activated Sludge	%	98	Osterhuis et al. 2013, Gaffney et al. 2017
River removal			
Half-life	d	24 – 28.3	Neamtu et al. 2014, Straub et al. 2019
Model assumption	1/h	0.0011	
Oxidation by OH radicals	1/h	0.0012	Neamtu et al. 2014
Kd river	L/kg	19	Scheurer et al. 2012
Consumption			
Per-capita consumption [GER]	kg/a/Inhabitant	0.0198	Sales data from IQVIA
Per-capita consumption [NL]	kg/a/Inhabitant	0.0136	Sales data from SFK
Hospital consumption [GER]	kg/(bed*a)	0.26	Obtained from local hospitals
Hospital consumption [NL]	kg/(bed*a)	0.18	Obtained from local hospitals
Excretion	%	70	Moffart et al. 2011

The combination of large prescription numbers with a high excretion rate leads to high concentrations in raw wastewater of up to 129 mg/L (Scheurer et al., 2009; Van Nuijs et al., 2010). Fortunately, Metformin is efficiently removed in treatment plants by 90 % for lagoon and wetland treatment plants (Auvinen et al. 2017), and 97.5 % and 98 % for biofilm (Oosterhuis et al., 2013) and activated sludge plants (Oosterhuis et al., 2013, Gaffney et al., 2017), respectively. The K_d value was found to be 19 l/kg (Scheurer et al., 2012). Metformin is also not fully persistent in surface water according to the PBT assessment under REACh ($t_{1/2}$ < 40 days). For example, oxidation by OH radicals is reported to occur with an estimated half-life of 24 days (Neamtu et al., 2014) to 28.3 days (Straub et al., 2019) under simulated sunlight conditions. Nevertheless, Metformin is almost ubiquitously detected in

surface waters (Scheurer et al., 2009, Vulliet & Cren-Olive, 2011) in concentrations of up to 1700 ng/L.

To date, no legally binding environmental quality standard (EQS) has been set. Proposed values range from 88 µg/L (Godoy et al. 2018) up to 780 µg/L (RIVM, 2014). An environmental risk assessment document of one of the major producers reports a PNEC (predicted no-effect concentration) value as low as 10 µg/L (AstraZeneca 2017). This is still at least factor six higher than the above reported surface water concentrations.

For model evaluation, we used monitoring data from a 2018/2019 sampling campaign (van Heijnsbergen, in preparation), where 116 samples from 32 sites within the Vecht catchment were analysed for metformin with a standard combination of high-performance liquid chromatography and mass spectrometry known as LC/MS-method (e.g. Trautwein & Kümmerer, 2011; Scheurer et al., 2012).

Catchment Area

The study area comprises the catchment area of the German-Dutch border river Vecht (see Fig. 1), a tributary of the Dutch river Ijssel. The cumulated length of surface waters in the catchment sums up to 2,760 km with approximately 2,000 km of rivers and around 760 km of canal-like structures. The longest possible flow path through this network is about 187 km considering the way from the spring of the Vecht to its outlet point north of Zwolle. A summary of important catchment characteristics can be found in Table 2. The only relevant lake in the catchment area is Lake Vecht with an average depth of 1.67 m and a surface area of 160,000 m² (Messager et al., 2016). The lake serves as an artificial sediment trap (NLWKN 2012), which also makes it a sink for substances adsorbed to suspended matter. The residence time of water in the lake is between 11 hours and 4 days, depending on the actual discharge conditions in the Vecht.

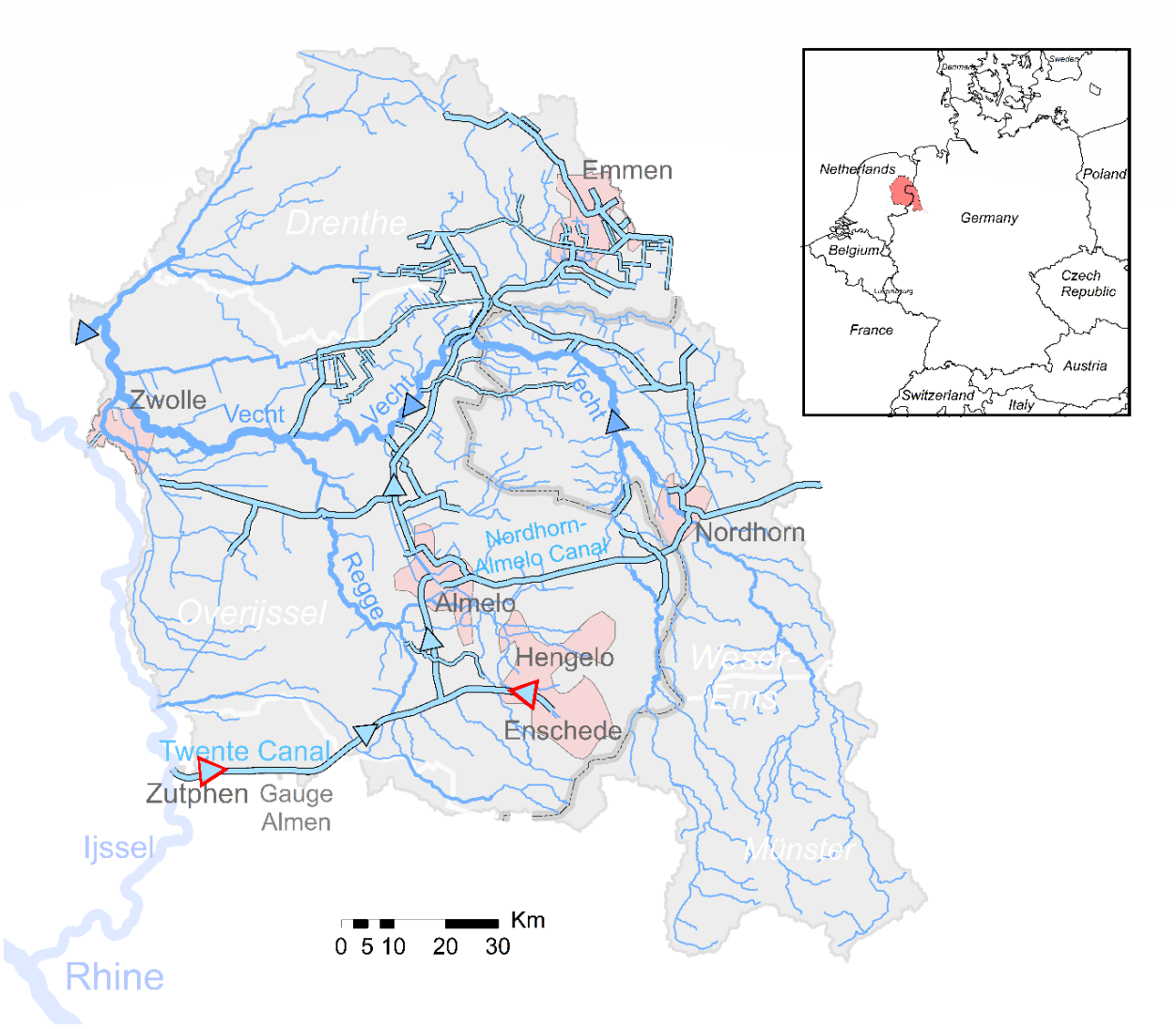

Fig 1.: The cross-border Vecht catchment in Germany and the Netherlands. Rivers are indicated as blue lines, while canals are given as framed cyan lines. Blue arrows symbolize the natural flow direction in the Vecht River. Cyan arrows with red frame symbolize artificially changed flow directions due to pumping activities in summer (at Zutphen) and year-round (at Enschede).

In the past, the Vecht used to have natural flow conditions with relatively high peaks in wet periods and sometimes extremely low water levels in summer (Lulofs & Coenen, 2007), mostly in the period between May and September. Today, this is still the case in the German part, while on the Dutch side the Vecht has been canalized from 1896 on, when it was declared a state waterway. Because of the intensive straightening, water levels in summer were lowered while flow rate and velocity increased during wet seasons (Lulofs & Coenen, 2007). In order to maintain ecosystem services for tourism, shipping and irrigation provided by the Vecht, a minimum water level is necessary. Therefore, in summer water

from the Ijssel is pumped into the Vecht basin via the Twente Canal (RWS, 2017). Pumping stations are located at Delden (near Enschede) and Eefde near Zutphen (see Fig. 1). The former is working almost all year round to prevent the city of Enschede from being flooded, while Eefde is running only during the dry periods that can occur between March and November. The main canal waterways in the Dutch part of the catchment are designed to handle up to 8 m^3/s of additional water from pumping activities. Surplus water is either distributed via the canal system to the numerous withdrawal points installed for irrigation purposes or routed into the Vecht main river. Flow direction in large parts of the catchment are reversed and river flow is strongly affected when the pumps are in action.

Table 2: Characteristics of the Vecht catchment.

	Germany	Netherlands
Catchment Area	1,800 km^2	4,300 km^2
Provinces included	Lower Saxony, North Rhine-WeWWTPhalia	Drenthe, Overijssel
Vecht River length	107 km	80 km
Outlet	Dutch-German border near Hardenberg	Zwarte Warter (near Zwolle)
Average annual flow (MQ) at outlet	20 m^3/s	35 m^3/s
Average annual low flow (MNQ) at outlet	1.5 m^3/s	3 m^3/s
Relevant tributaries	Steinfurter Aa, Dinkel	Regge
Largest cities	Nordhorn, Gronau	Enschede, Emmen, Almelo, Zwolle
WWTPs	25	32
Connected inhabitants	300,000	1,100,000
Hospitals	7	7
Hospital beds	1297	1960

Hydrological parameterisation

The hydrological representation in the model has two prerequisites. First, the river network must be topologically sound with defined outlet points, so that it is possible to traverse through the river system (along defined flow directions) from any point in the river network to the designated outlets. Secondly, stream flow information must be available for each river segment. Due to the transboundary nature of the Vecht catchment river network, data from two German authorities (NLWKN, LANUV) and three Dutch water boards (WVS, WRIJ, WDOD) had to be collected. As there are no international or even national standards, available data substantially differ in the level of detail leading to barely compatible datasets. More details on how the river network was created under these boundary conditions can be found in the SI (S2).

Average effective precipitation data for Germany was taken from the Hydrological Atlas (HAD; Leibundgut & Kern, 2003) for the period from 1960 to 1990. The HAD offers one grid (1x1 km) each for low flow and average conditions. For the Dutch part of the catchment, however, comparable data in a ready-to-use format are not publicly available. Therefore, based on the assumption that long-term effective precipitation patterns do not differ greatly over short distances in this relatively flat landscape, the HAD runoff grid was extrapolated across the German border to the Dutch area. Resulting uncertainties in the river flow estimation from not taking into account different soil properties are compensated for in the calibration procedure.

The resulting MQ and MNQ estimations were calibrated against long-term data from 43 gauging stations, which are evenly distributed across the Netherlands and Germany, considering daily discharges from 2000 to 2017. However, at some of the Dutch gauges (e.g. Almen gauge) negative daily flow rates are reported when the flow direction is reversed during the dry season making calibration of the dry summer scenario with the original data impossible. Therefore, daily flow data from the gauging stations were separated and assigned to one of the two hydrological scenarios.

Regional-specific pumping activities

For this case study, two different hydrological conditions during dry summer days (equivalent to MNQ conditions) and average humid days (equivalent to MQ conditions) are considered and represented in separate databases. The latter database reflects regular average flow conditions (Q_{avg}) without artificial pumping and the former represents the dry-summer-period (Q_{low}), where under low flow conditions water is pumped from the Ijssel into the Vecht catchment. Pumping data during periods of water compensation are specified in the 'Waterakkoord Twenthekanalen / Overijsselsche Vecht' (RWS, 2017). The gauging station 'Almen' in the Twente Canal is located next to the Eefde pumping system (see Fig. 1) and is used to monitor the effect of the pumping action in the calibration of the two different hydrological scenarios. First, pumping days were defined as to when the pump was active for at least 12 hours supplying 1 m3/s of Ijssel water or more. Secondly, hourly flow data were separated into the two scenarios and re-aggregated to give estimates for MQ, Q50 and MNQ representing the respective situation. Negative values were interpreted as flow rates in opposite direction to natural flow. The resulting data set was used for calibration of MQ, Q50 and MNQ in the two scenario databases Q_{avg} and Ql_{ow}. The specific simulation parameters for Q_{low} can be found in the following table 3.

Table 3: Specific simulation properties during dry periods

	Dry-Summer-Database (Q_{low})
Applicability	Dry periods without rainfall between March and October
Ijssel water pumping	Yes
Pumping description	Approx. 120 days a year between March and November (Netherlands)
Pump power “Eefde” (Zutphen)	1.6 m³/s (mean); 14 m³/s (maximum)
Pump „Delden“ (Enschede)	Running in both scenarios
Reversed flow direction in	Twente Canal, Zijkanaal Almelo, Canal Almelo-De Haandrik, and several emerging smaller canals

In a similar approach, Coppens et al. (2015) chose the driest and wettest periods of the year, i.e. from July to September and October to December, and selected data from extreme years for both conditions (2003 and 1998, respectively) to predict the maximum and minimum concentrations that can be expected. The Q_{avg} and Q_{low} set-up is similar, but we think closer to reality, since the year is divided into the period from November to March and from March to November with regard to pumping activities and not barely to seasons.

Inflow from the Ijssel

GREAT-ER usually propagates emissions from all known contaminant sources through the whole river basin network starting with the segments at the individual springs down to the outlet point(s). In contrast to country-based approaches (Coppens et al., 2015; Vissers et al., 2017), this catchment approach normally avoids uncertainties attributed to the inflow from upstream areas originating from other countries. Without inclusion of these areas into the model, such upstream emissions can hardly be estimated a priori, but have to be estimated from monitoring data. The Vecht catchment in our study is represented by the complete hydrological network including all source regions and three outlets (Zwaarte Water, Ems-Vecht Canal, Twente Canal). However, due to pumping action under Q_{low}, Ijssel water enters the catchment turning the former outlet point Twente-Canal into a potential inflow point for chemicals from the Ijssel. Realistic parameterization of this situation constitutes a major challenge in the simulations.

The LANUV operates a gauging and monitoring station in the Rhine near Lobith directly at the Dutch-German border, from which concentration data of several hundred substances including metformin are available (ELWAS, 2020). The average metformin load at the monitoring site was estimated from these data using equation (1). Since input occurs only under active pumping, we considered only concentration data from sampling days when the dry summer scenario applied in the study area resulting in 35 samples in the period from 2013 – 2019.

Via the Nederrijn and Ijssel, Rhine water reaches the Twente Canal after about 50 km flow length corresponding to a travel time of 10 - 15 hours (RWS, 2020). Before entering the Twente Canal near Zutphen, wastewater from WWTP Etten (136,000 connected inhabitants), Nieuwgraaf (177,000) and 8 smaller treatment plants (145,000 connected

inhabitants) is introducing additional wastewater from 458,000 inhabitants. Loss processes along the flow path are taken into account with the same first-order loss rate k that is used as simulation parameter in the GREAT-ER model. To estimate the substance loads from these point sources at the Twente Canal inlet, equations (2) and (3) were applied.

In the Q_{low} database, a virtual emission source is then placed at the inlet near Zutphen, which provides the estimated load via the Ijssel inflow in the simulations according to the formula already introduced.

Results and Discussion

Average-flow-scenario

Figure 2 (A) shows simulated mean predicted environmental concentrations (PEC) in the whole river basin in the standard Q_{avg} scenario assuming MQ discharge conditions. Predicted mean concentrations are almost completely within the range of 100 ng/L – 1,700 ng/L, which is in agreement with observations from other studies (Scheurer et al., 2012). Higher concentrations are found at the outlets of WWTPs with unfavorable dilution ratios. For example, predicted concentrations downstream of WWTPs Enschede-West, Hengelo or Oldenzaal reach values of more than 2,000 ng/L. Overall, 961 kilometers of river segments (making up 35% of the total river network) are predicted to exhibit metformin concentrations larger than zero. In contrast to large-scale, national simulations (e.g. Coppens et al. 2015), the model can identify river reaches with potential high concentrations also in small brooks serving as receiving waters. Such information is important when nature protection is not restricted to the main rivers in the basin. It supports planning of monitoring campaigns and development of targeted local reduction measures or regional mitigation strategies.

In general, simulated concentrations are higher in the Netherlands due to the higher population density. This effect is intensified by the fact that the per-capita consumption of metformin in the Dutch part of the catchment is 45 % higher than in the German part (based on IQVIA and SFK numbers). Nevertheless, mean PEC values do not exceed the

proposed EQS values in none of the countries in the average scenario indicating that the substance does currently not carry a substantial aquatic risk potential. At this point, it has to be emphasized that risk assessment should not only be based on single values from grab samples or mean values from model simulations. Natural flow variability can cause large concentration differences over time even when the assumption of more or less constant mass flow of a pharmaceutical compound was true.

Dry-summer-scenario

In the dry summer scenario, simulated metformin concentrations show significant differences compared to the average scenario due to the pumping activities along with generally lower flow values in summer. The respective color-coded concentration map can be found in the SI (Fig. S3). For example, the metformin concentration at the outlet Zwarte Water increases from 450 ng/l to 1300 ng/l. The effect of the pumping action can best be seen by the difference in estimated loads between the two scenarios (Fig. 2 (B)).

A major difference occurs at the Twente Canal, which in the dry summer scenario serves as additional metformin source. Applying equations (1) – (3) an additional input of 0.28 kg metformin per pumping day was estimated with metformin concentrations at the confluence of around 700 ng/L. This inflowing water is either distributed for irrigation purposes or remaining in the river system to secure water levels necessary for shipping. As a consequence, some parts of the catchment that are pristine under average conditions experience substance loads in the Q_{low} scenario through the re-routing of Ijssel water into the Vecht catchment. Respective segments appear blue in Fig. 2 A (zero concentration), but colored in Fig. 2 B due to the corresponding daily loads. Metformin concentrations in these segments are estimated to be partly above 2 µg/l, which is graphically highlighted in Fig. SI 4.

No load differences (grey segments in Fig. 2(B)) occur at Enschede, since here pumping is consistently maintained all-year long. The same applies to all other segments that are pristine or equally contaminated in both scenarios, e.g. the more naturally part of the catchment in Germany.

Surprisingly, metformin loads at the outlet are lower in the Q_{low} scenario than in Q_{avg} (see

Fig. 2B) despite the additional input from the Ijssel. First, more than 70% of the additional metformin load from the Ijssel inflow in the dry period do not remain in the water body (RWS 2017), since the water is used for irrigation. This mass transfer into ditches or directly onto agricultural fields is explicitly considered in the model as localized system outflow. The remaining Ijssel water fraction is used to maintain sufficiently high water levels for navigation in the Dutch part of the catchment. Due to the changing flow directions this results in large-scale metformin load redistributions (Fig. 2B). Loads that enter the Vecht River under Q_{avg} conditions ending up in canals under Q_{low} result in higher concentrations in some of the channels connected to the Vecht, e.g. the Meppeldiep or the Overijssels Canal (marked in orange). These concentration shifts had also been observed by Coppens et al (2015), but could not investigated in detail due to the lower spatial resolution of their model approach. In addition, slower flow velocity in summer results in higher residence times of metformin and associated slightly increased degradation.

It must be pointed out that lower emissions do not automatically translate into lower concentrations. Due to the much higher flow rates under average conditions (approximately factor 10, see Table 1), concentrations are expected to be significantly lower only by the dilution effect. However, the decrease in metformin PEC values from 1300 ng/L to 450 ng/L is much smaller (factor three).
This is a good example of how the model can explain respective monitoring results by considering the effects of overlying processes in a geo-referenced approach.

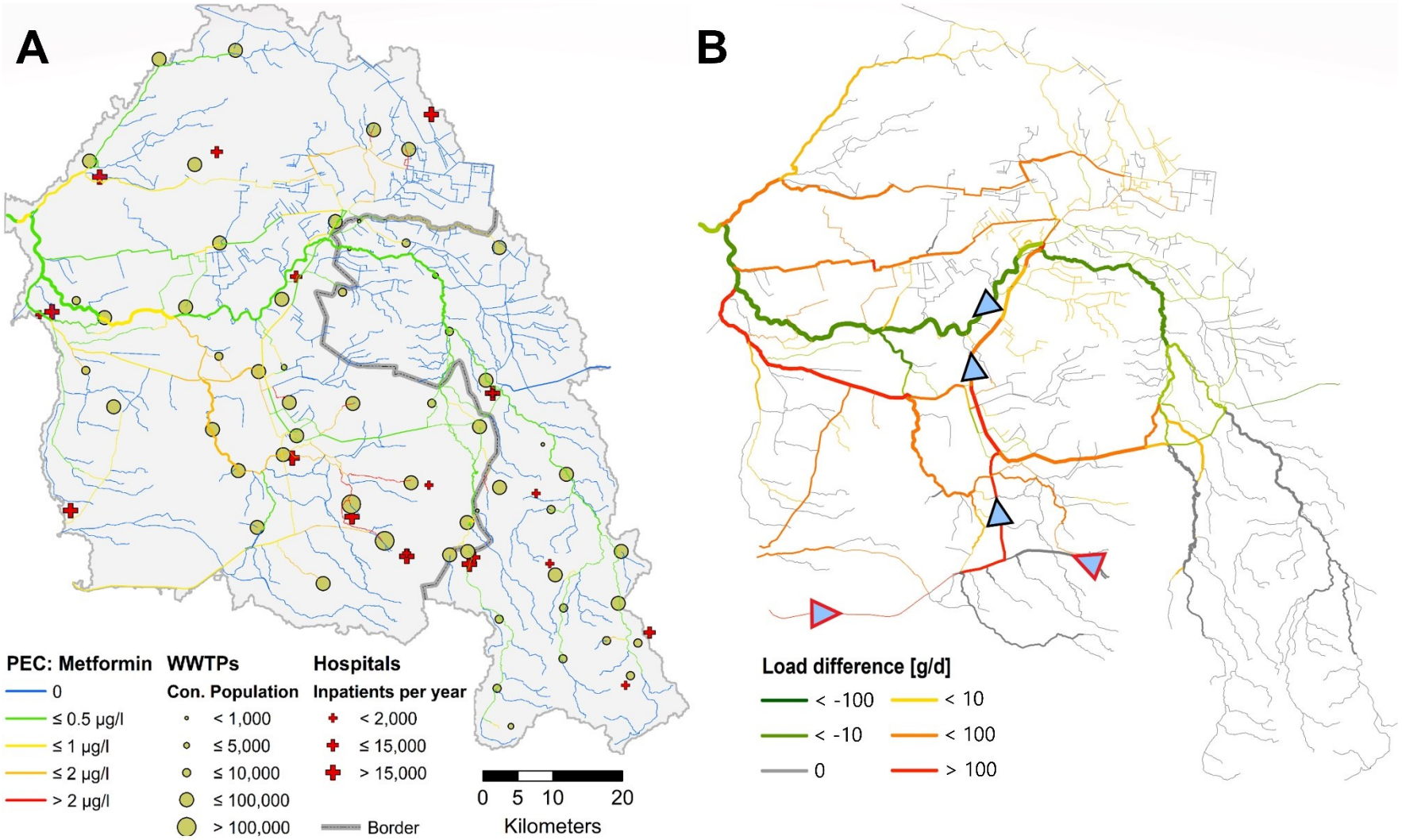

Fig. 2: A: Predicted environmental concentrations (PEC) of metformin in the Vecht catchment for average flow conditions (MQ) within the Q_{avg} scenario. WWTPs in the catchment varying in size with regard to the connected inhabitants. Marked as red crosses are the hospitals in the catchment area. B: Difference of simulated metformin loads between dry-summer-scenario Qlow and average-flow-scenario (2 A). Negative values indicate higher loads in the average scenario. Arrows mark the specific flow directions in Q_{low}

To compare the spatial concentration distribution between the two scenarios, Fig. 3 shows the cumulative distribution function (CDF) of the spatially resolved predicted concentrations. Data points indicate the fraction of total river length in the catchment below the respective concentration. Therefore, the outmost left data point specifies the fraction of total river length with zero concentrations. This means that in the Vecht catchment approx. 62% of river length are not polluted with metformin under average conditions, while in Q_{low} this fraction reduces to 49%. This difference is a result from water redistribution due to the pumping activities and irrigation (as highlighted in Fig. SI 4).

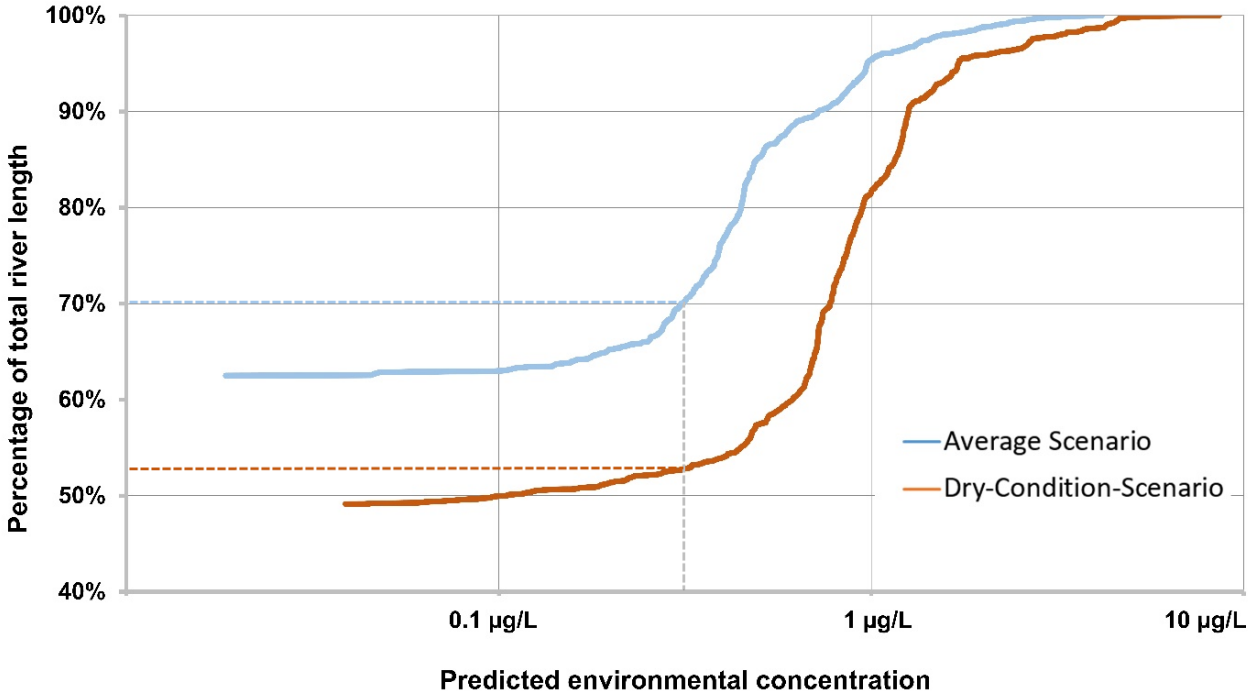

Fig. 3: Cumulative distribution functions of the regular (blue) and the dry-season scenario (red). The solid lines indicate the fraction of total river length in the catchment below the respective concentration. The dashed lines illustrate the example given in the text.

In general, PEC values are shifted towards higher concentrations in the dry summer scenario. For example, in the average scenario 70% of total river length exhibits metformin concentrations below 500 ng/l, while in the dry summer scenario this fraction is only 52.5%. This result is a combination of the effect of lower flow values and additional metformin input from the Ijssel.

Highest concentrations of up to 8 µg/l (Fig. 3) are predicted in small creeks serving as receiving river for WWTP effluents (see also red marked stretches in Fig. SI3), since they offer a very unfavorable dilution ratio with effluent fractions of more than 80% during dry periods. These values are close to the proposed PNEC value of 10 µg/L (AstraZeneca 2017) indicating the potential for temporary risk.

Model evaluation

Results of the two scenarios were compared with available monitoring data. Measurements were carried out over a period of 12 months so that data under conditions representative for both of the two hydrological scenarios could be obtained. According to the available pumping information at the sampling day, monitoring data were assigned to one of the scenarios. Fig. 4 shows the longitudinal PEC profile along a 187 km flow path starting at the spring of the Steinfurter Aa to the Vecht entering the Ijssel at Zwarte Water along with multiple monitoring data from 11 sampling sites.

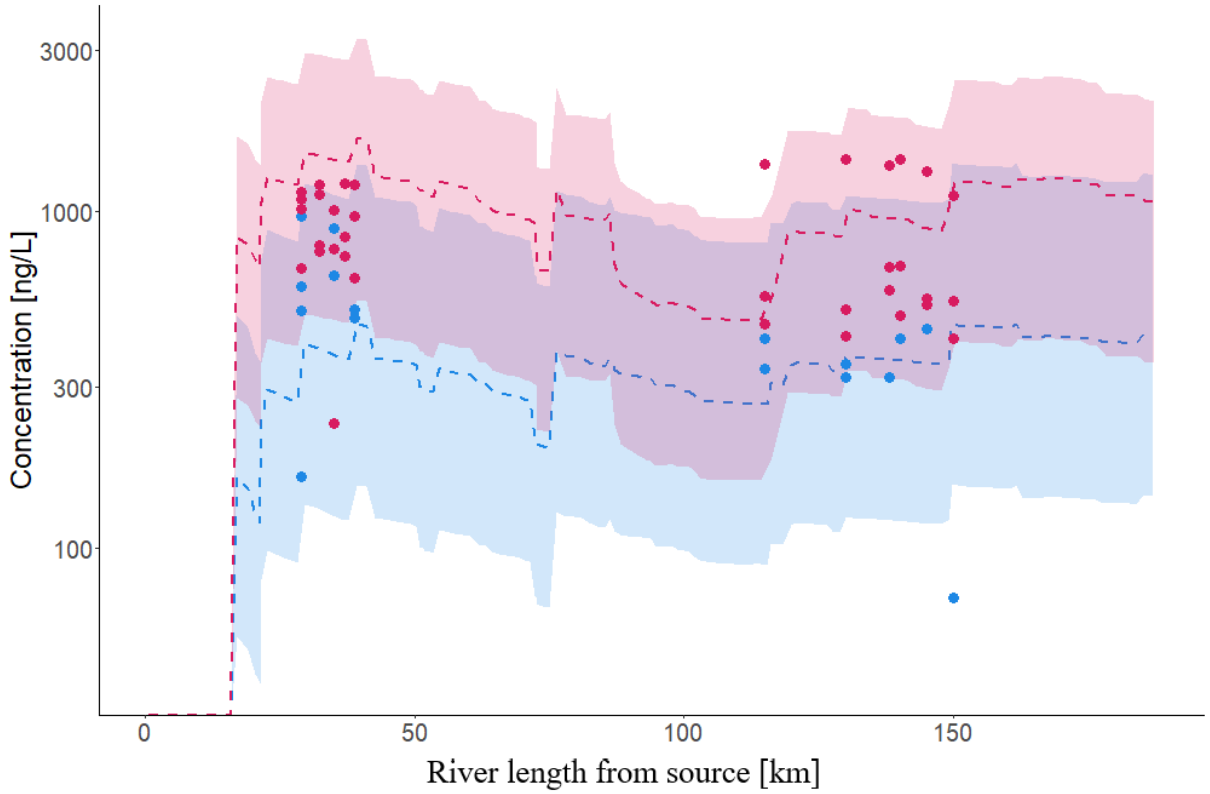

Fig. 4: Concentration profile of metformin along the longest flow path under regular (blue) and the dry-summer (red) conditions. Corresponding monitoring data are marked in the same color. Shaded areas represent the range of deviation of factor 3.

First, it can be seen, that measured concentrations at the individual sites vary considerably for both conditions due to natural flow variability. For this reason, a maximum deviation of factor three is generally accepted as quality criterion for good agreement between monitoring and modelling results (Ort et al., 2009; Verlicchi et al., 2014; Gimeno et al., 2017). This region is displayed as shaded area around the mean PEC in figure 4. Most of the data points are covered by this region in both scenarios indicating that the model parameterization allows for realistic predictions of metformin concentrations in the Vecht catchment.

Both scenarios show a concentration drop at km 75, which is caused by Lake Vecht. The calculated residence time of up to 4 days along with the partitioning coefficient between water and suspended particles (Kd) of 19 L/Kg (Scheurer et al., 2012) is sufficient to reduce metformin by sedimentation. Directly after the lake a WWTP is causing concentrations to rise again. At km 118, the additional load from the Twente Canal results in a concentration increase in the Ql_{ow} scenario. Another WWTP at km 119 introduces metformin in both scenarios causing the concentration to rise. This is covered in Q_{low} by the input from the Twente Canal, because the treatment plant is too close to this point and can be mistaken otherwise.

The accuracy of the model predictions can be assessed by comparing PEC values with measured environmental concentrations (MEC). According to the environmental conditions during sampling, data were assigned to one of the two scenarios resulting in 53 measured values for Q_{low} and 51 measured values for Q_{avg}. However, statistical evaluation is difficult, since MEC values from grab samples at the very same monitoring site are affected by the natural variability of the flow rate (Factor 3, see Fig. 4). Model simulations represent the hypothetical situation of average flow conditions in the whole catchment and are thus, hardly comparable to single measurements. Instead, the median of all metformin data at each of the 21 sites was used to calculate the correlation coefficient R^2 for the two simulation runs. The R^2 values are 0.57 for Q_{avg} and 0.47 for Q_{low} with a significance of $p < 0.005$. The corresponding graphs are shown in the SI as Fig. S5.

Secondly, in order to evaluate the degree of realism of the summer scenario we compared this scenario with the standard simulation setup (Q_{avg}), but under MNQ conditions, i.e. a simulation, in which pumping activities and reversed flow directions are not included (Q_{MNQ}). The comparison of these two simulation runs demonstrates the necessity of the model adaptations. From Fig. 5, it can be seen that the standard GREAT-ER run Q_{MNQ} clearly underestimates measured environmental concentrations whereas the adapted model in the dry-summer-scenario Q_{low} is in much better accordance with the monitoring data.

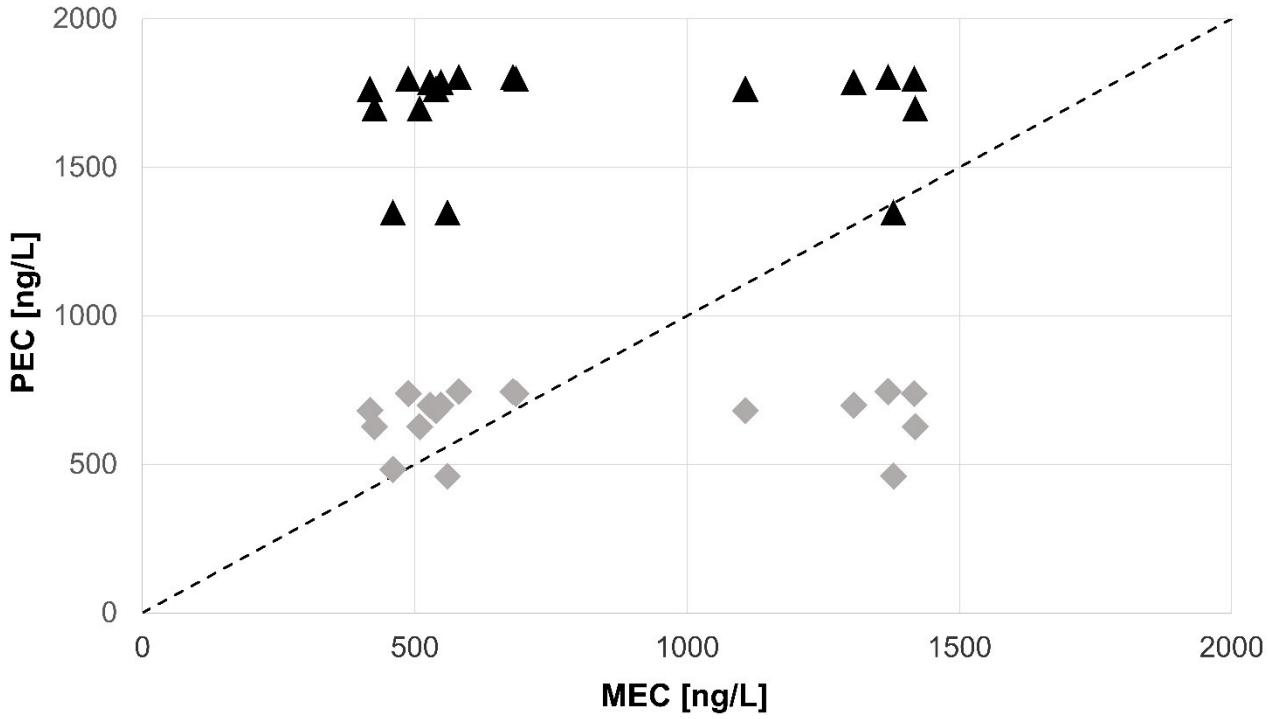

Fig. 5: Comparison of predicted versus measured environmental concentrations of metformin under Q_{low} (grey diamonds) and Q_{MNQ} (black triangles) conditions.

This result again confirms the assumption that during Q_{low} a redistribution of loads into canals and onto agricultural land takes place, so that the major part of the additional Ijssel emissions does not end up in the Vecht (see Fig. 2B). Since these processes are not taken into account in Q_{MNQ}, a much higher concentration is incorrectly predicted in the Vecht, even despite the lack of input from the Ijssel.

The adequacy of the assumptions made can be checked by calculating the mean squared error (MSE) of the PEC from the MEC using the following formula:

$$MSE = \frac{1}{n} * \sum_{i=1}^{n} (C_{MECi} - C_{PECi})^2 \qquad (4)$$

where C_{MECi} is the measured concentration at monitoring site i and C_{PECi} is the corresponding predicted concentration. The result is a calculated MSE of 0,176 µg/L for Q_{low} and 0,982 µg/L Q_{MNQ}, supporting the improvements achieved with the adaptions made within Q_{low}.

Conclusions

Existing models for exposure assessment of chemicals in surface water are usually not prepared to represent hydrological conditions that are strongly affected by anthropogenic interventions in a realistic way. We adapted the existing model GREAT-ER to reflect such a complex hydrology by implementing different databases for distinct hydrological scenarios. The usefulness of the approach was demonstrated in a case study for metformin in the German-Dutch cross-border catchment of the River Vecht. It was shown that metformin concentration data from samples taken in the dry summer season are much better represented by model simulations adapted to the specific situation of changing flow directions caused by pumping actions in the Dutch part of the catchment during summer. As a result, a significant part of previously pristine river segments of the catchment area is affected during these periods. The observed redistribution of pollution patterns in the Vecht catchment by the anthropogenic interventions is also relevant for other, possibly more hazardous substances (Neamtu et al. 2014). The use of the GREAT-ER model in the modified application allows for more insight into these issues as compared to standard model approaches. The adapted methodology opens up the possibility for application of the GREAT-ER exposure model in anthropogenically modified catchments in a more realistic way. It can be used in other catchments worldwide, for which the challenges faced in the Vecht basin also apply. Additionally, anthropogenic overprinting of river systems may increase further (Vitousek et al., 1997; Petts, 2007; Scorpio et al., 2018), which makes inclusion of such influences into modeling approaches even more important.

Declarations

Funding

The authors acknowledge funding by the European Regional Development fund of the European Union under the project MEDUWA-Vecht(e) (project number 142118).

Conflicts of interests

The authors have no conflicts of interest to declare that are relevant to the content of this article.

Availability of data and material (data transparency)

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Code availability

Current GREAT-ER model version can be downloaded under: https://www.usf.uni-osnabrueck.de/en/research/applied_systems_science/great_er_project.html

Ethics approval

Not applicable

Consent to participate

Not applicable

Consent for publication

Not applicable

Author contributions

All authors contributed to the study conception and design. All authors performed material preparation, data collection and analysis. The first draft of the manuscript was written by Volker Lämmchen and Jürgen Berlekamp. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Conceptualization: Volker Lämmchen, Jörg Klasmeier, Jürgen Berlekamp; Methodology: Volker Lämmchen, Jörg Klasmeier, Lucia Hernandez-Leal, Jürgen Berlekamp; Formal analysis and investigation: Volker Lämmchen, Jörg Klasmeier, Jürgen Berlekamp; Writing - original draft preparation: Volker Lämmchen, Jürgen Berlekamp; Writing - review and editing: Volker Lämmchen, Jörg Klasmeier, Lucia Hernandez, Jürgen Berlekamp; Funding acquisition: Jörg Klasmeier; Supervision: Jürgen Berlekamp, Jörg Klasmeier

Acknowledgements

The authors would also like to thank the water authorities Agency for Nature, Environment and Consumer Protection NRW (LANUV), Lower Saxony Water Management, Coastal Defence and Nature Conservation Agency (NLWKN) and the water boards of Waterschap Vechtstromen (WVS) and Waterschap Drents Overijsselse Delta (WDOD) for providing data.

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6. Ecological risk assessment of pharmaceuticals in the transboundary Vecht River (Germany/Netherlands) - Article 3

Published as:

Duarte DJ, Niebaum G, Lämmchen V, van Heijnsbergen E, Oldenkamp R, Hernández-Leal L, Schmitt H, Ragas AMJ, Klasmeier J, 2021. Ecological Risk Assessment of Pharmaceuticals in the Transboundary Vecht River (Germany and The Netherlands). Environ. Toxicol. Chem. (00), 1-15. https://doi.org/10.1002/etc.5062

The discovery and manufacture of APIs have brought human and veterinary medicine into a modern era (Erhardt, 2006). Many healthcare and agricultural food production systems around the globe rely on APIs to prevent and cure a variety of diseases in humans and animals, which has led to the continued consumption of APIs (Klein et al., 2018). Accompanying, this has led to a massive release of APIs into the environment (Carlsson et al., 2006; Comber et al., 2018). As has been shown many times up to this point, GREAT-ER is a suitable tool to evaluate these environmental impacts.

Since the work in this article was implemented within the framework of the Meduwa project already described, the area of consideration in this case is again the German-Dutch catchment of the Vecht river. While the previous article was mainly concerned with the hydrological conditions of the catchment area and how to model the particularities, the following article conducts a comprehensive risk assessment in the area. This study thus also follows the catchment-based approach required by the WFD (EC, 2000), moving away from national risk assessments and administratively drawn borders (e.g. van der Aa et al., 2013) replacing them with more detailed, transboundary, catchment-wide approach, which also takes into account country-specific differences.

Dealing with all APIs that might be present in the water would have been beyond the scope of Meduwa. Therefore, 15 reference substances were selected at the start of the project. These represent a broad spectrum of drugs of different therapeutic classes for use in human medicine, but also some important veterinary antibiotic compounds. The focus of the selection was to represent a good range of physicochemical properties and

biological transformation potential, compounds already relatively well studied, and others with relatively little empirical data. More on this topic can be found on the already linked project website.

In order to obtain information on the potential ecological risks of the drugs during the project period, all project partners have, as far as possible, always considered all of these 15 substances in their subprojects. Thus, in the context of this article, eight of these fifteen substances are considered in more detail using the methods presented for risk assessment. To accomplish this, the study defines ecological risk profiles for surface water concentrations for the following APIs: Carbamazepine, ciprofloxacin, cyclophosphamide, diclofenac, erythromycin, 17α-ethinylestradiol, metformin and metoprolol.
Ecological assessments of streams conducted in Europe and elsewhere have consistently found that APIs and other emerging contaminants pose a potential risk to freshwater biota (Gómez-Canela et al., 2019). So in addition to other unwanted effects, the selected APIs may have adverse effects on wildlife in the environment, particularly aquatic life. Therefore, it is important to also assess the potential adverse effects on aquatic ecosystems as part of a risk assessment.

The article is composed of three building blocks: 1) the georeferenced estimation of active ingredient concentrations in surface water using the GREAT-ER model, 2) the derivation of new predicted non-effect concentrations (PNECs) the studied active ingredients, performed by the University of Nijmegen, and 3) the generation of detailed spatially explicit ecological risk profiles of active ingredients under two different water flow scenarios.
The hydrologic model and the flow scenarios used in this study were set up in the previous article (Lämmchen et al., 2021b) and were further refined for this work, as will be described in the article. The hydrology and the simulations run on it form the basis for many of the analyses performed in this work. In this context, data acquisition and processing for model parametrization, as well as scenario set-ups were performed collaboratively with Gunnar Niebaum accompanied by advisory exchange with Jörg Klasmeier. Calculation of seasonal surface photolysis rates were performed by Jörg

Klasmeier. Gunnar Niebaum was in charge of the model evaluation, i.e. comparing predicted WWTP loads and in-stream concentrations against measured values. The latter were obtained as part of a one year monitoring campaign in the Vecht catchment and provided by co-authors from WETSUS, European Centre of Excellence for Sustainable Water Technology. I was involved in the planning of the monitoring campaign which was performed by WETSUS under the lead of Eri van Heijnsbergen. The comparison of PECs and PNECs was performed jointly by the first authors (D. Duarte, G. Niebaum, V. Lämmchen; as marked in the article). PNECs were derived by Daniel Duarte, Rik Oldenkamp and Ad Ragas. The first authors contributed equally to the writing of the original draft of the manuscript. All authors contributed equally to reviewing and editing the manuscript.

Ecological Risk Assessment of Pharmaceuticals in the Transboundary Vecht River (Germany and The Netherlands)

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Received: 11 December 2020 / Revised: 18 January 2021 / Accepted: 31 March 2021

Abstract

Millions of people rely on active pharmaceutical ingredients (APIs) to prevent and cure a wide variety of illnesses in humans and animals, which has led to a steadily increasing consumption of APIs across the globe and concurrent releases of APIs into the environment. In the environment, APIs can have a detrimental impact on wildlife, particularly aquatic wildlife. Therefore, it is essential to assess their potential adverse effects to aquatic ecosystems. The European Water Framework Directive sets out that risk assessment should be performed at the catchment level, crossing borders where needed. The present study defines ecological risk profiles for surface water concentrations of 8 APIs (carbamazepine, ciprofloxacin, cyclophosphamide, diclofenac, erythromycin, 17α-ethinylestradiol, metformin, and metoprolol) in the Vecht River, a transboundary river that crosses several German and Dutch regions. Ultimately, 3 main goals were achieved: 1) the geo-referenced estimation of API concentrations in surface water using the geography-referenced regional exposure assessment tool for European rivers; 2) the derivation of new predicted-no-effect concentrations for 7 of the studied APIs, of which 3 were lower than previously derived values; and 3) the creation of detailed spatially explicit ecological risk profiles of APIs under 2 distinct water flow scenarios. Under average flow conditions, carbamazepine, diclofenac, and 17α-ethinylestradiol were systematically estimated to

surpass safe ecological concentration thresholds in at least 68% of the catchment's water volume. This increases to 98% under dry summer conditions.

Keywords

Pharmaceuticals; Water quality; Ecological risk assessment; Geographic information systems; Environmental modeling; Surface water; Toxic effects; Geo-referenced modeling

Introduction

The discovery and manufacture of active pharmaceutical ingredients (APIs) have prompted human and veterinary medicine to a modern era. Many health care and agriculture food production systems around the globe rely on APIs to prevent and cure a wide variety of illnesses in humans and animals, which has led to a sustained consumption of them (Klein et al., 2018). Next to the benefits of APIs, their widespread use has also led to unintended consequences such as antimicrobial resistance (Young, 1993; Hernando-Amado et al., 2019) and environmental pollution (aus der Beek et al., 2016). The occurrence of APIs in the environment can have detrimental impacts on wildlife (Shultz et al., 2004; Jobling et al., 2006; Saaristo et al., 2018). To guarantee a good surface water quality, it is essential to assess potential adverse effects of APIs to aquatic ecosystems. The corresponding legal framework comprises the European Union's Water Framework Directive (European Commission 2000) and the Priority Substances Directive (European Commission 2008). These directives impose the protection of water resources on European Union member states, for example, by defining environmental quality standards (EQSs) for 45 priority substances. However, none of these substances is an API. Instead, a limited set of APIs is covered in a biennial watch list of water pollutants that should be carefully monitored because of insufficient monitoring data and concerns about their ecological impact. The Water Framework Directive calls for a basin approach, moving away from national risk assessments (Coppens et al., 2015; Vissers et al., 2017) and complementing it with more detailed, in some cases transboundary, catchment-wide risk assessments. Determination of the chemical status of a surface water within the context of the Water Framework Directive relies on the quantification of risk by integrating exposure and effect assessments.

Exposure assessment can be based on measured environmental concentrations (MECs), predicted environmental concentrations (PECs) using chemical fate models or a

combination of both. In the past 30 yr, a variety of models have been developed to derive PECs for chemicals, such as ePiE (Oldenkamp et al., 2018), iStream (Kapo et al., 2016), a contaminant fate model (Grill et al., 2016), PhATE™ (Anderson et al., 2004), STREAM-EU (Lindim et al., 2016), GLOBAL-FATE (Font et al., 2019), and the geography-referenced regional exposure assessment tool for European rivers (GREAT-ER; Feijtel et al., 1997; Kehrein et al., 2015; Lämmchen et al., 2021), varying in complexity and geographical and temporal resolution. The concentration gradient along a watercourse is highly dependent on local socioeconomic and environmental factors. Therefore, the degree of access to detailed local data (e.g., pharmaceutical consumption patterns) and spatiotemporal information (e.g., seasonal hydrological landscape) is an important driver for the accuracy of exposure models at the catchment level (Tiedeken et al., 2017; Oldenkamp et al., 2018; Font et al., 2019).

A comprehensive effect assessment requires extensive ecotoxicological information to derive safe concentration thresholds for aquatic ecosystems, for example, predicted-no-effect concentrations (PNECs) or EQSs. To optimize the accuracy of the assessment, it is common practice to gather all available toxic effect data on a substance and select an extrapolation method that matches the available data. Therefore, the estimation and accuracy of useful PNECs is highly dependent on up-to-date ecotoxicological data and requires continuous revision to accommodate new evidence.

Riverine ecological assessments conducted in Europe and elsewhere have recurrently found APIs and other emerging pollutants to pose a potential risk to freshwater biota (Gómez- Canela et al., 2019). A main obstacle to modeling studies of API residues in transboundary catchments is the restricted access to detailed national and regional API-specific consumption data (Tiedeken et al., 2017). Additional obstacles include different national and regional water management strategies, diverse wastewater treatment efficiencies, the heterogeneity of the landscape, seasonal variation in environmental conditions, and variable demographics (Popelka and Smith 2020).

The main aim of the present study was to construct ecological risk profiles for surface water concentrations of 8 environmental residues of APIs in the European transboundary Vecht River, a river that crosses several German and Dutch regions. Firstly, an exposure assessment was performed by the applying the geo-referenced model GREAT-ER, which

has a good track record for predicting pharmaceutical PECs in river catchments (Schowanek and Webb 2002; Capdevielle et al., 2008; Cunningham 2008; Hannah et al., 2009; Alder et al., 2010; Aldekoa et al., 2013; Hanamoto et al., 2013; Zhang et al., 2015; Archundia et al., 2018; Caldwell et al., 2019). Secondly, an effect assessment was performed based on existing ecotoxicological information. This information was used to determine PNECs by incorporating recent test results. Finally, PECs and PNECs were coalesced into ecological risk quotients (RQs) throughout the Vecht River network under 2 distinct water flow condition scenarios. This helps improve our understanding of the risk posed by APIs to local freshwater communities and advances the ability to evaluate and prioritize potential (local) mitigation strategies before their implementation by competent authorities (Government of The Netherlands 2019).

Materials and methods

Pharmaceuticals

Ecological risks were assessed for 8 selected APIs (Table 1). These represent only a subset of APIs detected in the Vecht River catchment (data not shown). The selection covers a wide range of consumption patterns, therapeutic classes, chemical properties, and levels of data availability (Supplemental Data).

TABLE 1: Names, Chemical Abstracts Service numbers, Anatomical Therapeutic Chemical codes, and therapeutic classes of the 8 active pharmaceutical ingredients assessed in the present study

API	CAS no.	ATC code	Therapeutic class
17α-Ethinylestradiol[a]	57-63-6	G03CA01	Sex hormones
Carbamazepine[c]	298-46-4	N03AF01	Antiepileptics
Ciprofloxacin[b]	85721-33-1	J01MA02	Antibacterials
Cyclophosphamide	50-18-0	L01AA01	Antineoplastics
Diclofenac[a]	15307-86-5	M01AB05	NSAID
Erythromycin[a]	114-07-8	J01FA01; QJ01FA01[d]	Antibacterials
Metformin[c]	657-24-9	A10BA02	Antidiabetics
Metoprolol	37350-58-6	C07AB02	Beta-blockers

[a]Substance excluded from the watch list under the Water Framework Directive (Gomez Cortes et al., 2020).
[b]Substance included in the watch list under the Water Framework Directive (Gomez Cortes et al., 2020).
[c]Candidate substance suggested by individual member for inclusion for the next watch list under the Water Framework Directive (Gomez Cortes et al., 2020). [d]Substance used in human and veterinary medicine.
API = active pharmaceutical ingredient; CAS = Chemical Abstracts Service; ATC = Anatomical Therapeutic Chemical.

Case study area

The study area comprises the catchment area of the German and Dutch transboundary Vecht River, a tributary of the Dutch IJssel River. The area is under the influence of diverse anthropological stressors (e.g., treated wastewater emissions, water level control via pumps and locks; Lulofs and Coenen 2007; Wöhler et al., 2020; Lämmchen et al., 2021). The catchment extends over an area of approximately 6100 km². The total length of the Vecht River itself amounts to 167 km, of which approximately 107 km are located in Germany.

The German part of the catchment is located in the western part of Lower Saxony and in small sections of North Rhine- Westphalia, comprising the smaller part of the total catchment area with a share of 1800 km² (Figure 1). In Germany, the Vecht is a medium-sized river (long-term annual average flow of approximately 18.5 m³/s at the German–Dutch border) with many small tributaries, for example, the Steinfurter Aa and the Dinkel.

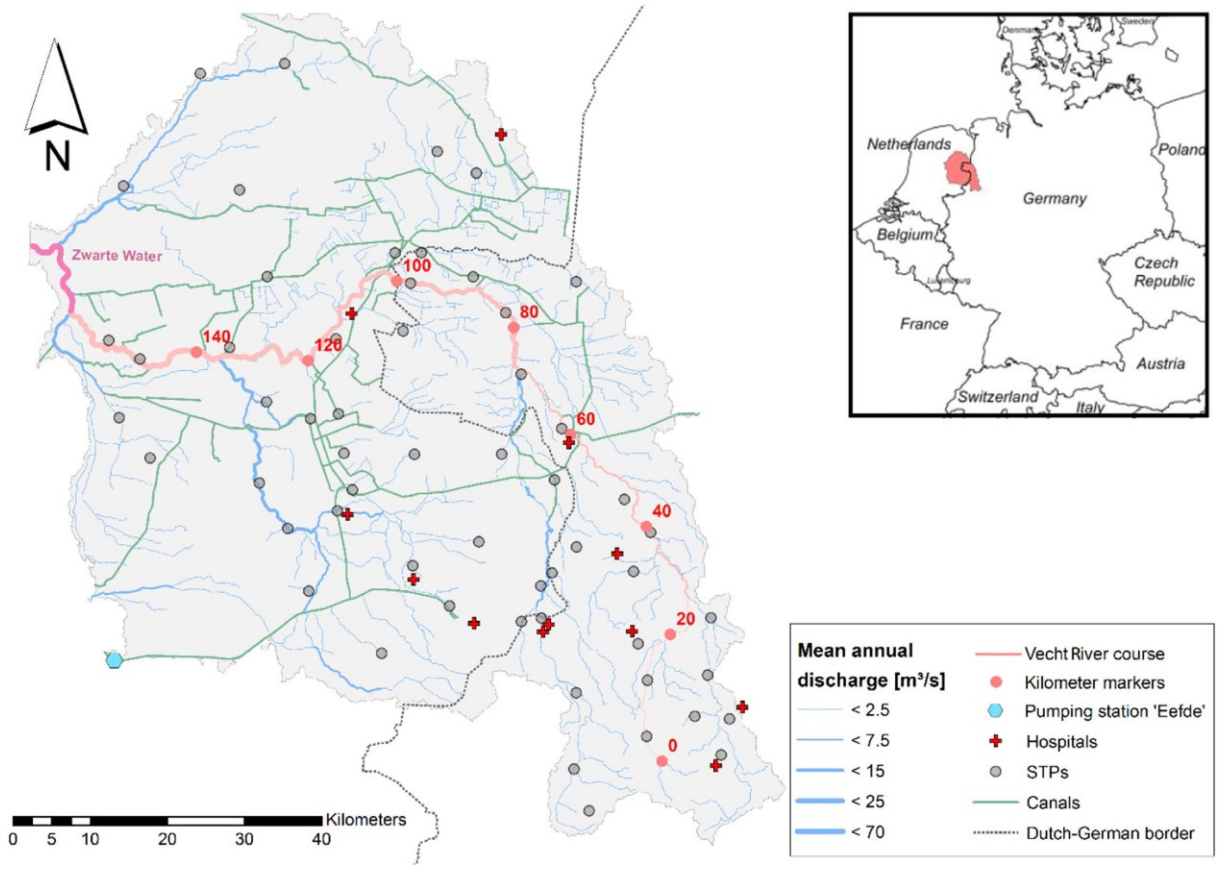

FIGURE 1: Vecht River basin. Kilometer markers start at the confluence of the Vecht tributaries Burloer Bach and Rockeler Mühlenbach. STPs = sewage treatment plants.

The river system is still in an almost natural state in the German regions (Lulofs and Coenen 2007), with a few canals (e.g., Ems-Vecht Canal and the Nordhorn-Almelo Canal) having negligible influence on river flow. The German part is less densely populated (160 inh/km2) than the Dutch part (260 inh/km2) because only small towns such as Nordhorn and Gronau (≈50 000 inhabitants) are located in this area. In total, emissions from approximately 400 000 inhabitants connected to 25 sewage treatment plants (STPs) enter the German Vecht. In addition, the wastewater of 6 hospitals with approximately 1200 beds in total is treated by the STPs.

Approximately 4300 km² of the transboundary catchment is located in The Netherlands, namely in the provinces of Overijssel and Drenthe. This part of the catchment is highly influenced by anthropogenic activities, which resulted in canals, sluices, pumps, and river straightening (Lulofs and Coenen 2007; Lämmchen et al., 2021). Larger cities with more than 100 000 inhabitants are Enschede, Zwolle, and Emmen. In total, more than 1 000 000 inhabitants are connected to 32 STPs, as are 7 hospitals with approximately 2000 beds in total. The Zwarte Water River, a short prolongation of the Vecht River and an inflow of the Zwarte Meer Lake, was integrated into the model representation.

Environmental exposure assessment

The GREAT-ER model was used to predict environmental concentrations of the 8 case study APIs. The GREAT-ER model was originally developed to predict spatially explicit stationary exposure concentrations of “down-the-drain” chemicals in surface waters at the catchment level (Feijtel et al., 1997). The model has been successfully applied to various chemicals in different European catchments (Hüffmeyer et al., 2009; Alder et al., 2010; Aldekoa et al., 2013; Kehrein et al., 2015). A detailed description of the functions of the model and its latest extensions can be found in Kehrein et al., (2015; Lämmchen et al., 2021). The model mainly consists of 3 components: the hydrological network, the emission model, and the fate model. The hydrological network is the centerpiece of the GREAT-ER model. The water network is discretized into river segments with a length of up to 2 km. Each segment carries a property vector that is used to calculate the chemical's fate and concentration.

Exposure scenarios

The steady-state model GREAT-ER represents a static hydrological situation over time. Two different scenarios were set up for the hydrological network, a low-flow condition scenario (mostly dry periods in summer) and an average-flow condition scenario (Table 2). This allows for considering the effect of the change of flow directions in some parts of the network during dry periods caused by pumping systems in the Dutch canals (Lämmchen et al., 2021).

TABLE 2: Characteristics of the simulated low-flow and average-flow condition scenarios

	Dry summer scenario	Average condition scenario
Applicability	Dry periods without rainfall between June and September	Humid periods throughout the year
Flow rate at the border (m^3/s)	2.82	18.5
Flow rate at the Zwarte water (m^3/s)	11.31	63.45
Flow velocity at the border (m/s)	0.22	0.6
Flow velocity at the Zwarte Water (m/s)	0.33	0.85
Pumping activity	Yes	No
Pumping description	120 d/yr between March and October (Netherlands)	---
Pump power "Eefde" (Twente Canal; m^3/s)	1.6 (mean), 14 (maximum)	---
Changes in flow direction	Yes Twente Canal, Zijkanaal Almelo, Canal Almelo-De Haandrik and several emerging smaller canals	No

Model parameterization

A key input parameter is the consumption of APIs in the investigated area. It is well known that consumption patterns sometimes vary between countries and regions, which holds true for some of the investigated compounds in The Netherlands and Germany (Table 3). Regional sales data for the Vecht catchment from 2017 were acquired for the regions in Germany and The Netherlands from IQVIA Commercial GmbH & Co. OHG (IQVIA, Frankfurt am Main, Germany, unpublished data) and the Dutch Foundation for Pharmaceutical Statistics (SFK, The Hague, Netherlands, unpublished data) at the

postcode level (Supplemental Data, Table S1). Data include pharmacy sales but not the amount dispensed in hospitals, nursing homes, or by general practitioners. Drugs sold over the counter are included in the German data set but not in the Dutch data set. Annual prescription data were divided by the population number in the respective area, resulting in average per-capita consumption values (Supplemental Data, Table S1). The contribution of hospitals was considered in terms of a per-bed application. This number was different for the 2 countries and was estimated from available prescription data of selected hospitals on both sides of the border (Supplemental Data, Table S1).

TABLE 3: Relative percentage differences of prescribed per-capita pharmaceutical masses in the Vecht River basin regional area, Germany and The Netherlands

	Regional-to-national (%)		Germany-to Netherlands (%)	
	Germany	Netherlands	Within region	Between countries
17α-Ethinylestradiol	12	−2	-75	−78
Carbamazepine	−4	16	2	25
Ciprofloxacin	9	10	27	28
Cyclophosphamide[a]	33	n.a.	n.a.	n.a.
Diclofenac	−2	−2	183	183
Erythromycin	56	−13	1594	853
Metformin	−14	6	−26	−9
Metoprolol	−8	22	−10	20

[a]Cyclophosphamide is restricted to clinical use. The Dutch Foundation for Pharmaceutical Statistics only collects domestic pharmaceutical consumption. Therefore, no cyclophosphamide is recorded for The Netherlands.
n.a. = not applicable.

Emission loads into the sewer system of an STP were estimated by multiplying the per-capita and per-bed application rates with the number of connected inhabitants or hospital beds, respectively. Because most APIs are metabolized after uptake, only the excreted fraction was considered (Supplemental Data, Table S2). Metabolites such as glucuronides, which react back to the parent compound after release into the sewer, were also included (Heberer and Feldmann 2005).

A fraction of the excreted amount is removed during wastewater treatment in STPs. In the Vecht River catchment, all STPs are equipped with biological treatment with no additional stage for further elimination of micropollutants such as ozonation, ultrafiltration, or activated charcoal filtration. Although removal efficiencies may depend on the specific

operating conditions (Verlicchi et al., 2012), equal removal efficiency for each API in all STPs was assumed.

From a comprehensive literature search, removal efficiencies determined in STPs equipped with biological treatment collected as composite samples (>24 h) were used to calculate median values for the model simulations (Supplemental Data, Table S4).

The estimated load in treated effluents is routed into the receiving rivers at the respective discharge points. Cumulated loads are propagated through the river network and used to estimate spatially resolved API concentrations (PECs) through division of the load by the respective river flow rate. In addition, the fate model accounts for physicochemical loss processes such as (bio)degradation, sedimentation, and photolysis. Degradation via hydrolysis and dissipation via volatilization were not accounted for because of their negligible influence on APIs (Patel et al., 2019). A detailed overview of the parametrization of in-stream processes is provided in Supplemental Data, Table S5.

Model evaluation

The model performance was evaluated stepwise by comparison of simulation results with monitoring data for selected APIs in STP influents and effluents as well as at selected river sites (Figures 2 and 3). A comprehensive description of the sampling strategy is provided elsewhere (Heijnsbergen et al., unpublished manuscript). A brief overview and details for the chemical analysis are provided in Supplemental Data, S1.1 and S1.2.

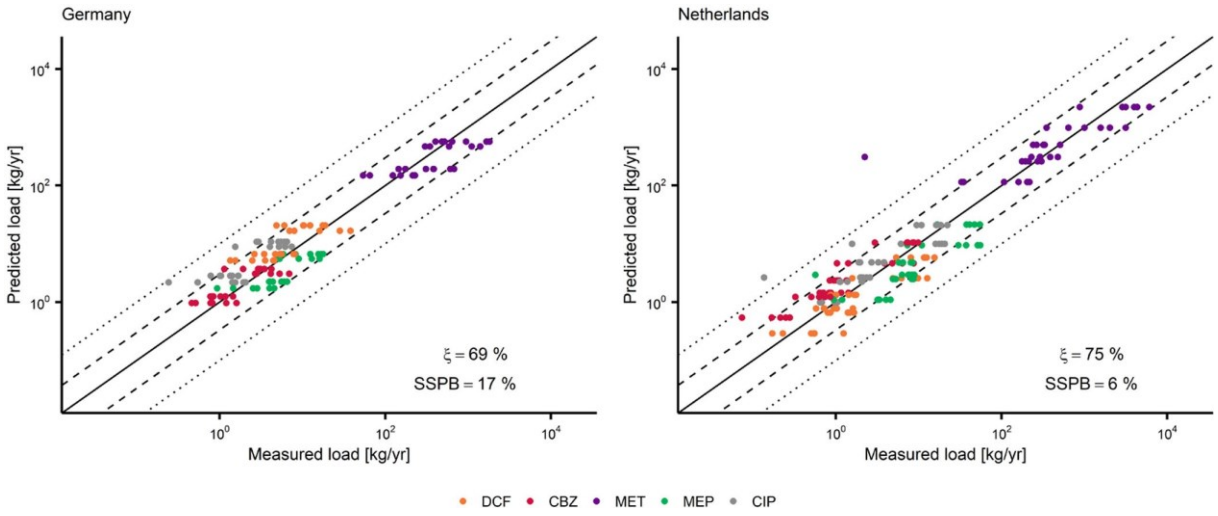

FIGURE 2: Predicted and measured sewage treatment plant (STP) influent loads of 5 pharmaceuticals (with quantification frequency >90%) in German STPs (n = 125) and Dutch STPs (n = 170). Dashed lines indicate the 1:3 and 3:1 ratios; dotted lines indicate the 1:10 and 10:1 ratios. SSPB = symmetric signed percentage bias; DCF = diclofenac; CBZ = carbamazepine; MET = metformin; MEP = metoprolol; CIP = ciprofloxacin.

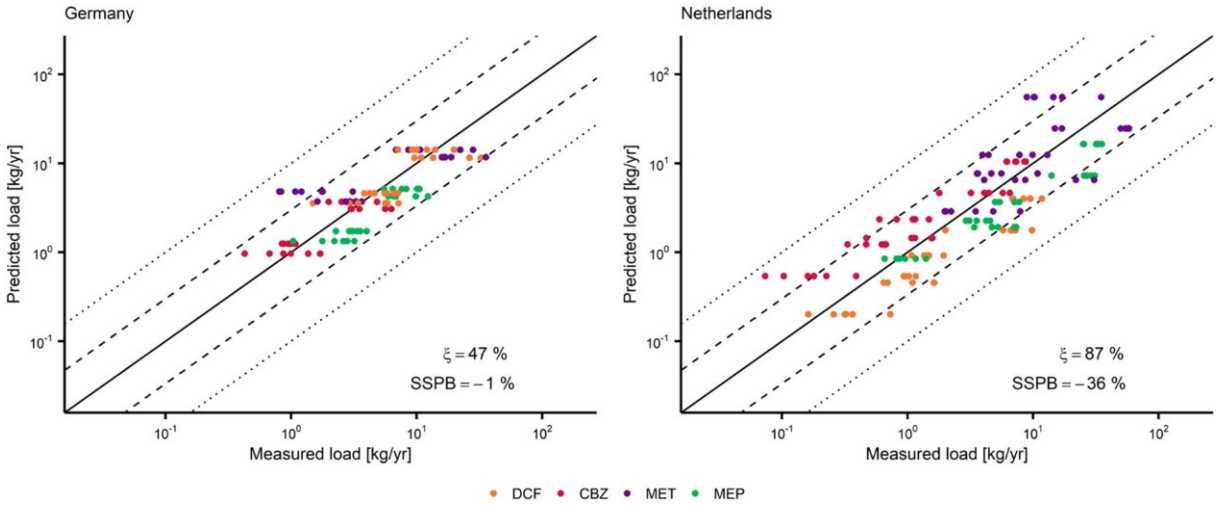

FIGURE 3: Predicted and measured sewage treatment plant (STP) effluent loads of 4 pharmaceuticals (with quantification frequency >90%) in German STPs (n = 100) and Dutch STPs (n = 132). Dashed lines indicate the 1:3 and 3:1 ratios; dotted lines indicate the 1:10 and 10:1 ratios. SSPB = symmetric signed percentage bias; DCF = diclofenac; CBZ = carbamazepine; MET = metformin; MEP = metoprolol.

Two model performance quantitative measures were applied: median symmetric accuracy (ξ) and the symmetric signed percentage bias (SSPB; Morley et al., 2018),

1) $$r_i = \frac{X_{i,pred}}{X_{i,meas}}$$

2) $$\xi(\%) = 100 \times (e^{M(|\ln r_i|)} - 1)$$

3) $$\text{SSPB}(\%) = 100 \times (e^{|(M(\ln r_i)|} - 1) \times \text{sgn}(M(\ln r_i))$$

where r_i is the ratio of the predicted/measured pair (e.g., loads), $x_{i,pred}$ is the predicted value, $x_{i,meas}$ is the corresponding value from the measurement data, M is the median function, sgn is the sign function, and is the index within a subgroup of all predicted/measured pairs for a single compound, scenario, country, sampling site, or a combination of these.

The median symmetric accuracy (Equation 2) is a measure of central tendency that is robust to the presence of outliers and resistant to data spanning several orders of magnitude. For the scope of the present study, we consider ξ values up to 100 and up to 200% as indicative of "good agreement" and "acceptable agreement" between measurements and predictions, respectively. Values of ξ > 200% indicate "poor agreement" between measurements and predictions. A ξ = 100% indicates that the median of the absolute ratios ($|r_i|$) is 2 (i.e., 50% of predicted values deviate from measured values by less than a factor of 2). The symmetric signed percentage bias (Equation 3) can be interpreted similarly to a mean percentage error, but it penalizes underestimation and overestimation equally. Positive values indicate a tendency to overestimate predictions, whereas negative values indicate a tendency to underestimate predictions. In the present study, absolute values of SSPB up to 50, 100, and 200% were considered as an indication of "small," "medium," and "large" overestimations or underestimations, respectively. Absolute values >200% were considered "very large" overestimations/underestimations. An SSPB = −50% indicates that the median of relative ratios (r_i) is 50% lower in the predictions compared to measured data. This implies that 50% of the predicted values underestimate the measurements by at least a factor of 1.5. Predictions of STP emissions were evaluated on a load-based approach. Measured concentrations in STP influent and effluent were multiplied with the annual discharge of the corresponding STP and compared to model

predictions. The APIs with a quantification frequency <90% were evaluated semi-quantitatively. Concentrations below the limits of quantification (LOQ) were processed as LOQ in the evaluation approach because they are expected to be close to the LOQ value as a result of the high quantification frequency.

Surface water PECs were evaluated using the "benchmark" concept, according to Kunkel and Radke (2012), with which concentrations of individual APIs are normalized to the concentration of a conservative tracer or reference. Thereby, river flow variations can be excluded from the evaluation process. Carbamazepine was selected as the conservative reference compound because of its persistence in the environment (Aminot et al., 2016). Benchmark ratios from the monitoring data could only be calculated if the concentration of the reference (carbamazepine) and that of the respective target API this approach, predicted carbamazepine concentrations were evaluated by comparison with measured concentrations (Supplemental Data, S1.3).

Environmental effect assessment

Search strategy

Aquatic ecotoxicity data were compiled without restrictions from the following databases: ECOTOX Knowledgebase (US Environmental Protection Agency 2019), e-toxBase (Posthuma et al., 2019), Wikipharma (Molander et al., 2009), FASS (Trade Association for the Research-Based Pharmaceutical Industry in Sweden 2019), iPiESum (Innovative Medicines Initiative 2019), and the EU WRC report (Johnson and Harvey 2002). To further supplement collected data, a literature review was performed by searching the Web of Science platform in March 2019 (Supplemental Data, Table S11). The search was restricted to publications from 2016 or later to capture information not covered by the other sources. The search returned 233 publications that were fully assessed.

Data extraction and harmonization

All relevant toxicological information referring to the 8 APIs of interest was extracted from the databases. Additional toxicity data were extracted from 40 publications identified in the public literature search. The following relevant information was extracted and compiled: substance name, Chemical Abstracts Service number, taxon, species, life stage and living compartment of the species tested, toxic effect, exposure type, exposure

duration, endpoint type, and endpoint value. This process resulted in an initial database with a total of 11 029 entries (Table 4). The data were harmonized to guarantee their consistency and usability, which included harmonizing the names of species, toxic effects, exposure duration and types, end points, and concentration units (Supplemental Data, S2).

TABLE 4: Number of ecotoxicological data entries per source in the database compiled in the present study

Source	Entries
ECOTOXbase	6510
Wikipharma	2802
e-toxBase	779
Literature	455
IpiESum	270
EU WRC report	140
FASS	74

Data selection

The information in the database was filtered to obtain only relevant data for analysis. Only aquatic or semiaquatic species were included. Entries referring to terrestrial species, communities, sediment tests with no reported water concentrations, or in vitro tests or with no single species name specified were excluded from the analysis. Only population- relevant endpoints were selected, that is, those which can adversely affect an organism's survival, ability to maintain its population numbers, reproduction, development, growth, or behaviour. Effect endpoints with right/left-censored values (i.e., <, >, ≤, ≥) were excluded. Similarly, identical effect entries from the same original source were excluded. Toxicity values for the same species and endpoint but originating from different studies were aggregated by taking the geometric mean weighted by the number studies with identical endpoints. This resulted in a final database containing 169 effect values usable for further analysis.

Data reliability

To ensure that we only included reliable and relevant toxicity studies in our assessment, all studies were assigned a criteria for reporting and evaluating ecotoxicity data (CRED) score (Moermond et al., 2016a). Studies classified as unreliable (R3), unassignable reliability (R4), irrelevant (C3), or unassignable relevance (C4) were excluded from further analysis.

We preferably used classification scores from official sources, such as the Dutch National Institute for Public Health and the Environment and the German Environment Agency.

Alternatively, the authors (D.J. Duarte, R. Oldenkamp, and A.M.J. Ragas) independently assigned CRED scores to critical studies according to Moermond et al., (2016a) after evaluating and discussing any inconsistencies (Supplemental Data, Table S12). Exceptionally, experiments on 17α-ethinylestradiol without classifications from official sources were not evaluated because of the extensive number of studies and additional complexity of assessing the quality of ecotoxicological studies testing endocrine-disrupting effects; such an exhaustive assessment was considered beyond the scope of the present study.

PNECs

Two extrapolation methods for the derivation of chronic PNEC values are typically used in effect assessment: the species sensitivity distribution (SSD) and the assessment factor (European Commission 2000, 2006). According to European Union guidance, an SSD-based PNEC requires a considerable amount of data covering at least 3 trophic levels (primary producers, plant-eating animals, and predators), at least 8 taxonomic groups, and at least 10 effect values (one per species per substance). As for the assessment factor approach, at least one short-term median effective concentration from each of the 3 trophic levels is the minimum requirement. Because the final database did not satisfy SSD data requirements for the derivation of PNECs, only the assessment factor approach was implemented (Supplemental Data, Table S15). The estimation of a PNEC using this deterministic approach was done by dividing the lowest effect concentration by an assessment factor, according to the European Union Water Framework Directive guidance for deriving aquatic EQSs (European Commission 2018). Depending on the available data, this factor varies between 10 and 1000. A collection of PNEC estimates from the literature and other sources was gathered for comparison (Supplemental Data, Table S16).

Ecological risk

Predicted environmental concentrations and PNECs were used to calculate a site-specific RQ associated with each API following the equation,

4) $$RQ_{s,p} = \frac{PEC_{s,p}}{PNEC_p}$$

where $RQ_{s,p}$ is the RQ at site for pharmaceutical p, $PEC_{s,p}$ (µg/L) is the PEC at site for pharmaceutical p, and $PNEC_p$ (µg/L) is the PNEC for pharmaceutical p. Evaluation of PNEC exceedance was performed based on the total river volume in the Vecht catchment and for the cumulated flow length of the water bodies in the catchment. Because of the steady-state assumption of the GREAT-ER model, a constant water volume in the system is assumed for each of the scenarios. Pharmaceutical mixture risk was calculated based on the conservative approach of concentration addition following the equation,

5) $$RI_s = \sum_{i=1}^{n} RQ_{s,p}$$

where RI_s is the risk index of a pharmaceutical mixture at site, $RQ_{s,p}$ is the risk quotient at site for pharmaceutical p, is the summation index, and is the total number of APIs. The concentration addition approach tends to overestimate the mixture risk of dissimilarly acting substances because it assumes a similar noninteractive mode of action of all mixture components. However, there is growing consensus on the pragmatic and precautious utility of this approach in aggregating risks of mixture components (European Commission 2012; Backhaus 2016; Posthuma et al., 2018; Hernandez et al., 2019; Kienzler et al., 2019).

Results and Discussion

Predicted surface water concentrations

Predicted carbamazepine concentrations were evaluated to provide a reliable baseline for the benchmark approach (Supplemental Data, S3). Because carbamazepine is consumed equally throughout the year, evaluation can be performed using all data without differentiation into the 2 exposure scenarios (see above, Exposure scenarios). Figure 4 shows an acceptable overall agreement between PECs and MECs (ξ = 106%), with a tendency to being rather overestimated (SSPB = 59%). Approximately 80% of the PEC and MEC data differ by less than a factor of 3, so we conclude that carbamazepine provided a

valid baseline for the application of the benchmark approach (Supplemental Data, Figure S3).

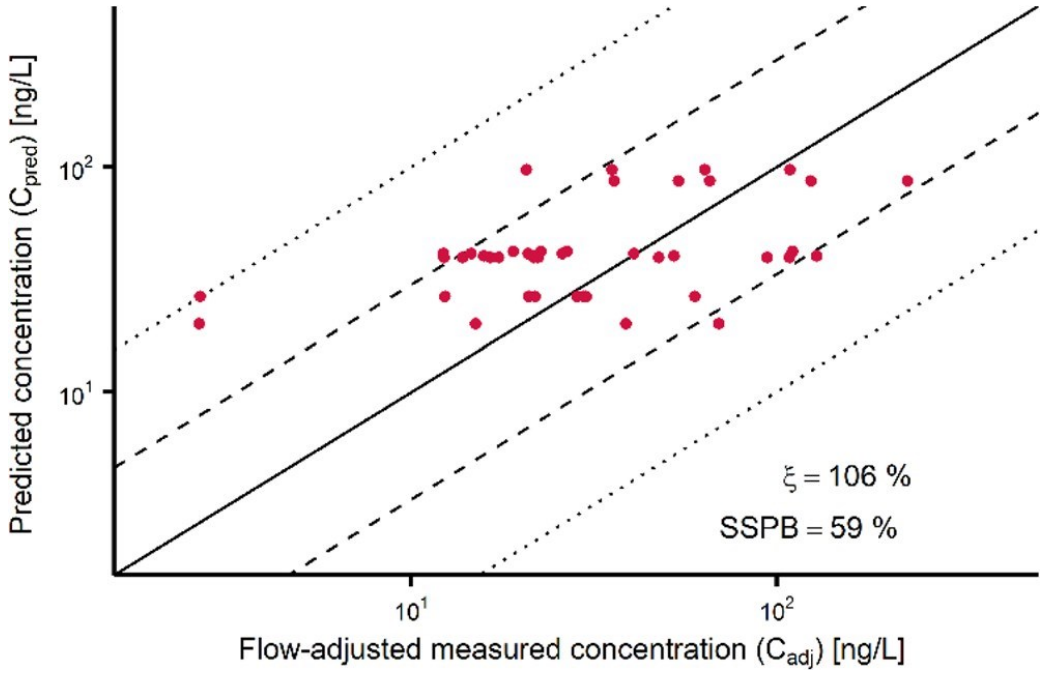

FIGURE 4: Comparison of predicted and measured carbamazepine concentrations in the Vecht catchment (n = 46) at monitoring sites where reliable gauging data of the corresponding sampling day were available (i.e., no change in flow direction, resulting in net flow rates of 0 m^3/s). Measured concentrations were adjusted to the flow rate used in the simulations. Dashed lines indicate the 1:3 and 3:1 ratios; dotted lines indicate the 1:10 and 10:1 ratios. SSPB = symmetric signed percentage bias.

The quantification frequency of erythromycin and ciprofloxacin in the river samples was <10%. Cyclophosphamide and 17α-ethinylestradiol were not analyzed at all because of the expectation of very low concentrations far below the LOQ. Because all predicted concentrations of these compounds were below the LOQ, qualitative agreement is given. Diclofenac, metformin, and metoprolol concentrations were evaluated separately for the 2 exposure scenarios because of obvious seasonal differences (see above, Exposure scenarios). Predicted and measured benchmark ratios agreed well for both the average condition scenario (ScnAC; ξ = 52%, SSPB = 10%) and the dry summer scenario (ScnDS; ξ = 59%, SSPB = 45%), with approximately 80% within the range of a factor of 3 (Figure 5).

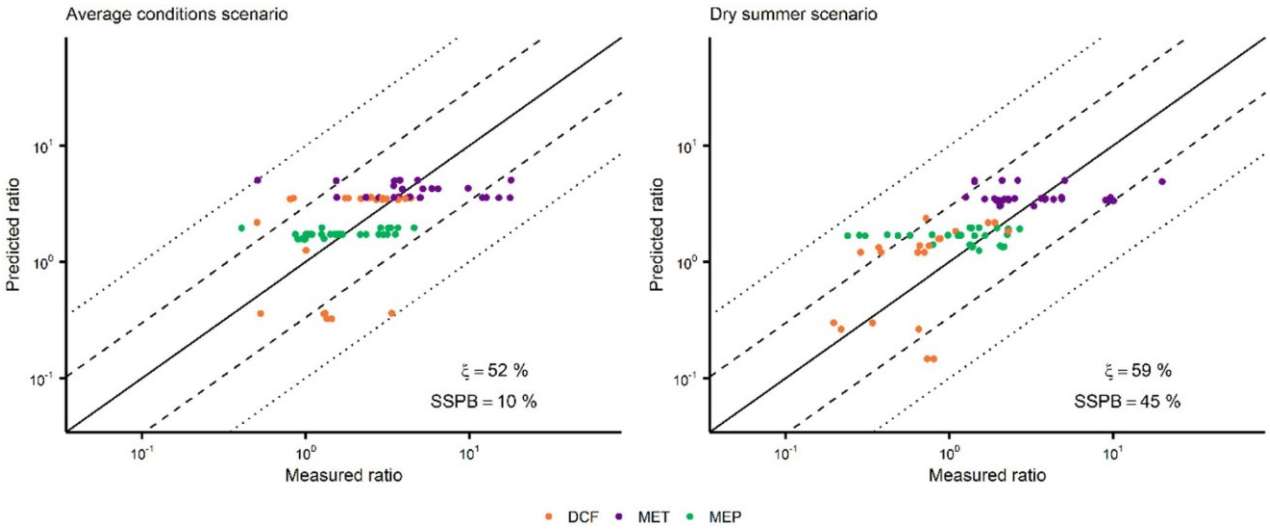

FIGURE 5: Predicted and measured benchmark ratios of 3 pharmaceuticals at monitoring sites in the whole Vecht River catchment (average condition scenario n = 80, dry summer scenario n = 81). Dashed lines indicate the 1:3 and 3:1 ratios; dotted lines indicate the 1:10 and 10:1 ratios. SSPB = symmetric signed percentage bias; DCF = diclofenac; MET = metformin; MEP = metoprolol.

Based on the successful model evaluation of PECs, simulations for the entire Vecht River catchment were performed. In the ScnAC, metformin, metoprolol, and carbamazepine had the highest PECs at watercourses affected by upstream STPs, with median concentrations of 0.19 (0.01–3.03), 0.07 (2 × 10−3–1.44), and 0.043 (2 × 10−3–0.84) µg/L, respectively. Similarly, the highest median PECs in the ScnDS were 0.57 (0.01–19.43), 0.25 (4 × 10−3–4.08), and 0.18 (0.01–2.36) µg/L for metformin, metoprolol, and carbamazepine, respectively. The preceding median, minimum, and maximum PEC values exclude river segments with a PEC of zero. In previous studies, these APIs have been predicted or measured at similar concentration ranges in Dutch (Oosterhuis et al., 2013; Moermond et al., 2020) and German (Scheurer et al., 2009; Meyer et al., 2016; Dusi et al., 2019) surface waters. Although metformin is effectively transformed into guanylurea during wastewater treatment (Oosterhuis et al., 2013), it exhibited the highest PEC among the investigated APIs. This is a consequence of the high consumption of metformin (twelfth highest defined daily dosage [DDD] and seventeenth most frequently used in The Netherlands; Dutch National Health Care Institute 2020) and its relatively high excretion rate. The lowest PECs in watercourses affected by STP effluents were exhibited by 17α-Ethinylestradiol and cyclophosphamide, with median concentrations in ScnAC of 0.02 (3 × 10−4–0.82) and

0.37 (0.01–9.64) ng/L, respectively. As for ScnDS, the concentrations for 17α-ethinylestradiol and cyclophosphamide were estimated at 0.05 (2 × 10–4–0.99) and 1.17 (2 × 10–4–756.98) ng/L, respectively. These results were in line with the low consumption volumes of these APIs, despite a considerable fraction being excreted.

Concentration profiles of the Vecht River main stream are displayed in Figure 6 for the 8 APIs in the 2 exposure scenarios. The factors that cause differences in the PEC profiles observed along the main stream can be manifold and API-dependent. Erythromycin's low PECs in the Dutch regions coincide with the Dutch population's lower consumption patterns compared with their German counterparts. Persistent substances which are equally consumed on both sites of the border, such as carbamazepine, show higher PECs in Dutch regions because of the higher population density. Dilution ratios of treated effluent after entering the river system are lower if more people are connected to rivers with comparable flow rates.

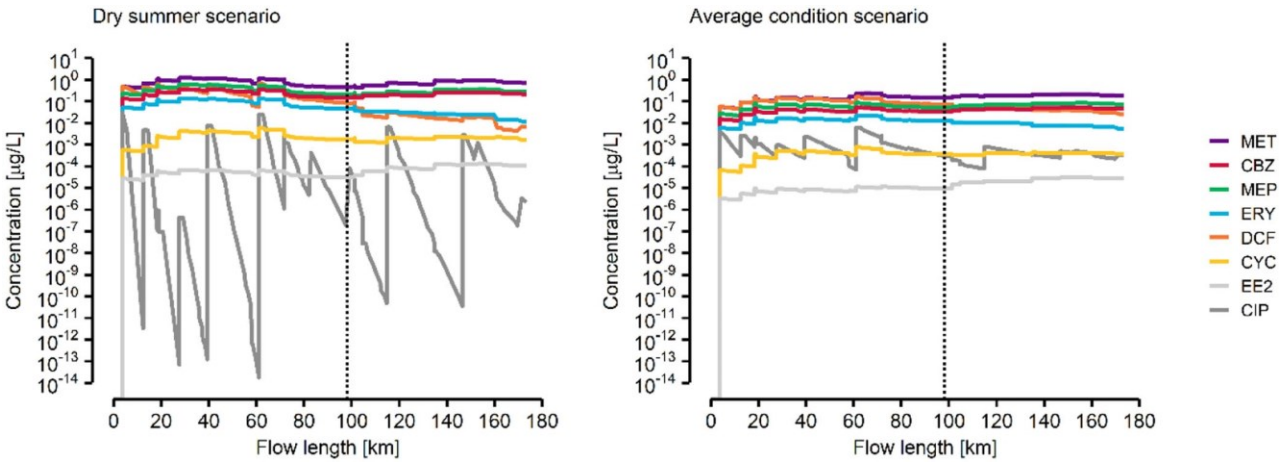

FIGURE 6: Predicted environmental concentrations of pharmaceuticals in the Vecht River main stream. The vertical black dashed line indicates the Dutch–German border. MET = metformin; CBZ = carbamazepine; MEP = metoprolol; ERY = erythromycin; DCF = diclofenac; CYC = cyclophosphamide; EE2 = 17α-ethinylestradiol; CIP = ciprofloxacin.

The effect of dilution is also clearly visible in the PEC profiles of the 2 scenarios: dilution in ScnDS is approximately 10 times lower than in ScnAC. Lower flow rates lead to higher residence times and lower water levels in the river system, resulting in a larger influence of dissipation processes in ScnDS than in ScnAC. As a result, predicted summer concentrations of most APIs (17α-ethinylestradiol, carbamazepine, cyclophosphamide,

erythromycin, metformin, and metoprolol) were on average a factor of 4 to 6 times higher than in ScnAC. Among the APIs studied, ciprofloxacin was the compound most susceptible to dissipation processes, namely via direct photolysis, resulting in drastically lower PECs in ScnDS than in ScnAC. Diclofenac is also prone to direct photolysis. This in combination with lower consumption rates in The Netherlands helps explain the low PECs downstream of the border in the ScnDS compared with ScnAC.

PNECs

In the environmental effect assessment, there was a clear disparity in data availability for different substances. The lowest chronic PNEC was exhibited by 17α-Ethinylestradiol (3.6 × 10−6 µg/L) and metformin the highest (440 µg/L). We revised existing chronic PNECs of the 8 APIs, including for diclofenac (0.01 µg/L), carbamazepine (0.02 µg/L), and cyclophosphamide (125 µg/L; Figure 7; Supplemental Data, Table S15), which were 2, 2.5, and 4.5 times lower than the lowest PNECs reported previously in the literature or regulatory documents (Supplemental Data, Table S16).

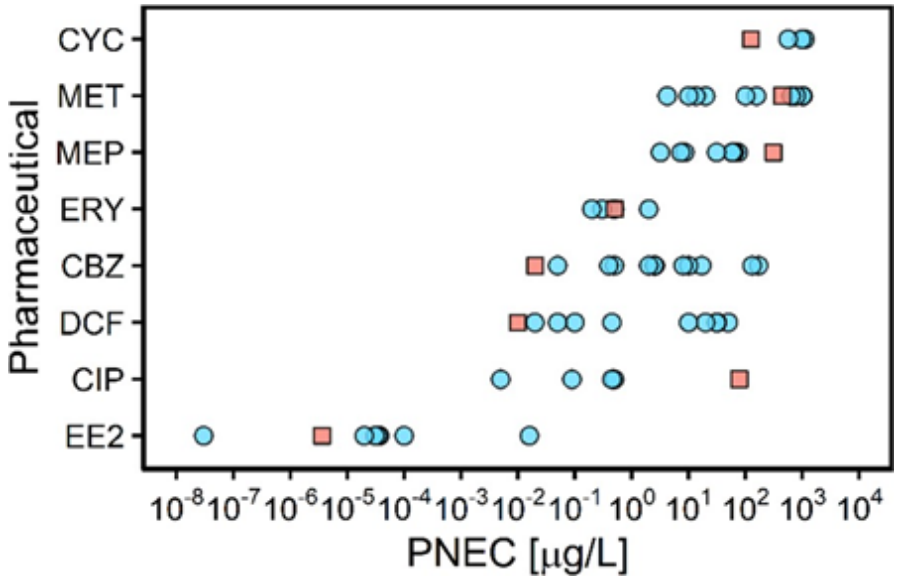

FIGURE 7: Predicted-no-effect concentrations (PNECs) from the literature and derived in the present study. Salmon-colored squares indicate the PNEC values derived in the present study. Light blue points indicate unique PNEC values found in the literature. CYC = cyclophosphamide; MET = metformin; MEP = metoprolol; ERY = erythromycin; CBZ = carbamazepine; DCF = diclofenac; CIP = ciprofloxacin; EE2 = 17α-ethinylestradiol.

These lower PNECs give cause for concern regarding the environmental impact of these APIs and indicate the need to revise proposed EQSs for these APIs. For metoprolol and ciprofloxacin, the PNECs estimated in the present study were 310 and 78 μg/L, which are 5 and 156 times the highest PNECs found in the literature, respectively. It should be stressed that any PNEC can be strongly affected by the accessibility of effect data, the thoroughness of the search, and the quality assessment procedure (Henning-de Jong et al., 2009; Oelkers 2020). This is illustrated by a suggestion we received from one of the anonymous reviewers, that is, to include the study of Ebert et al., (2011) in the derivation of the PNEC for ciprofloxacin. This is a critical study underlying the low ciprofloxacin PNEC of 0.089 μg/L listed in Supplemental Data, Table S16, yet it was not retrieved from any of the sources used in the present study. It explains the large difference in derived PNECs for ciprofloxacin observable in Figure 7 and illustrates more generally that PNECs and risk assessment outcomes based on the assessment factor approach are very sensitive to the effect data included in the assessment. Indeed, the differences in PNECs for the same API derived by different agencies and assessors range from a factor of 10 to almost 106 (Figure 7). Keeping this range in mind, it is defendable to use an RQ of 0.1, or even smaller, as a potential indicator of risk and as a trigger to critically review and potentially improve the assessment procedure. To account for uncertainty in the derivation of PNEC values, an assessment factor of 50 was applied to diclofenac and 17α-ethinylestradiol, whereas an assessment factor of 10 was applied to carbamazepine, ciprofloxacin, cyclophosphamide, erythromycin, metformin, and metoprolol. The use of a relatively low assessment factor (instead of 100 or 1000) suggests that the PNECs derived in the present study are not overly conservative.

Aquatic ecological risk

Single substance assessment

In the present study, RQ < 0.1 indicates a reason for no concern in terms of chemical pollution, 0.1 < RQ ≤ 10 indicates a potential reason for concern, and RQ > 10 suggests a reason for serious environmental concern. The specific boundary value(s) that qualifies as a “reason for concern” is malleable, depending on the empirical data that support it and personal values. In the present study, we chose to acknowledge the uncertainties that blur the meaning of this threshold (RQ = 1). Values of RQ > 1 can trigger follow-up measures,

via either additional ecotoxicity testing or the implementation of risk management measures (Posthuma et al., 2019; Zhou et al., 2019). In the present study, the PECs of 5 APIs were below their safe thresholds (PNECs). However, the PECs systematically exceeded PNECs in ascending order for diclofenac, carbamazepine, and 17α-ethinylestradiol (Figure 8). This observation holds for the average and dry summer scenarios, although risks were considerably higher in summer because of reduced dilution under dry weather conditions.

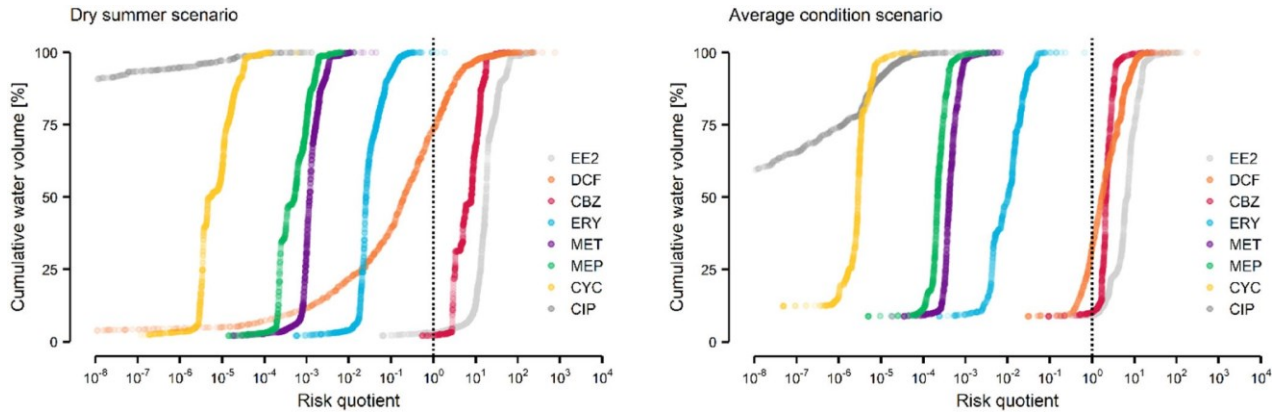

FIGURE 8: Percentage of the Vecht River catchment water volume at risk of environmental pharmaceutical pollution. Vertical black dashed line indicates the safe threshold, risk quotient = 1 (i.e., predicted environmental concentrations equal to the predicted-no–chronic effect concentration). In the average scenario, ciprofloxacin's risk quotients are <10−8; thus, they are not depicted. Each point depicts the relative water volume of a segment of ≤2 km. In the dry summer scenario, concentrations of ciprofloxacin <10−8 are also not depicted. EE2 = 17α-ethinylestradiol; DCF = diclofenac; CBZ = carbamazepine; ERY = erythromycin; MET = metformin; MEP = metoprolol; CYC = cyclophosphamide; CIP = ciprofloxacin.

Diclofenac, carbamazepine, and 17α-ethinylestradiol exceeded the safe PNEC threshold in at least 68 to 91% and 26 to 98% of the Vecht River catchment surface water volume during average conditions and dry summer conditions, respectively. In terms of the total flow length of all water bodies, the same APIs exceeded their PNECs in 31 to 38% and 24 to 53% during average conditions and dry summer conditions, respectively (Supplemental Data, Figure S4). In the average condition scenario, ciprofloxacin, cyclophosphamide, erythromycin, metformin, and metoprolol do not pose a concerning risk to the aquatic life (i.e., 93 to 100% of the water volume had RQ ≤ 0.1). In the dry summer scenario erythromycin showed concerning risk levels (RQ > 0.1) in 17% of the catchment's water volume. 17α-Ethinylestradiol exhibits the highest RQs despite showing the lowest PECs overall, with 25 and 87% of the catchment water volume showing concerning risk levels

(RQ > 10) in the average and summer scenarios, respectively (Supplemental Data, Table S17). In the Dutch municipality of Hengelo, 17α-ethinylestradiol showed a local risk of serious concern under average conditions in a small brook (RQScnAC = 144), whereas under dry summer conditions the risks were highest at local canals (<2 km) routing STP effluents into larger streams and canals, for example, Bornse Beek (RQScnDS ≤ 274). This synthetic hormone has been shown to particularly interfere with the endocrine system of fish and amphibian species, affecting their development, reproduction, growth, and, ultimately, ability to sustain a healthy population (Supplemental Data, Table S15). Eight of the 10 most sensitive species to ethinylestradiol identified in the present study are fish. Notably, Gobiocypris rarus (commonly known as rare minnow), a fish species endemic to China, is the most sensitive species (Zha et al., 2008). However, Rutilus rutilus (commonly known as roach) is a fish native to most European freshwaters including the Vecht River and is similarly sensitive (Lange et al., 2009). One study assessed the effect of wastewater estrogen exposure on roach population density in 2 English rivers over the span of a decade, finding no noticeable declines (Johnson and Chen 2017). Another study analyzed the results of fish samples over a period of 2 decades in German rivers and found a decrease in fish population density, although it could not attribute it to chemical pollution (Teubner et al., 2019). To our knowledge, there are currently no indications that the roach is subject to adverse effects in the Vecht River basin. Nonetheless, the results of the present study support the use of more sensitive analytical techniques combined with accurately modeled hotspots of estrogen pollution and fish species in the Vecht River basin, including the roach. Furthermore, considering that the majority of the catchment was predicted to be liable to serious environmental risk, chronic effects could be triggered because continuous exceedance of an RQ of 1 is very likely under the simulated scenarios. At catchment locations, these exceedances can vary substantially, which can provide an opportunity for motile organisms to avoid unfavorable conditions or endure them for shorter exposure periods.

Carbamazepine exhibited the second highest RQs, with 90% of the catchment water volume showing concerning risk levels (RQScnAC > 0.1; Supplemental Data, Table S17). Throughout the catchment, carbamazepine showed its highest risk (RQScnDS = 118, RQScnAC = 42) in a 7-km tributary segment under high-effluent influence, located in the

German municipality of Bad Bentheim. Carbamazepine causes a variety of toxicological effects at different taxonomic levels. The most sensitive species include the insect Stenomena sp. (Jarvis et al., 2014), the crustacean Daphnia similis (Chen et al., 2019), the algae Chaetophora sp. (Jarvis et al., 2014), and the fish Pimephales promelas (Thomas et al., 2012), for which carbamazepine affects behavior, reproduction ability, or population survival. It is unclear whether these species are present in the Vecht River, but given carbamazepine's diverse ecotoxicological potential, targeted monitoring of its concentration levels and the sensitive Stenomena sp. could help determine whether adverse effects occur under field conditions.

Diclofenac exhibited the third highest RQs, with 90% of the catchment water showing concerning risk levels (RQScnAC > 0.1; Supplemental Data, Table S17). At the same location in the German municipality of Bad Bentheim, diclofenac showed the highest risk quotient (RQScnDS = 754, RQScnAC = 302). Provided the high risk at this and other locations along the Vecht River basin, toxicological effects on growth and development could be expected on fish and algae. The most sensitive species to diclofenac is the widespread invasive bivalve Dreissena polymorpha, which may be indicative of the vulnerability of this taxonomic rank (mollusks) and the trophic level it represents (primary consumers). These freshwater mollusks provide essential ecosystem services, are key elements of the food chain, and play a major role in removing contaminants from high volumes of water. At the regional and local scales, pharmaceutical pollution could exacerbate the impact on what is already the most threatened animal group in Europe (Cuttelod et al., 2011).

In a Dutch governmental report, carbamazepine and diclofenac have previously been identified as contaminants of environmental concern to aquatic organism in The Netherlands (Moermond et al., 2016b); and, in a revised iteration, 17α-ethinylestradiol has also been identified as such, whereas carbamazepine was no longer of concern (Moermond et al., 2020). The revised PNECs in the present study suggest that the RQs of diclofenac and carbamazepine may be higher than anticipated (underestimated RQ). Exceptionally, erythromycin was also marginally predicted to occur at concentrations above the PNEC in the Vecht River catchment freshwater in a typical summer season (RQ = 1.8). In the river's main stream, RQs were low (RQ < 0.1), particularly in Dutch territory because of water

dilution and lower consumption. Furthermore, erythromycin's degradation in the water column is not expected to be substantial because of the limited residence time of APIs in the Vecht River main stream of 4 to 12 d for average and low-flow conditions, respectively (Liu et al., 2019; Li and Cui 2020). However, the unaccounted veterinary use of erythromycin in the present study could elevate the risks.

Metformin does not stand out from our risk profiling. However, metformin's main metabolite, guanylurea, is found in surface waters in quantities of up to 50% of the administered parent compound (Oosterhuis et al., 2013). Because guanylurea has a lower PNEC (0.16 µg/L) than metformin itself (Caldwell et al., 2019), risk assessment of metformin should include the metabolite because it could pose a risk related to widespread metformin application. The need to consider transformation products in aquatic risk assessment has been stated by other authors (Celiz et al., 2009; Han and Lee 2017).

Overall, 17α-ethinylestradiol, carbamazepine, and diclofenac may pose unacceptable environmental risks in at least 31% of the Vecht catchment flow length for average conditions. This risk aggravates up to 53% during summer, affecting 1483 out of 2772 km of total flow length (Supplemental Data, Figure S4). The average RQ increased consistently across APIs by approximately 10-fold between the average and dry summer scenarios. However, the most striking changes in PEC were observed at the confluence of polluted streams, effluent- dominated waters, or segments receiving STP effluents, with a few instances in which treated effluent discharge contributed up to 90% of the stream's volume. Other studies have also observed that proximity to STPs can more heavily influence pharmaceutical PEC than seasonality (Musolff et al., 2009; Balaam et al., 2010; Vieno and Sillanpää 2014). Because of human activity near the river source, API emissions result in residue concentrations exceeding the PNEC as early as 20 km downstream the Vecht River. In agreement with the present study, diclofenac and carbamazepine have also been predicted to display a high environmental risk in other European and international rivers (Chaves et al., 2020; Palma et al., 2020). The APIs with the highest RQs in the present study (17α- ethinylestradiol, carbamazepine, diclofenac, erythromycin) have recently been removed from the Water Framework Directive watch list, which may lead to losing sight of their ecological impact despite their potential risk. This is also emphasized by Burns et al., (2018), who identify these substances as common top-priority APIs. In addition, a review

on the development in the field of substances of emerging concern over the previous 20 yr emphasizes the exceedance of EQSs and the need for spatially explicit risk modeling approaches (Tiedeken et al., 2017). This review further supports the usefulness of generating spatially explicit risk profiles as conducted in the present study. Similar efforts open up the possibility for stakeholders to comply with the Water Framework Directive, starting with prioritizing APIs so that more refined and locally relevant targeted risk-management measures can be applied successfully.

Substance mixture assessment

In the Vecht catchment, a noticeable difference between the risk index in the average scenario and the dry summer scenario was observed (Supplemental Data, Figures S5 and S6). In the dry summer scenario, the mean risk index was estimated to be 3.4 times higher than in the average condition scenario. Likewise, the maximum risk indices were found in river segments of the Dutch municipalities of Hengelo and Coevorden under average and dry summer condition scenarios, respectively. This suggests that periods of dry, warm weather conditions in the Vecht River catchment may lead to risks to freshwater wildlife communities above the risks estimated for average weather conditions.

In the Vecht River main stream (Figure 9), the predicted cumulative risk in the polluted segments (i.e., risk index > 0) ranges between 6 to 22 and 23 to 104 in the average scenario and dry summer scenario, respectively. These risk index values in the main stream are lower than observed elsewhere in the catchment (Supplemental Data, Figures S5 and S6). However, this emphasizes the sustained cumulative risk in the Vecht River's main stream, particularly driven by diclofenac in the German region and 17α-ethinylestradiol in the Dutch region (Figure 8).

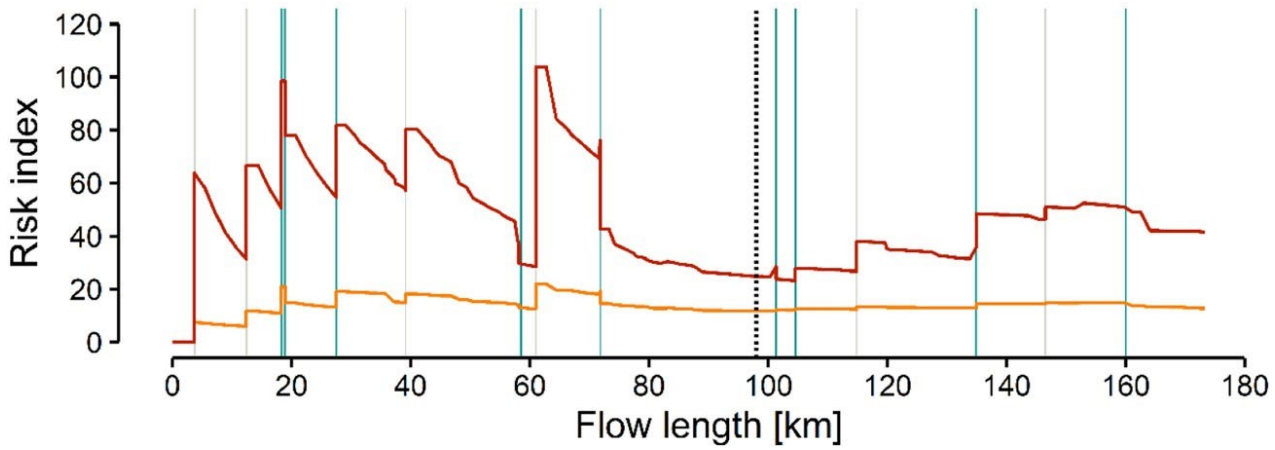

FIGURE 9: Risk index along the Vecht River main stream under typical dry summer (orange) and average weather (red) conditions. Eight pharmaceutical active ingredients are integrated in the risk indices depicted. Dashed vertical line demarks the German–Dutch border. Solid vertical lines depict sewage treatment plants (gray) and tributary confluences (turquoise).

Limitations

The present study embodies the ongoing attempt to predict API concentrations in freshwater and the associated risk of biological functional disturbance in regional ecosystems. Despite the advancements achieved, data scarcity, knowledge gaps, and procedural limitations often hamper the accuracy and significance of exposure and effect assessments. The sources of variability and uncertainty that can affect PECs and PNECs are manifold. The PEC can be affected by the excretion rate, sampling method, analytical chemistry technique, unaccounted point and diffuse emission sources, in-sewer (bio) transformation, disposal of unused medicine in the toilet, or household wastewater (van Nuijs et al., 2015). For example, there are uncertainties linked to the German consumption rate of erythromycin, which seems to have been overestimated. Furthermore, erythromycin and ciprofloxacin PECs are associated with higher uncertainties because these were not sufficiently detected in the Vecht water system to allow for a corroboration with measurements. Similarly, the accuracy of model predictions for cyclophosphamide and 17α-ethinylestradiol could not be firmly determined because of analytical limitations. Indeed, concentrations of these APIs in surface water were often below their limits of detection and quantification. This is particularly important for assessing the risks associated with substances like 17α-ethinylestradiol because of its very low safe PNEC. Therefore, under such analytical limitations, the crucial contribution of predictive models

is self-evident. The sensitivity of derived PNECs to data availability (e.g., effect studies that are missed, differently quality- assessed, or newly performed) is a typical feature of the assessment factor method. The alternative SSD method is less affected by this phenomenon because it uses the 5th percentile of the cumulative distribution function. As such, the sensitivity of PNECs to data availability also partly relates to the strict criteria on data availability that the European Union set for applying SSDs.

Conclusions

The present study achieved 3 main goals: 1) estimation of API surface water concentrations using the GREAT-ER model in the Vecht catchment; 2) derivation of new safe ecological threshold concentrations for 8 APIs, of which 3 were the lower than found in the literature; and 3) the creation of detailed, spatially explicit ecological risk profiles of APIs in a transboundary (sub-)catchment under 2 different seasonal scenarios. The exceedance of the acceptable ecological risk threshold in the Vecht River was found to be mainly driven by 17α-ethinylestradiol, diclofenac, and carbamazepine. These substances are among the most consumed APIs in The Netherlands. 17α-ethinylestradiol predominantly contributed to the aggregated risk profile and systematically exceeded the PNEC by at least one order of magnitude. This substance is the API with the twenty-third highest DDD and has seen a 4% increase from 2018 to 2019 (Dutch National Health Care Institute 2020). This prospect emphasizes the need for better pharmaceutical emission reduction strategies (e.g., wastewater treatment technology, hotspot analysis, and preventive health care) and continue to monitor its use and presence in surface waters (Government of The Netherlands 2019), including the Vecht River. The present study suggests that the Vecht River catchment is vulnerable to pharmaceutical pollution, with 26 to 98% of its surface waters and 24 to 53% of its length under potentially unacceptable ecological risk (RQ > 1), particularly during a dry summer season. European regulation demands that national and regional authorities take action in securing water bodies' good status. To this end, the present study demonstrated the value of tailor-made regional models and the continuous revision of ecotoxicological information. Furthermore, it highlighted the importance of assessing off-site risks of pharmaceutical emissions using (sub-)catchment modeling across national borders, therefore emphasizing the imperative for international cooperation. Ultimately, these results should encourage further cross-boundary action and initiative

from local authorities to comply with environmental standards via feasible and locally relevant risk-management strategies. Otherwise, risk reduction implementations in international river networks may not be sufficiently effective.

Supplemental Data

The Supplemental Data are available on the Wiley Online Library at https://doi.org/10.1002/etc.5062 and at the end of this thesis.

Acknowledgment

We thank the regional hospitals for providing pharmaceutical consumption information and D. de Zwart for kindly sharing e-toxBase data. The present study was supported by the European Regional Development Fund of the European Union under the project MEDUWA Vecht(e) (142118).

Disclaimer

The authors have no conflicts of interest to declare.

Author Contributions Statement

D. Duarte was responsible for conceptualization, methodology, formal analysis, investigation, writing–original draft, writing–review and editing, visualization; G. Niebaum was responsible for conceptualization, methodology, validation, formal analysis, investigation, writing–original draft, writing–review and editing, visualization; V. Lämmchen was responsible for conceptualization, methodology, validation, formal analysis, investigation, writing–original draft, writing–review and editing, visualization, E. van Heijnsbergen was responsible for methodology, validation, investigation, writing–review and editing; R. Oldenkamp was responsible for conceptualization, writing–review and editing, supervision; L. Hernandez-Leal was responsible for resources, writing–review and editing, project administration; H. Schmitt, A. Ragas, and J. Klasmeier were responsible for conceptualization, writing–review and editing, supervision, project administration, funding acquisition.

Data Availability Statement

Data, associated metadata, and calculation tools are available from the corresponding author (daniel.duarte@ru.nl). For data requests concerning the environmental exposure assessment, please contact J. Klasmeier (jklasmei@uni-osnabrueck.de). For data requests concerning the environmental effect assessment and aquatic ecological risk, please contact A. Ragas (a.ragas@fnwi.ru.nl).

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7. Improving the accessibility and dissemination of the model

So far, the articles in this thesis have highlighted several issues in which the model or its application has been improved. However, further model development does not have to deal (exclusively) with these (very important) scientific questions. Therefore, the objective of this PhD thesis was understood to also consider better accessibility and dissemination of the model.

It soon became clear that, due to growing interest in the application of the GREAT-ER model by German authorities and external scientists, acquisition and pre-processing of raw data required for catchment setup needed to be facilitated. Therefore, it was desirable to enable catchment preparation by the interested users. This included improvements of the semi-automated pre-processing tool as well as the transfer of the laborious data acquisition process to the designated end user of the catchment database. In the past, this often failed because the technical effort during conversion of the raw data for use in GREAT-ER databases constituted a high barrier for unexperienced first time users. Thus, it was more effective to process all raw data in-house and deliver the completed, executable database to the end users. Additionally, they were supported by one-day training courses at the end of the process. However, to allow us focussing more on the scientific advancement of the model, the concept of a basic GREAT-ER version was developed by the entire working group, to enable end users to be able to set up a catchment database on their own. The "pre-processing routine" already introduced with the GREAT-ER 4.0 version already allowed for semi-automatic execution of large parts of the data preparation that had to be done manually before. The idea was that the 4.1 version of the model along with the revised documentation and a detailed tutorial should allow potential users to start working with GREAT-ER more easily. In this context, existing manuals, documentations and tutorials were also translated from German into English to reduce language barriers. However, it must be pointed out that basic knowledge in ArcGIS® is still a prerequisite for working with GREAT-ER.

To help users get acquainted with the model approach, an exemplary database for a hypothetical small catchment was created, containing a simple river network with two wastewater treatment plants and one hospital in the form of raw data. In addition, the data collection contains an executable final database after pre-processing, where we already processed the raw data correctly. We therefore call this approach the 'blueprint approach'. For training purposes, the user should try to process the raw data into this final database by themselves, guided by the detailed bilingual documentation. After successful database generation, users can start simulations with the basic version of the model. This slimmed down version contains the basic core functions of the model, but some analysis tools, sub-models and display options have been removed as the more sophisticated sub-models included in the full version still require specific data pre-processing steps and the total number of functions would most likely overstrain first time users. A later upgrade to the full version should work without complications for the users. The blueprint files, the model core and the documentation are available for free download on the GREAT-ER project website[6].

Another intention was to allow for application of GREAT-ER for a larger number of interested parties and to promote the model in a wider context. This included classic ways of scientific promotion such as publishing the articles included in this thesis and giving oral and poster presentations at scientific conferences (e.g. SETAC 2019 Helsinki). One talk and one poster presentation were even awarded (SETAC GLB 2019 Landau, ICRAPHE 2019 Barcelona). As another mean of wider distribution, we used the MEDUWA project. Within this project the already mentioned "Watershed Information System" for the Vecht catchment, a web-based platform for dissemination of the project results to the broader public, was created under the direction of Geoplex GmbH. This platform displays selected GREAT-ER simulation results independent from proprietary software such as ArcGIS®, which has the advantage that a much larger group of potential users has access to the project findings. The platform is adapted to current viewing and usage habits and includes information boxes providing some background. This science communication tool is innovative in terms of presentation of

[6] https://tinyurl.com/y8h9y8rq

the model and project results to a broader range of interested people in an easy to access and easier to use kind of way.

Altogether, the detailed but technically streamlined bilingual instructions and the "blueprint" database example for the basic model version have significantly lowered the entry barrier for model use. Interested users in science and agencies are now enabled to easily test the usefulness of the model for their purpose. They can also do most of the pre-processing steps by themselves only requesting advice or support from the IUSF in special cases. At the same time the aforementioned classic and new ways were contested to improve the visibility and perception of the model. This can support the wider spread of the model and a broader use for exposure assessment of emerging contaminants in river basins and could in turn enhance the degree of popularity and acceptance of the model, leading to a growing number of conference presentations or publications related to GREAT-ER applications.

8. Outlook

The GREAT-ER model has been subject to an evolution of further developments for more than 20 years now, which have been traced in this thesis up to version 4.1. Over the years, the model has been improved and adapted and has been applied to tackle many different research questions in numerous projects, publications, and dissertations, many of which are listed and named in this thesis.

However, further efforts are needed to ensure the sustainability of what has been achieved so far. For example, in this work it was shown to what extent highly anthropogenic watersheds can be represented in the GREAT-ER model framework to allow realistic simulations. However, the proposed procedure can certainly be simplified further as it still requires a high degree of manual intervention, which should still be automated where possible. In terms of process parameterization, further optimization of flow velocity estimation, e.g. in canals, has been internally discussed, but not finally decided upon on how to implement this.

Although GREAT-ER per se is not a dynamic model, nor was it intended to be from the beginning, this work has shown that, to a certain degree, it can be used to get insight into effects of dynamic processes in watersheds on substance concentrations. However, one future task will be to check to which degree GREAT-ER can be adapted to represent dynamic emission events, such as combined sewer overflows (CSO). A possible approach is presented in article 2 showing that the creation of multiple scenario databases representing different boundary conditions can be helpful. A second approach was to make more use of the already implemented probabilistic simulation routine and extend it to allow for better representation of dynamic effects. This includes understanding of the variability and uncertainty of input parameters to enable definition of reliable frequency distributions of values for the simulation runs. This is particularly important because, as this work has also emphasised, the informative value of deterministic simulations is limited. Comparison with single monitoring data from grab samples – often collected under unknown boundary conditions - is not sufficient for reliable risk assessment, as this work has also demonstrated. In this context, the approach of the WFD, which relies on environmental quality standards to

be assessed against year-round average monitoring data from 12 (monthly) samples, must once again be critically noted (Rico et al., 2021; Lämmchen et al., 2021a).
The integration of e.g. passive samplers or other enhancements of monitoring campaigns is not an issue for GREAT-ER in this context, as the integration of monitoring data into the model approach is independent of its quantity, quality or origin.

Attempts to extend GREAT-ER beyond its current fields of application have already been made in the past (Hüffmeyer et al., 2009), and further attempts are currently in progress. This includes adaptation of the model to simulate bacteria (Van Heijnsbergen et al., 2021; in prep.) and microplastics (MicBin research project[7]). It turned out, that some processes and model parameters need to be considered more explicitly than it is currently the case, e.g. the role of sedimentation. This also applies to the influence of temperature, which plays an essential role in the simulation of bacterial loads (Auer & Niehaus, 1993), but showed low sensitivity in simulations of priority pollutants.

In addition, further research should be done on how to improve interpretation of model results and subsequent risk assessment. Some approaches have been applied in article 3. An interesting feature to be included in this context is the comparison of exposure concentrations with so-called Species Sensitivity Distributions (SSD; Newman et al., 2000; Monti et al., 2018). This could provide a more holistic risk assessment taking into account concentration variability and ecotoxicological response sensitivity at the same time.
It may also be useful to describe selected processes by sub-models that are more detailed. In the past, there have already been efforts to integrate the WWTP model SimpleTreat (Struijs, 2014) into GREAT-ER to increase the level of detail for handling of individual treatment plants. Currently, several other models are being tested for possible inclusion in or coupling with GREAT-ER, e.g. Vantom (Brouwer, 2020) and Pesera (Kirkby et al., 2004). While Vantom is a model with the aim to model the overland transport of antibiotics after application to the soil, Pesera is an approved

[7] https://www.fona.de/de/mikroplastik-im-donaugebiet-wie-gross-ist-die-belastung

erosion model (Kirkby et al., 2008). These models can be used to model diffuse emission sources (agricultural areas) and can be used as the starting point of a GREAT-ER simulation, which currently uses a very rudimentary wash off estimation (t/ha/a) for this purpose. Other model couplings tested are QMRAcatch (Schijven et al., 2015), which simulates microbial quality of water resources or the widely used water balance simulation model WaSiM-ETH (Gurtz et al., 2003; Cullmann et al., 2006). Test implementations on small spatial scales (sub-catchments) are in progress with a focus on proof-of-concept. In the end, such more detailed approaches could be applied in a second tier assessment in regions that were identified as hot spots or areas of concern in first tier simulations on the catchment scale.

9. Conclusions

GREAT-ER is a steady-state model which assumes that emissions of substances are more or less constant over time. As has been shown in numerous previous publications and confirmed for additional examples in this work, this is, at a regional scale, true for many pharmaceuticals emitted via point emissions, but challenging watersheds can force one to take local conditions into account. Variability and/or uncertainty of events can be represented by using probability distributions for selected model parameters or by setting up special scenarios. This has been shown in article 1 within the catchments of Main and Lenne and the Vecht catchment in article 2. In the Lenne (and in principle), the input of iodine-containing X-ray contrast media is strongly dependent on the number of large medical devices available locally and also has a strongly event-driven character. In the Vecht, changing hydrological conditions also alter the distribution behaviour and dilution of substance concentrations. In general, it was shown that the more realistically and completely the conditions in the catchment area are addressed, the better the simulation results correspond with the real situation.

The used case studies within the articles point out once more a misunderstanding often associated with evaluating model results by using monitoring data. Due to the temporal variability of key parameters, such as runoff or per capita consumption, concentrations in surface water often vary by several factors (Ort et al., 2010, Ort et al., 2014), as was the case with clarithromycin in the Main River basin or the Vecht watershed. As all articles have shown, it is not possible to do reliable risk assessment based on random individual grab samples. To assess water quality, a series of samplings at carefully selected locations would be required that determine the substance concentration under different hydrological conditions.

Here, models can help to better understand individually measured values and effectively reduce the monitoring effort that is actually necessary. Additionally, probabilistic simulations are apt to predict the range of expected concentrations due to natural temporal variability. Nevertheless, a combination of modelling and targeted monitoring is often the best strategy in exposure assessment (Johnson et al., 2008). GREAT-ER should therefore always be understood as a complementary and supportive, and never a substitutional approach to water quality assessment. As has

been addressed, especially comprehensive risk assessment of 17a-ethynylestradiol and other substances detectable in comparably low concentrations in surface waters can only be achieved with modelling support because applied analytical methods do not always have adequate detection limits (Loos et al., 2018). Monitoring of the proposed EQS and especially an assessment of potential measures cannot be fully accomplished without model coupling.

In this context, the simulation of whole watersheds with GREAT-ER is in line with the requirements formulated by the WFD. GREAT-ER can therefore be considered a valuable tool that can provide contributions to the issues of risk assessment and decision making and help in the process of implementing the objectives of the WFD. However, it must be emphasized that it is not sufficient for environmental risk assessment to look, for example, at whether the mean of monthly sample measurements is above the EQS, as required by the WFD's AA-EQS approach (Vorkamp et al., 2014; Rico et al., 2021). This has been briefly discussed in article 1 and shown in the Vecht scenarios used in article 2 and 3, where hydrological parameters can change drastically throughout the year and change concentration patterns enormously. Measuring at certain points twelve times a year does not address these situations and cannot be the basis for reasonable risk assessment. Additionally, chronic effects can be caused by endocrine disrupting substances already in short time periods (Saal & Hughes, 2005; Vandenberg et al., 2012), but a mean value can never be sensitive to this. Article 3 and the outlook show some approaches and ideas with which a better risk assessment can be made.

Finally, it can be concluded, that the newly developed version GREAT-ER 4.1 with all the additions (Blueprint, Light-Version, WIS) creates a reliable framework for wider applicability of the model, while the three articles have demonstrated that GREAT-ER can meet the requirements of modern risk assessment even in challenging watersheds. At the same time, there is still enough room for model improvements and expansions that future PhD generations would be able to work on for another 20 years. First successful steps have been taken on this way as was described in the outlook.

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Appendix

A. Software structure

Model structure

The GREAT-ER model was developed to predict spatially explicit steady-state exposure concentrations of chemicals in surface waters of entire watersheds (Feijtel et al., 1998). The surface water network is represented by two-dimensional geometries that form a directed graph without cycles. Direction of water flow within the watershed is represented by the orientation of the edges of the graph; flow values and other relevant features such as flow velocity are stored as attributes of the water body edges. All model elements such as emission sources and river sections are implemented in an object-oriented manner. They also carry attributes relevant to the model equations such as the number of inhabitants connected to a wastewater treatment plant. During simulations, substance loads are transported both within the emission pathways and downstream in the stream network. Each stream segment can receive loads that are transferred into the segment from upstream segments and from emission sources. The general model structure of emission pathways from the source through the input pathway to the surface water is identical for all complexity modes, but may differ with respect to the model equations used. Within this work, the latest GREAT-ER model version 4.1 was used, which superseded version 4.0 in 2018.

Data Management

The simulation of substance fate on a regional scale requires a large amount of data. This data has to be stored in a fashion which ensures easy access and expandability, permits sharing of data and results, and enables the reuse of existing datasets. GREAT-ER 4.1, as well as the preceding model version 4.0, stores all spatial and non-spatial data within user-manageable databases, which are based on the well-accepted ArcGIS® Arc Hydro data model designed for hydrological models. Arc Hydro is a database layout which was developed by the Center for Research Water Resources of the University of Texas in Austin and ESRI (Maidment, 2002). Arc Hydro was developed to create an ambient framework in which spatial hydrological data can be stored and processed in a standardized way to support the use and exchange of these data (Shamsi, 2008). Arc Hydro's database layout

was extended during the development of GREAT-ER 4 to fit the needs of the exposure model. These database types are usually stored on the user's computer and can be copied, shared, and edited by the user. Each database stores parameterizations of a river system, emission sources, substances, scenario settings, and scenario results. Watershed attributes can be changed permanently at any point by the user if required because all data is stored locally. From GREAT-ER 4.0 onwards, model parameters for a particular scenario can be modified without affecting other scenarios or simulation runs. Version 4.1 additionally allows for displaying all scenario results in one table. This enables comparison of the collected results in the river basin in tabular form, where before only the option to (graphically) compare two selected scenarios was given.

Data compilation and processing

The data model provides the framework that has to be filled with actual data about the catchment being modelled. Simulating the fate of chemicals within a river network requires information about river and catchment geometries, river attributes, emission sources, and substance properties. To date, mostly European watersheds have been prepared and validated for use with the GREAT-ER model (Hüffmeyer et al., 2009; Alder et al., 2010; Kehrein et al., 2015), but application to watersheds on other continents are also possible (Archundia et al., 2018).

Geometries of river networks can be obtained from available datasets such as the 1:250,000 digital landscape model (BfG, 2014) for Germany or the CCM River and Catchment Database for pan-European rivers (de Jager and Vogt, 2010) and HydroSHEDS (Lehner et al., 2008) for the global scale. Since levels of detail are different but significant for the results and application, this should be considered in selecting the most appropriate data source.

Catchments of individual river sections are usually derived from digital elevation models. These data, e.g., from the SRTM data source (Shuttle Radar Topology Mission data; Jarvis et al., 2008) obtains elevation information, which is used to calculate catchment boundaries with the ArcHydro toolset (Djokic et al., 2011). For Germany, a 1:200,000 resolution can be obtained free of charge since 2015 (BfG, 2015). In the last years, problems

with storage limitations and insufficient processing speeds of large datasets have been overcome, so that it is also possible to download and store continental datasets such as the European Digital Elevation Model (EU-DEM; Gonzalez et al., 2015) for extracting selected river basins on demand. Within Europe, ready-to-use river basin representations can be obtained covering the water bodies in the basin areas of the EU water framework directive. Experience showed that these datasets could be used alternatively with GREAT-ER. Unfortunately, no general overview of available catchments exists, so that the user has to search the geoportals of the federal states (e.g. http://www.wasserdaten.niedersachsen.de/cadenza/).
In other countries in Europe these services tend to be decentralized as well. In the Netherlands, for example, the data stocks are divided between Rijswaterstraat (RWS), the regional Waterschaps and a national contact point (nationaal georegister).

Hydrological information such as river flow and flow velocities are estimated using external model approaches that provide fixed deterministic values for defined hydrologic situations. In recent years, this has included long-term mean discharge (MQ), long-term average low flow (MNQ), and 10-day low flow (MAM10). This was supplemented in GREAT-ER 4.1 by the integration of long-term median discharge (Q50). These discharge values are estimated from surface runoff information via implemented routines and are calibrated against data from gauging stations, which need to be implemented manually into the database. Information about surface runoff in Germany is taken from the Hydrological Atlas (HAD; Leibundgut and Kern, 2003). Comparable data all over Europe is are not yet available. In the border regions, we thus extrapolate German data across the border, since the values vary little within short distances.
Required data for runoff-effective rainfall can also be estimated from precipitation, evaporation and infiltration using appropriate models. Sometimes, the information is directly provided by other models such as Persera (Pan-European Soil Erosion Risk Assessment; Kirkby et al., 2008). Since the model approaches differ to some extent, different models may give different runoff values for the same region. Since river flow estimates are always calibrated against gauging data, this will finally be equalled by the applied correction factors.

Extreme hydrological conditions such as extended droughts or floods and other dynamic events such as tidal influence or anthropogenic interventions (see Article 2 in this work) cannot be realistically described by a simple probability distribution as is used in the current simulation approach. Therefore, the model should not be used in these regions without further validation or adjustments. This work shows how one can significantly improve the usability of the model in such regions.

In European watersheds, data collected under the European Urban Wastewater Treatment Directive (EUWWTD; EU, 1991; EU, 2013) provide broad information on wastewater treatment plants. They can be downloaded from the EUWWTD website since 2012. However, the dataset lacks certain plant attributes needed for the GREAT-ER model and does not cover all types of treatment processes and plant sizes. More detailed information usually needs to be collected from local agencies and municipalities.

The European CORINE Land Cover project (Büttner, 2014) collects data on land use patterns that can be used to estimate non-point emissions in European watersheds. Either way, supplementary information, e.g., on fertilizer application rates, is also needed here to ultimately estimate emission levels.

To meet the requirements of the model, some data must be pre-processed before use. This pre-processing is usually performed once for a selected watershed, but moderate modifications and extensions of the database by the user are also possible after pre-processing. During pre-processing of a river network, data from different sources are merged. Some attributes can be adopted from data sources without modification, while others must be derived from raw data sets. All pre-processing of spatial data for GREAT-ER 4.1 is done using ArcMap®. A detailed description of the pre-processing routine is beyond the scope of this paper, but can be found in the corresponding manuals.

GREAT-ER software versions

The list of emissions and fate processes considered is virtually unchanged since the first version of the GREAT-ER software (Table 1). In version 4.0, only a few nonpoint emission routines were added to the model. Version 4.1 does not include new process descriptions except for the hospital sub-model. However, a routine for considering differences in point source attributes, e.g. across different countries, was added.

The proprietary database layouts used in GREAT-ER versions 1 to 3 were not compatible between the different model versions and are not simply transferable into the GREAT-ER 4 format. The latter is a consequence of the switch in database layout from version 3 to version 4. Although databases constructed under 4.0 are not directly compatible, they can be easily adapted to the 4.1 version with just a few adaptations. Many parts of version 4.1 are intentionally integrated into the model in such an optional way that this effort has been minimized as far as possible. In order to be able to use the full range of 4.1 functions, all necessary steps must be carried out, of course, and a manual has been prepared for this purpose to ensure that all existing GREAT-ER 4.0 databases remain potentially usable in the future. Also to show this general compatibility, it was therefore deliberately refrained from talking about a model version 5.

GREAT-ER 4.0 has been integrated as Add-In for ArcGIS® to allow for taking advantage of the powerful geo-processing capabilities of this software. This greatly facilitates further development and retrofitting of pre-processing steps, analysis tools, merging of datasets, and evaluation of scenario results. This has enabled a number of improvements, bug fixes and corrections also improving user-friendliness of the GREAT-ER 4.1 model, especially when compared to the raw GREAT-ER 4.0 version from 2015.

Table 1: Comparison of features of existing GREAT-ER versions (adopted from Kehrein et al., 2015)

GREAT-ER version					
	v1	**v2**	**v3**	**v4.0**	**v4.1**
Model					
Processes considered	Point source emissions, removal by sewage treatment, transport, sedimentation, volatilization, degradation			additional implementation of average emissions from diffuse non-point sources	additional implementation of hospital sub-model and country-specific parameterization
Watershed Data					
Required data sets	River network, lakes, discharge sites, catchment boundary (geometry & attributes)				
Data formats	Proprietary predefined text formats		slightly different formats	All common GIS data formats supported	
Pre-processing	Script-based from raw data in predefined text format			GIS-based toolset	GIS-based toolset, supplemented by own tools
Database system	ESRI Shapefile	Oracle DB	PostgreSQL	ESRI Geodatabase	
Software					
User interface	ESRI ArcView 3	Thuban geodata viewer		ESRI ArcGIS 10.2	ESRI ArcGIS 10.5.1
Geo-editing of model objects	Not supported			Supported	
GIS functionality	Limited	Visualization only		Fully supported	
Analysis tools	Color-coded map, concentration profiles, comparison of results to selected target values		in addition: Calculation of equilibrium concentration in sediment	in addition: Comparison with monitoring data, cumulative distribution function	in addition: sewage fraction calculations, monitoring display tools and new export function
Scenario definitions and analysis	Not supported (only by editing model parameters manually)			Dedicated scenario creation, scenario comparison tool	
References	Feijtel et al, 1998; Fox et al., 2000; Schulze and Matthies, 2001; Heß et al ., 2004.	Koorman et al., 2006; Bester et al., 2008; Alder et al., 2010	Schowanek et al., 2012	Klasmeier et al., 2011, Kehrein et al., 2015	Lämmchen et al., 2021a, Lämmchen et al., 2021b, Duarte et al., 2021

B. Model equations

The model core is subdivided into three modules that estimate emission loads, sewage treatment removal, and in-stream loss processes. Basic model equations have not largely been changed across the different versions and the current state thus represents the evolution of 20 years and the work of dozens of PhD students and scientists. As already noted in the actual work, the following list represents the current state of the model equations, which have only experienced minor changes since publication in Kehrein et al. (2015) and is listed here again in the most current version for the sake of completeness.

Emission module

Point emissions are generally estimated from an average substance-specific emission rate for each source if feasible. It is assumed that emission is more or less directly proportional to a reference parameter such as population number or drainage area. For many household chemicals and pharmaceuticals, it can be assumed that an average application rate per capita exists so that the number of connected inhabitants serves as a good proxy to estimate the emission of these substances into domestic wastewater and sewage treatment plants. Thus, substance specific per-capita emission rates (r_{dom}) are extracted from available data and statistical information and multiplied by the number of connected inhabitants (Inh) to give the domestic emission into a specific sewage treatment plant (STP) i.

$$E_{dom,i} = Inh_i \cdot r_{dom}$$

Non-point emissions from impervious areas or diffuse emissions from agricultural areas can be estimated by applying a similar procedure. Here, area-related emission rates (r_{area}) are multiplied by the total specific area drained into the sewer system or a specific river segment to give the emission load.

$$E_{area,j} = Area_j \cdot r_{area}$$

The newly implemented hospital sub-model separately estimates emissions via hospital wastewater. Hospitals are implemented as point sources, where each hospital carries the attribute ID of the corresponding wastewater treatment plant receiving the wastewater.

Hospital emissions are treated as additional influent fraction simulated via per patient (r_{pat}) or per bed consumption rates (r_{bed}).

$$E_{Hosp,i} = Bed_i \cdot r_{bed} \qquad \text{or} \qquad E_{Hosp,i} = Patient_i \cdot r_{pat}$$

The input load into an individual STP is then given by addition of all domestic and hospital inputs.

Emissions from industry cannot be estimated independently and thus require specific information on average annual loads (E_{ind}). Such information may be included in the European Pollutant Release and Transfer Register (PRTR) or has to be collected from local authorities. Emission loads of indirect emitters are directed into the respective WWTP, while direct emitters are treated as separate emission points.

Sewage treatment module

Due to the high degree of connection to the sewer system in Germany, household emissions are almost exclusively transported into sewage treatment plants before entering the environment. Emissions from hospitals and industrial indirect emitters also contribute to the input load of STPs.

In an STP, a certain fraction of the pollutants is removed by either degradation or adsorption to sewage sludge reducing the load in the treated effluent. The efficiency of removal depends on the type of treatment applied. GREAT-ER distinguishes four basic treatment types, namely wastewater lagoon, constructed wetland, biofilm and activated sludge. For each of the four treatment types, substance-specific removal efficiencies (f_{STP}) are used. The removal efficiency of an STP may also depend on operational management parameters. However, complex STP models such as Simple Treat 4.0 (Struijs, 2014) require a large amount of information about substance properties and STP operation, which cannot be collected on a regional scale with reasonable effort. Therefore, in its simplest mode GREAT-ER assumes constant substance-specific removal efficiencies for each treatment type. In GREAT-ER 4 the option to define tertiary wastewater treatment steps such as ozonation or activated carbon filtration for selected STPs was added. In 4.1 this option can be used more general as ‘customized treatment’ allowing the definition of tailor-made

specific post-treatment steps (e.g. nanofiltration) with substance-specific removal efficiencies. This option was used for simulation runs within the MEDUWA project. The removal efficiency of these post-treatment steps (f_{tert}) is related to the substance mass in secondary wastewater. In general, STPs may be retrofitted with more than one tertiary treatment step so that the emission load from STP i into the receiving river segment (E_i) is estimated from the total load entering the STP ($E_{tot,i}$) and the respective removal efficiencies ($f_{tert,k}$) according to

$$E_i = E_{tot,i} \cdot (1 - f_{STP}) \cdot \prod_k (1 - f_{tert,k})$$

River module

Each river segment may receive substance loads from one or more upstream segments, from treated effluent of connected STPs, or direct industrial emitters as well as from drainage area runoff. Along each segment, a substance may undergo different loss processes such as degradation, volatilization or sedimentation. GREAT-ER 4.1 assumes pseudo-first order removal for each process. The initial mass flow rate (F_{init}) is correspondingly reduced to give the mass flow rate at the end of the segment (F_{end}).

$$F_{end,j} = F_{init,j} \cdot e^{-\lambda_j \cdot \tau_j}$$

Here, τ represents the travel time of the substance in the segment, which in case of rivers is calculated as the ratio of the flow velocity u_j and the length of the segment L_j. Correspondingly, for lakes and reservoirs residence times are estimated from the average water volume (V_j) divided by the discharge at the outflow (Q_j).

$$\tau_{j,river} = \frac{L_j}{u_j} \; ; \; \tau_{j,lake} = \frac{V_j}{Q_j}$$

The removal processes are described by a lumped first-order removal rate constant λ. For mode 1 calculations, a global substance-specific rate constant is required that is applied for each segment independent of local environmental conditions.

A more detailed picture can be achieved using mode 2. In this case, each loss process is considered separately by segment-specific first-order rate constants, which are summed up

to give individual values of λ for each segment. The rate coefficients of the different sub-processes are calculated in individual sub-models.

Biodegradation

A spatially independent biodegradation rate (k_{bio}) is assumed which is applied to all segments. This is due to the lack of spatially distinguished estimation routines for biodegradation.

Hydrolysis

The hydrolysis rate constant k_{hydro} describes the sum of neutral, acid, and base hydrolysis in water. The user needs to collect data for the pseudo-first order rate constant $k_{neutral}$ as well as the second-order rate constants k_{acid} and k_{base} in units $h^{-1}\ (mol\ L^{-1})^{-1}$ from the literature.
The hydrolysis rate constant is then calculated taking into account the pH value according to the following equation (Mabey & Mill, 1978):

$$k_{hydro} = k_{neutral} + k_{acid} \cdot 10^{-pH} + k_{base} \cdot 10^{pH-14}$$

Photolysis

Photolysis rate constants are estimated taking into account the photolysis rate constant at the water surface ($k_{phot,surf}$), the light extinction in the water column depending on the average decadic light absorption coefficient at 254 nm α and the river depth d (Schwarzenbach et al., 2003, p.639).

$$k_{phot} = k_{phot,surf} \cdot \frac{1 - e^{-2.3 \cdot \alpha \cdot d}}{2.3 \cdot \alpha \cdot d}$$

Volatilization

Simulation of volatilization takes into account the dependence of mass exchange on the surface to volume ratio (expressed as average depth) of the individual segments. The first order volatilization rate (k_{vol}) in unit h^{-1} is calculated as the ratio of the overall mass transfer velocity (v_{aw}) of the compound across the air-water interface and the average depth d of the river segment. Currently, v_{aw} has to be externally estimated by the user and entered into the substance database as general substance parameter.

$$k_{vol} = \frac{v_{AW}}{d}$$

Sedimentation

The first order net sedimentation rate (k_{sed}) of suspended solids in unit h^{-1} is calculated as the ratio of the settling velocity (v_{sed}) and the average depth of a segment:

$$k_{sed} = \frac{v_{sed}}{d}$$

For river segments, the settling velocity is a user-defined input parameter, while for lakes it is estimated from the average annual sediment growth (g_{sed})

$$v_{sed} = \frac{g_{sed} \cdot \rho_{suspM} \cdot (1 - \varepsilon_{sed})}{8760 \cdot suspM}$$

with g_{sed} being the average annual sediment growth ($m\ a^{-1}$), *suspM* the suspended matter concentration in the water phase ($g\ L^{-1}$), P_{suspM} the density of suspended matter ($g\ L^{-1}$), ε_{sed} the porosity of the sediment, and 8760 being the unit correction factor from 1 year (a) to hours (h). Default values for g_{sed} are stored in the 'Config' table of the GREAT-ER database and can be adjusted if necessary.

It is assumed that only the sorbed fraction of the chemical (f_s) is prone to sedimentation and only the dissolved chemical fraction (f_d) can undergo volatilization. The fractions of sorbed and dissolved chemical are calculated from the partition coefficient (K_d), the total concentration (C_{tot}) and the suspended solids content of the river ($SuspM$) as follows:

Dissolved fraction:
$$f_d = \frac{C_d}{C_{tot}} = \frac{1}{1 + C_s / C_d} = \frac{1}{1 + 10^{-3} \cdot K_d \cdot SuspM}$$

Sorbed fraction:
$$f_s = \frac{C_s}{C_{tot}} = 1 - f_d$$

If K_d is not given, it is estimated as: $K_d = f_{oc} \cdot K_{oc}$

Finally, the lumped first order-rate constant for each segment then calculates to
$\lambda = k_{hydro} + k_{phot} + k_{bio} + f_s \cdot k_{sed} + f_d \cdot k_{vol}$

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Article supportive information

In the following section, the supporting information of the articles included in this thesis are attached for the interest of completeness. The information is attached unchanged in terms of content, as it can also be downloaded from the online versions of the articles. Only the layout has been minimally modified to ensure readability and to establish some consistency with the rest of the work.

Supporting material to article 1

Table S1: Substance properties for model simulations

		Clarithromycin	Iopamidol	Ethinylestradiol	Reference		
		I	II	III	I	II	III
Phys. chem. properties	Unit						
Molar mass	g/mol	747.96	777.08	296.1	[24]	[21]	[11]
log Kow		3.16	- 2.42	3.67	[24]	[21]	[11]
Water solubility	mg/l	0.336	120	11.3	[24]	[21]	[26]
pKa		8.95	10.7	10.4	[24]	[21]	[26]
WWTP removal							
Lagoon	%	30.5	< 10	>70	[20]	[10]	[8]
Wetland	%	30.5	< 10	>70	[20]	[10]	[8]
Biofilm	%	44	60 – 80	87	-	[6]	[4]
Activated Sludge	%	44	35	87	[9], [19], [24]	[10]	[4], [15]
River removal							
Half-life	d		> 44			[17]	
Model assumption	1/h		6.6e-4			[23]	
Near surface photolysis	1/h	0.001	-	5,50e-03	[20]	-	[16]
Kd river	L/kg	335	-	140	[1]	-	[16]
Consumption							
Per-capita consumption	kg/(Inhabitant*a)	1.28e-04	6.6e-04	5,596e-07	[22]	[13]	IMS, 2014
Hospital fraction	%	15.2	87.5	-	0	[7]	-
Excretion	%	30	87.5	40	[2], [19]	[7]	[14]
EQS	ng/l	130	-	0.35	[3]	-	[3]

Table S2: Main characteristics of investigated river basins

		Main	Lenne	Naab
	Unit			
Size	[km²]	27,250	1,352	5,225
Connected inhabitants		~ 3,800,000	~ 380,000	~ 500,000
Number of WWTPs		848	36	192
Flow length of the main stream	[km]	527	129	98
Cumulated length of the simulated river network	[km]	10,273	5,156	2,077
MQ-Discharge at the outlet point	[m³/s]	~250	~ 28	~ 50

References of the supporting material to article 1

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Supporting material to article 2

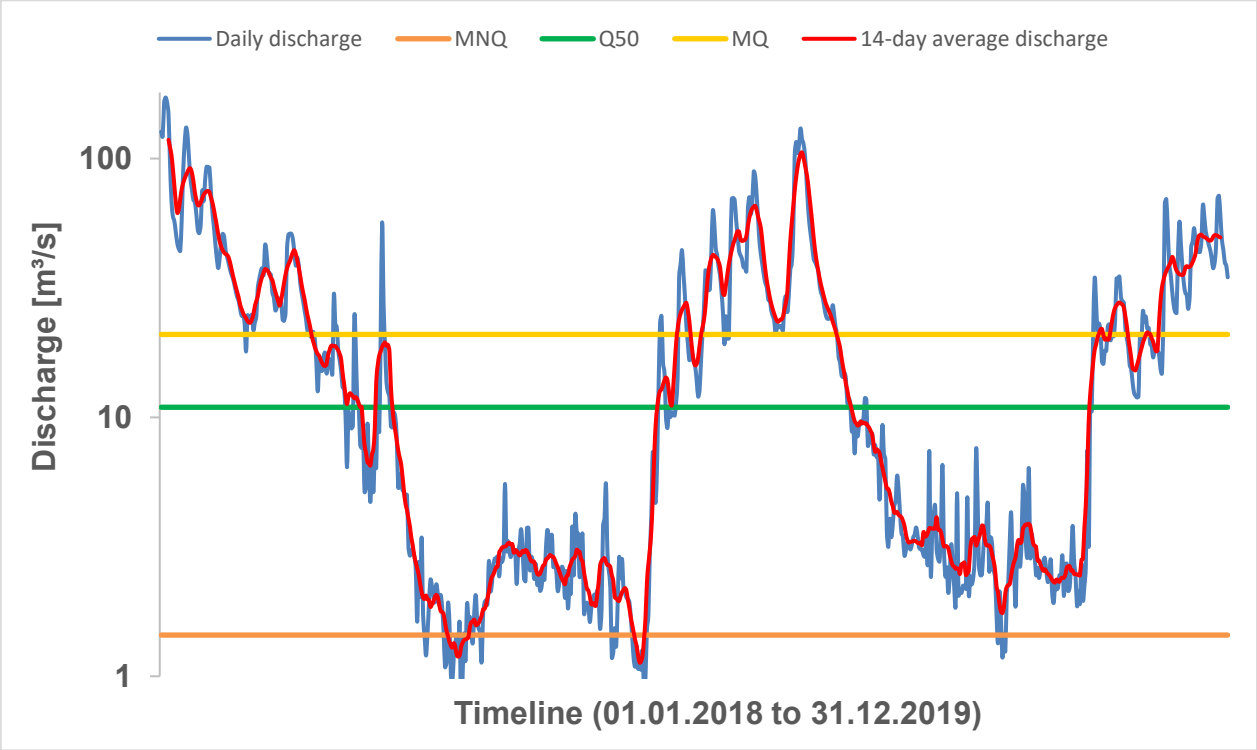

Fig. S1: Discharge variability shown at one exemplary gauge. Daily discharges (blue) and smoothed 14-day discharges (red) at gauge Ommen from 01.01.2018 to 31.12.2019 (blue); Additionally, long-term calculated hydrological parameters MNQ (orange), Q50 (green) and MQ (yellow) for the time-period 2000-2019 are shown.

Creation of the hydrological network used in the simulations

Before merging the different datasets, a common criterion for the spatial resolution had to be defined. Given by statistics provided within the Dutch and German datasets, the exclusion criteria were defined as minimum stream flow of 750 L/s at least once a year (Dutch data) or annual average stream flow of at least 50 L/s (German data). These are arbitrary limits, but they harmonize the level of detail quite well and, at the same time, allow a level of detail almost comparable to the level of the German DLM250 (https://www.bkg.bund.de/DE/Produkte-und-Services/Shop-und-Downloads/Digitale-Geodaten/Landschaftsmodelle/Deutschland/deutschland_cont.html).

Existing gaps between administrative borders had to be closed manually using ArcMap®. A geometric, directed network can then be created from this harmonized, gapless river network. Based on the GREAT-ER requirements, the network was split into segments of no more than 2 kilometers in length. This resulted in 2082 individual segments that are used for later simulations.

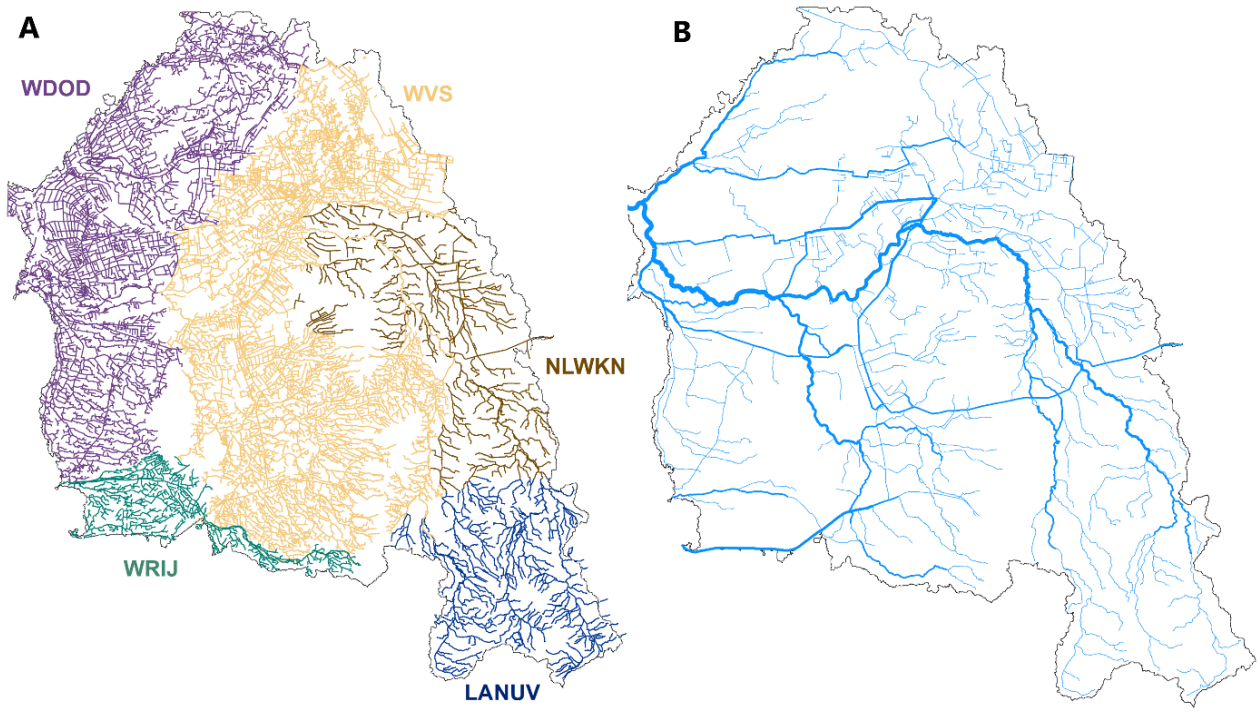

Fig. S2: A: Original geodata of river networks as they have been made available by the authorities in different parts of the catchment; B: Harmonized river network of the Vecht, which was derived from the original data as described and is used in the simulations

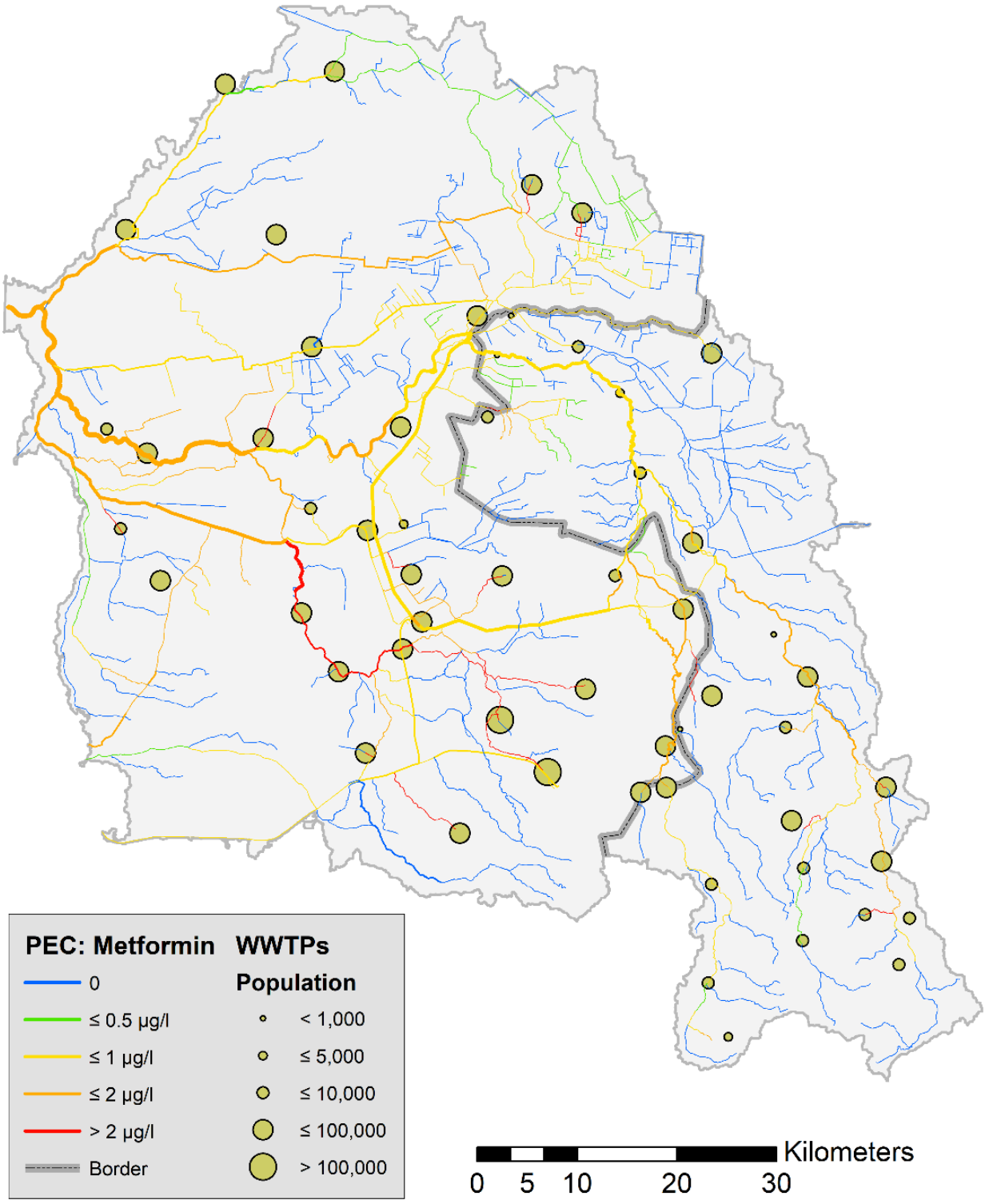

Fig. S3: Predicted environmental concentrations (PEC) of metformin in the river Vecht basin, resulting from a deterministic simulation run for low flow river conditions (MNQ) within the Q_{low} scenario

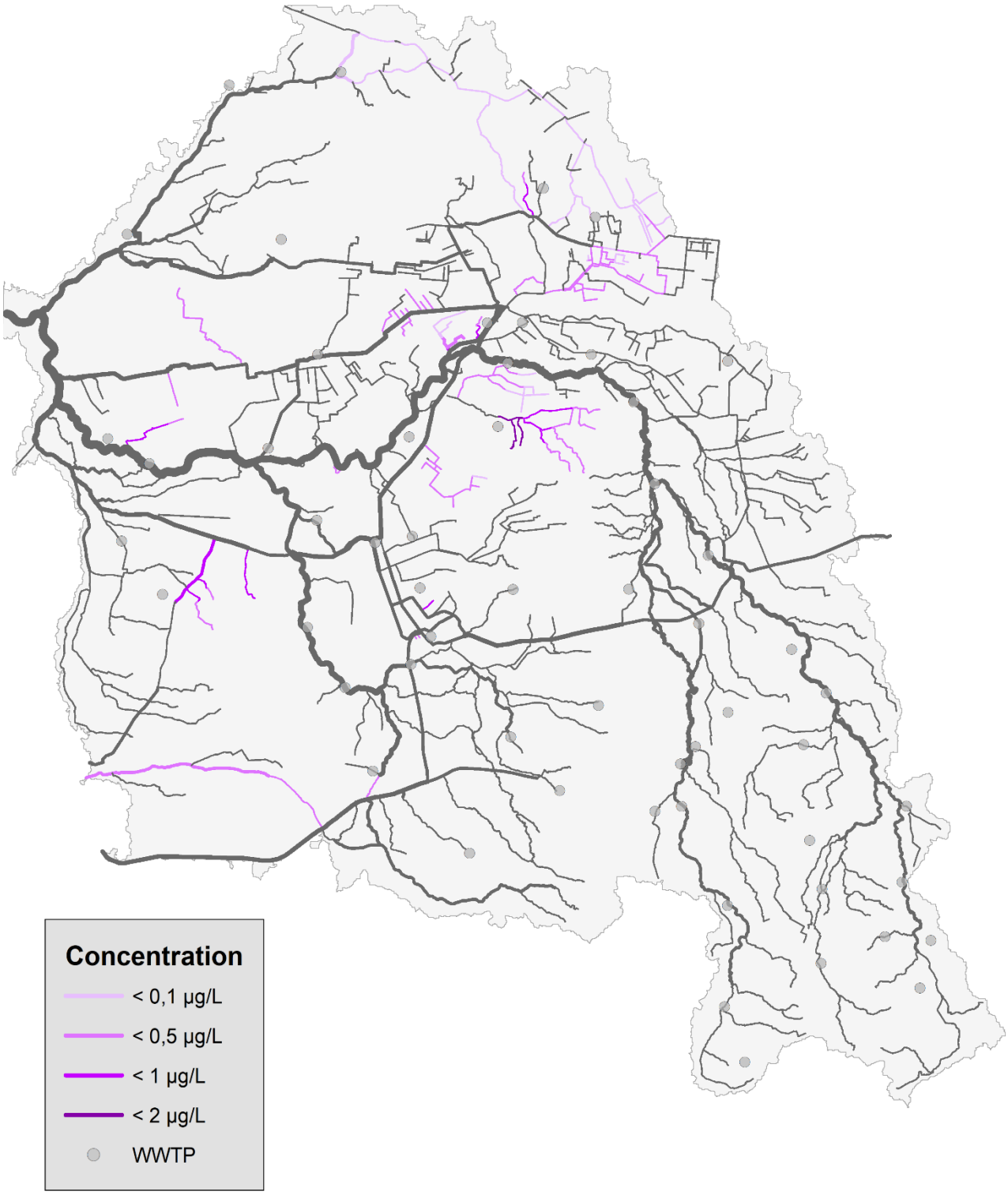

Fig. S4: Predicted environmental concentrations (PEC) of metformin in the river Vecht basin for river stretches that have been pristine in the Q_{avg} scenario, that are only polluted in Q_{low} (marked in purple). Segments that are pristine or polluted in both scenarios, i.e. show no variation, are marked in gray. Output resulting from a deterministic simulation run for low flow river conditions (MNQ) within the Q_{low} scenario displayed in Fig. S3.

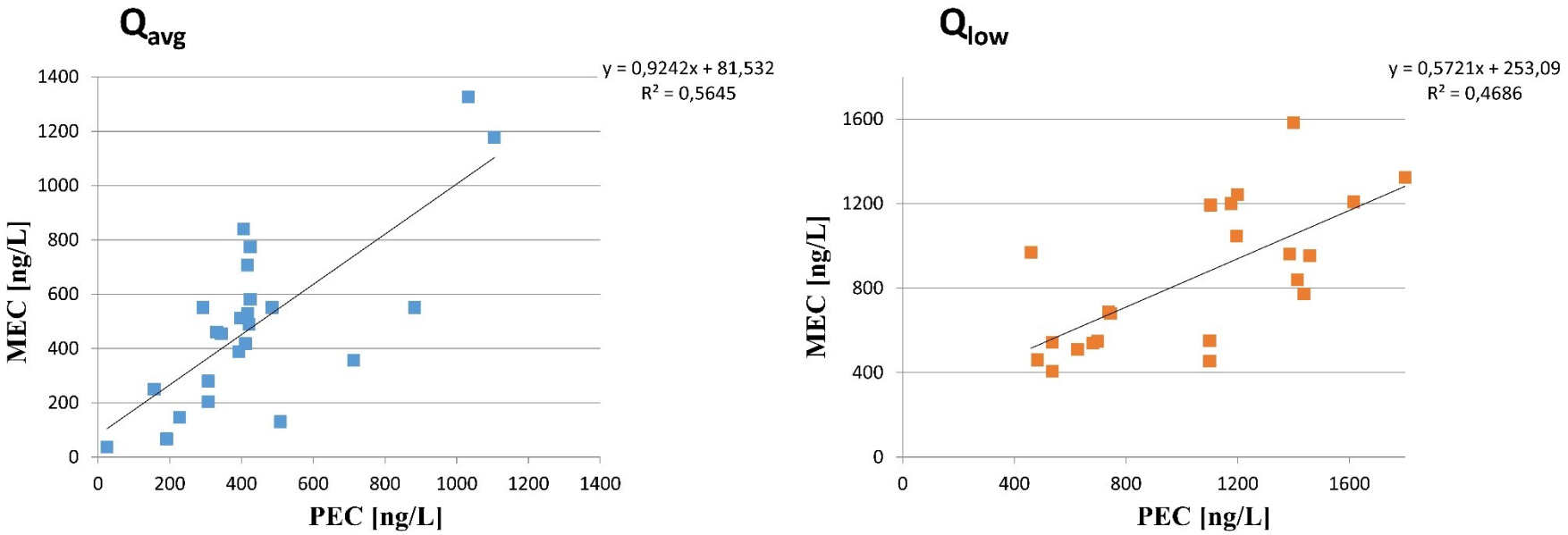

Fig. S5: Predicted environmental concentrations (PEC) of metformin are plotted against the median of measured environmental concentrations (MEC) at 23 monitoring sites. The accuracy of the prediction made is shown by calculating and plotting R^2. The left panel includes data of 51 monitoring samples taken under Q_{avg} scenario conditions, the right panel includes data of 53 monitoring samples taken under Q_{low} scenario conditions.

Supporting material to article 3

TABLE S1: Pharmaceutical consumption rates.

Compound	German per capita consumption Vecht catchment [kg/(cap yr)] a	Dutch per capita consumption Vecht catchment [kg/(cap yr)] b	Ratio German to Dutch per bed consumption c
17α-Ethinylestradiol	1.50x10-7	6.39x10-7	n.a.d
Carbamazepine	4.36x10-4	4.56x10-4	203%
Ciprofloxacin	2.75 x10-4	2.32x10-4	131%
Cyclophosphamide e	1.93 x10-6	0	46%
Diclofenac	6.73x10-4	2.54x10-4	198%
Erythromycin	3.14x10-4	1.98x10-5	117%
Metformin	1.36x10-2	1.97x10-2	144%
Metoprolol	1.47x10-3	1.74x10-3	123%

a IQVIA Commercial GmbH & Co. OHG, calculations based on IMS PharmaScope® (2018).
b Dutch Foundation for Pharmaceutical Statistics (2018).
c Annual per bed consumption rates were calculated as the mass of prescribed pharmaceuticals in a hospital devided by the number of beds in the respective hospital. These values were averaged for German and Dutch hospitals, respectively. Due to the limited number of hospitals which provided data and data security issues only ratios of the average per bed consumption ratios can be displayed. Excluding ethinylestradiol and cyclophosphamide, the per-bed consumption rate is 1 to 40 times higher than the per capita consumption rates of the respective countries.
d In both countries, no hospital consumption data was reported; n.a., not applicable.
e Cyclophosphamide is restricted to clinical use in the Netherlands. SFK only collects domestic pharmaceutical consumption. Therefore, no domestic cyclophosphamide use is recorded in for the Netherlands.

TABLE S2: Pharmaceutical excretion data. Urinary and faecal excretion percentages. Glucuronide conjugates of the parent compound are shown in brackets a. For the modelling exercise (sixth column), mean urinary excretion and 20% of mean faecal excretion were applied.

Compound	Urine (+ conjugates) [%]	Faeces (+ conjugates) [%]	Urine + faeces (+ conjugates) [%]	Source	Modelled fraction entering STPs [%]
17α-Ethinylestradiol	10.1 (17.2)	23.1		12	32%
Carbamazepine	< 10	< 30		1	15%
	0.8 (11)	13 (?)		2	
	2	< 28		3	
	1.44	12.3		4	
			2.7 – 15% (0%)	5	
	1	28		6	
			1 – 2% (~ 30%)	7	
			31%	8	
Ciprofloxacin	40 – 50	< 20 – 35		1	54%
	< 70	15		1	
	44.7	25		3	
	61.5	15.2		3	
Cyclophosphamide	25	“small amounts”		1	25%
Diclofenac	? (< 15)	< 5		1	10%
	2 – 23 b	1 – 4 b		9	
			1 (10 – 15)	5	
			0.05 – 0.1 (0.5 – 1.5)	5	
	6	< 35		6	
			2% (15)	8	
			15 (< 1)	7	
			< 1 (5 – 10)	10	
Erythromycin	4 – 20	40 – 50		11	19%
			4	8	
	5 – 10	“large amounts”		1	
	5	“mainly”		3	
	12 – 15	“mainly”		3	
Metformin	30 – 50	30		1	74%
	35 – 50	30		13	
	79	0		13	
	100	0		14	
	100	0		15	
Metoprolol	< 10	-		1	8%
	< 5	-		3	
	3 – 10			16	
	9.4	-		17	
	< 5.2	-		17	
			7	8	
			3 – 10	7	
	5 – 10	-		10	

1. Moffat et al., (2011). 2. Bahlmann et al., (2014). 3. Swissmedic (2020). 4. Björlenius et al., (2018). 5. Heberer and Feldmann (2005). 6. Zhang et al., (2008). 7. Ternes and Joss (2008). 8. Khan and Ongerth (2004). 9. Johnson et al., (2007). 10. Kummerer et al., (2011). 11. Göbel et al., (2005). 12. Johnson and Williams (2004). 13. Tucker et al., (1981). 14. Robert et al., (2003). 15. Bristol-Myers Squibb Products & Medicines (2018). 16. Alder et al., (2010). 17. Regårdh et al., (1974).

a Glucuronide conjugates can react back to the parent compound in the sewer (Gao et al., 2017; Heberer and Feldmann 2005; Kumar et al., 2012). For this study, we assume that the entire fraction excreted as glucuronide associated parent compound will react back to the parent compound in the sewer. Therefore, we aggregate the excretion rates of the parent compound and the glucuronide conjugates of the parent compound in a single excretion rate.
b No distinction between parent compound and conjugates.

Except for diclofenac and erythromycin, all compounds were applied systematically solely. For the latter STP inflow loads (L_{in} [kg/yr]) were calculated as

$$L_{in} = pCC \times Inh \times f_{ex}$$

where pCC is the per capita consumption rate [kg/(cap yr)], Inh [cap] is the number of inhabitants in the STP catchment and f_{ex} is the fraction that is excreted in the unchanged or conjugated state.

Only the absorbed portion of topically applied erythromycin and diclofenac are thought to undergo metabolism. Sioufi et al., (1994) found relative proportions of parent compounds and metabolites after topical application compared to oral application for diclofenac. The portion that is not absorbed either goes into clothing, bandages or is wiped off with e.g. paper and then thrown in the trash (Heberer and Feldmann 2005). According to Heberer and Feldmann (2005), STP inflow loads of diclofenac can be estimated as

$$L_{in} = (f_{sys} \times f_{ex} + f_{top} \times f_{ab} \times f_{ex} + f_{top}(1 - f_{ab})) \times pCC \times Inh$$

where f_{sys} is the systematically applied fraction, f_{top} is the topically applied fraction and f_{ab} the fraction that is absorbed after topical application. For the scope of this study we use worst case estimations and assume that the fraction which is not absorbed $(1 - f_{ab})$ ends up in the wastewater, e.g. via washing of clothing or bandages. In the model of Heberer and Feldmann (2005) it is assumed that 100% of the parenterally or orally administered dose is absorbed leading to the same excretion rate regardless of the route of administration. This model is also used to calculate the influent loads of erythromycin. Parameters for Germany and the Netherlands are shown in Table S3. The result for diclofenac is that in Germany 52 % and in the Netherlands 15 % of the total prescribed mass ends up in wastewater. For erythromycin this results in 21 % and 31 % for Germany and the Netherlands, respectively.

TABLE S3: Diclofenac and erythromycin inflow model parameters.

	Germany [1]		*Netherlands* [2]			
Compound	f_{sys}	f_{top}	f_{sys}	f_{top}	f_{ab}	f_{ex} [5]
Diclofenac	0.51	0.49	0.97	0.03	0.07 [3]	0.10
Erythromycin	0.99	0.01	0.86	0.14	0.00 [4]	0.19

[1] IQVIA Commercial GmbH & Co. OHG, calculations based on IMS PharmaScope® (2018). [2] Dutch Foundation for Pharmaceutical Statistics (2018). [3] Hui et al., (1998). [4] Systematically exposure of topically applied erythromycin is negligible (Carls et al., 2014). [5] Table S2.

TABLE S4: Summary of removal efficiencies published in literature. Removal efficiencies have to be interpreted as percentage change of mass loading in effluent versus influent. Negative removal efficiencies may occur when the back-reaction of labile intermediates to the parent compound outweigh the actual removal or due to experimental and analytical uncertainty for compounds with low removal efficiencies (< 10 %). STP, sewage treatment plant; SD, standard deviation.

Compound	Number of STPs	Mean [%]	SD [%]	Median [%]	Sources
17α-Ethinylestradiol	3	72.5	5.5	70.5	3, 18
Carbamazepine	33	-5.8	27.5	0.0	1, 3, 4, 7, 8, 10, 11, 12, 13, 15, 18, 20, 21
Ciprofloxacin	22	71.1	20.1	78.0	1, 4, 6, 9, 21
Cyclophosphamide	1	59.0	0.0	59.0	2
Diclofenac	19	25.5	22.7	31.2	3, 4, 8, 11, 12, 13, 15, 17, 18, 19, 20
Erythromycin	21	14.0	29.7	14.6	1, 4, 5, 6, 8, 9, 10, 12, 13, 14, 16, 18
Metformin	6	97.4	1.2	97.5	4, 11, 15
Metoprolol	16	22.1	27.6	22.9	4, 7, 8, 11, 12, 13, 15, 18, 19, 21, 22

1. Castiglioni et al., (2006). 2. Česen et al., (2015). 3. Clara et al., (2005). 4. Jesus Gaffney et al., (2017). 5. Göbel et al., (2007). 6. Guerra et al., (2014). 7. Gurke et al., (2015). 8 Kasprzyk-Hordern et al., (2009). 9. Li and Zhang (2011). 10. Nakada et al., (2007). 11. Oosterhuis et al., (2013). 12. Radjenovic et al., (2007). 13 Radjenović et al., (2009). 14. Roberts and Thomas (2006). 15. Sacher (2014). 16. Senta et al., (2019). 17. Sui et al., (2011). 18. Ternes et al., (2007). 19. Thomas et al., (2007). 20. Vergeynst et al., (2015). 21. Vieno et al., (2006). 22. Wick et al., (2009).

TABLE S5: Parametrization of in-stream processes. CBZ, carbamazepine; CIP, ciprofloxacin; CYL, cyclophosphamide; DFC, diclofenac; ERY, erythromycin; EE2, 17α-ethinylestradiol; MET, metformin; MEP, metoprolol.

Compound	Surface photolysis rates a [1/h]	Source	First order degradation rate a [1/h]	Source	Bio degradation rate [1/h]	Source	Kd b [L/kg]	Source
CBZ	ScnAC: 1.1x10-4 ScnDS: 2.2x10-4	Estimated with a quantum yield of 1.1x10-5 (Calisto et al., 2011)			< 1x10-4	Durán-Álvarez et al., (2015)	13.3 d	Radović et al., (2016)
CIP	ScnAC: 0.647 ScnDS: 1.311	Estimated with an average quantum yield of 8.5x10-3 (at pH 7.5)			No degradation	Girardi et al., (2011)	250	Tolls (2001)
CYC			7x10-4	Buerge et al., (2006)	< 1x10-4	Lutterbeck et al., (2016)	4.4 e	Azuma et al., (2017)
DFC	ScnAC: 0.018 ScnDS: 0.049	Estimated with a quantum yield of 0.038 (Andreozzi et al., 2003)			Recalcitrant	Lahti and Oikari (2011)	14.4 d	Radović et al., (2016)
ERY			0.003	Batchu et al., (2014)	< 1x10-4	Alexy et al., (2004)	139.7 d	Radović et al., (2016)
EE2	0.0029 c	Jürgens et al., (2002)			Resistant to biodegradation	Zuo et al., (2013)	278	Ternes et al., (2004)
MET			0.0012	Neamţu et al., (2014)	Not readily biodegradable	Trautwein and Kümmerer (2011)	19	Scheurer et al., (2012)
MEP			0	Baena-Nogueras et al., (2017)	0.001	Baena-Nogueras et al., (2017)	18.1d	Radović et al., (2016)

a Seasonal surface photolysis rates were estimated based on wavelength-dependent sunlight intensities at 50 degree north latitude (Apell and McNeill 2019) and available light absorption spectra of the substance. Quantum yields were taken from the literature. No quantum yields and no seasonal photolysis rates were available for ethinylestradiol. Therefore, we applied the same literature photolysis rate for both scenarios. Cyclophosphamide, erythromycin, metformin and metoprolol do not effectively absorb sunlight in the photochemically relevant wavelength range between 295 nm - 400 nm. For these compounds, lumped pseudo first order degradation rates reported in the literature were used without correction for seasonal influences due to a lack of more detailed information.

b The distribution coefficient Kd is an input parameter of the GREAT-ER model to estimate the chemical fraction of a chemical prone to sedimentation in a river segment. Sedimentation is modelled using the equilibrium distribution assumption represented by an average Kd value between suspended matter and water. The model includes a basic assumption on the average suspended matter concentration which is used to estimate the adsorbed fraction. Spatial information about the composition and properties of suspended matter in the Vecht River catchment was not available. Furthermore, information about Kd values between suspended matter and water in natural rivers was not available for the investigated APIs. However, Kd values are reported in the literature for the sediment-water, soil-water and sludge-water equilibrium. Therefore, those values were used as a proxy to describe the suspended matter water distribution in the Vecht River catchment.

c Based on assumed 12 hours of sunlight exposure per day.

d Average value of four sediments.

e Average value of two sediments.

Monitoring campaign

As a part of a one-year sampling campaign of bacteria and bacteria resistance genes in the Vecht catchment (omitted author, in preparation) a subset of collected STP and in-stream samples was analysed for pharmaceuticals (Tables S6-8). The selection of STPs was the same as in the grand sampling campaign. Selection was based on the plant location (Germany/Netherlands), the plant scale (small to large) and, if the plant was or was not treating hospital wastewater. Approximately 50 % of STP influent and effluent samples were analysed for pharmaceuticals. This was thought to be sufficient to cover pharmaceutical variability in STP influent and effluent in Germany and the Netherlands. The sampling months of the STP measurements are displayed in Table S7. For two STPs a gradient measurement was performed, i.e. Hardenberg and Steinfurt-Burgsteinfurt. For these plants, one surface water sample upstream of each plant was taken (sampling sites H00 and B00 respectively), as well as several surface water samples downstream of the plants (sampling sites H01-H06 and B02-B06 respectively). Furthermore, several surface water locations were sampled for other interests. One sample was taken on the location where the river crosses the German-Dutch border (sampling site G11). The other sampling sites were distributed across the catchment (sampling sites G02, G04, G05, G07, G08, G09, G10). The in-stream sampling sites represent a subset of the sampling sites in the grand monitoring campaign and were taken on locations that were important for evaluation of the GREAT-ER model. At each of these sampling sites a fraction of samples was analysed for pharmaceuticals. These fractions were selected based on the date of sampling and the hydrological conditions on the respective day. At Dutch sampling sites pumping activities were also taken into account. The in-stream sampling sites and their allocation to the scenarios are summarized in Table S8.

TABLE S6: Number of the sampling sites and number of samples taken in the Vecht catchment. For a comprehensive overview see omitted author (unpublished manuscript). STP, sewage treatment plant.

	STP (influent and effluent)	In-stream
Germany	Gronau, Nordhorn, Schüttorf, Steinfurt-Burgsteinfurt (ninfluent = 25, neffluent = 25)	B00, B02, B03, B04, B05, B06. G02, G04, G05 (nScnDS = 18, nScnAC = 28)
Netherlands	Almelo-Sumpel, Dalfsen, Enschede-West, Hardenberg, Ootmarsum, Vroomshoop (ninfluent = 34, neffluent = 33)	H00, H02, H03, H04, H06, G06, G07, G09, G10, G11(nScnDS = 19, nScnAC = 27)

TABLE S7: Sampling dates of the subset of samples and allocation to scenarios.

Sampling month and year	STP a
July 2018	W01, W02, W04, W05, W07, W09, W10, W11
August 2018	W01, W02, W04, W05, W07, W09, W10, W11
November 2018	W01, W02, W04, W05, W07, W09, W10, W11
December 2018	W03, W06
January 2019	W03, W04, W06, W07
February 2019	W01, W02, W03, W04, W05, W07, W09, W10
March 2019	W03, W04, W05, W06, W07, W09
April 2019	W01, W02, W03, W04, W05, W06, W07, W10, W11
May 2019	W02, W03, W06, W09, W11

a W01, Hardenberg. W02, Enschede. W03, Steinfurt-Burgsteinfurt. W04, Nordhorn. W05, Ootmarsum. W06, Gronau. W07, Schuettorf. W09, Almelo-Sumpel. W10, Dalfsen. W11, Vroomshoop.

TABLE S8: Sampling dates of the subset of samples and allocation to scenarios. ScnDS, Dry summer scenario; ScnAC, average condition scenario.

Allocated scenario	Sampling month and year	Sampling sites
ScnDS	June 2018	B00, B02, B03, B04, B05, B06, G02, G04, G05, G07, G08, G09, G10, G11, H00, H02, H03, H04, H06
ScnDS	August 2018	B00, B03, B04, B05, B06, G02, G04, G05, G07, G08, G09, G10, G11, H00, H03, H04, H06
ScnDS	September 2018	B02
ScnAC	October 2018	B00, B02
ScnAC	November 2018	B00, B02, B03, B04, B05, B06, G02, G04, G05, G07, G08, G09, G10, G11, H00, H03, H04, H06
ScnAC	December 2018	B00, B01, B03, B04, B05, B06
ScnAC	February 2019	B00
ScnAC	March 2019	B00, G05, G07, G08, G09, G10, G11, H00, H03, H04, H06
ScnAC	April 2019	B00, B03, B04, B05, B06, G02, G04, G05, G07, G08, G09, G10, H00, H03, H04, H06
ScnAC	May 2019	B00, G11

Determination of micropollutants

Water samples were taken and stored at -20°C within 6 hours of collection. For sample preparation 2000 µL of thawed sample was mixed with 200µL of methanol and 100 µL of modifier solution, shaken for 30 minutes at high speed using a Heidolph shaker. After centrifugation, 900 µL of supernatant was pipetted into LC-MS vials. 13C standard addition was carried out in all samples and results have been corrected accordingly. The analysis was conducted using a Agilent 6420 Triple Quadrupole LC-MS/MS system with an electrospray ion source. A thorough description of the analysis has been reported elsewhere (omitted author unpublished manuscript). For this study, four compounds have been added to the method later. The mass/charge per compound and recovery rates are listed in Table S9 and Table S10, respectively.

TABLE S9: Mass/charge per compound.

Compound	Precursor ion	Product ion	Retention time (min)	Fragmentor voltage (V)	Collision energy (V)	Polarity
Metoprolol	268.2	191	4.75	125	15	Positive
Metoprolol	268.2	116	4.75	125	16	Positive
Carbamazepine	237.2	194.2	5.83	155	16	Positive
Carbamazepine	237.2	179.1	5.83	155	40	Positive
Naproxen	231	185	6.48	90	10	Positive
Naproxen	231	170	6.48	90	28	Positive
Diclofenac	296	215	7.22	95	17	Positive
Diclofenac	296	214	7.22	85	32	Positive

TABLE S10: Compound recovery rates. Recoveries for the measured compounds varied between 70-136 %. Recoveries were determined individually for each samples to cancel any variations do to the water matrix.

Compound	Mean recovery (standard deviation) [%]
Carbamazepine	91.50 (27.19)
Ciprofloxacin	77.52 (32.60)
Diclofenac	136.00 (34.04)
Erythromycin	85.93 (30.55)
Metformin	77.60 (29.35)
Metoprolol	90.88 (27.04)

Baseline for 'benchmarking'

To provide a reliable baseline for the 'benchmarking' approach, predicted carbamazepine concentrations (C_{pred} [ng/L]) were first evaluated by comparison with measured concentrations (C_{meas} [ng/L]). To make predicted and measured concentrations comparable, concentration data from monitoring sites where daily flow rates (Q_{meas} [m^3/d]) were available were adjusted (C_{adj} [ng/L]) to the flow rate used in the model simulation (Q_{model} [m^3/d]),

$$C_{adj} = C_{meas} \times \frac{Q_{meas}}{Q_{model}}$$

TABLE S11: Literature studies retrieved from Web of Science Core Collection ('Topic' search mode).

Data extracted?	Reference
NO	Aaen, S. M., & Horsberg, T. E. (2016). A screening of multiple classes of pharmaceutical compounds for effect on preadult salmon lice Lepeophtheirus salmonis. Journal of Fish Diseases, 39(10), 1213-1223. doi:10.1111/jfd.12463
YES	Aderemi, A. O., Novais, S. C., Lemos, M. F. L., Alves, L. M., Hunter, C., & Pahl, O. (2018). Oxidative stress responses and cellular energy allocation changes in microalgae following exposure to widely used human antibiotics. Aquatic Toxicology, 203, 130-139. doi:10.1016/j.aquatox.2018.08.008
NO	Affek, K., Zaleska-Radziwill, M., Doskocz, N., & Debek, K. (2018). Mixture toxicity of pharmaceuticals present in wastewater to aquatic organisms. Desalination and Water Treatment, 117, 15-20. doi:10.5004/dwt.2018.21964
NO	Ajima, M. N. O., Pandey, P. K., Kumar, K., & Poojary, N. (2017). Neurotoxic effects, molecular responses and oxidative stress biomarkers in Nile tilapia, Oreochromis niloticus (Linnaeus, 1758) exposed to verapamil. Comparative Biochemistry and Physiology C-Toxicology & Pharmacology, 196, 44-52. doi:10.1016/j.cbpc.2017.03.009
NO	Alfei, S., Catena, S., Ponassi, M., Rosano, C., Zoppi, V., & Spallarossa, A. (2018). Hydrophilic and amphiphilic water-soluble dendrimer prodrugs suitable for parenteral administration of a non-soluble non-nucleoside HIV-1 reverse transcriptase inhibitor thiocarbamate derivative. European Journal of Pharmaceutical Sciences, 124, 153-164. doi:10.1016/j.ejps.2018.08.036
NO	Alimba, C. G., Adekoya, K. O., & Soyinka, O. O. (2019). Exposure to effluent from pharmaceutical industry induced cytogenotoxicity, hematological and histo-pathological alterations in clarias gariepinus (Burchell, 1822). Excli Journal, 18, 63-78. doi:10.17179/excli2018-1916
NO	Almeida, A. R., Jesus, F., Henriques, J. F., Andrade, T. S., Barreto, A., Koba, O., . . . Domingues, I. (2019). The role of humic acids on gemfibrozil toxicity to zebrafish embryos. Chemosphere, 220, 556-564. doi:10.1016/j.chemosphere.2018.12.133
NO	Al-Saeedi, A. H., Al-Ghafri, M. T. H., & Hossain, M. A. (2017). Brine shrimp toxicity of various polarities leaves and fruits crude fractions Ziziphus jujuba native to Oman and their antimicrobial potency. Sustainable Chemistry and Pharmacy, 5, 122-126. doi:10.1016/j.scp.2017.03.003
NO	Alyahya, S. A., Govindarajan, M., Alharbi, N. S., Kadaikunnan, S., Khaled, J. M., Mothana, R. A., . . . Benelli, G. (2018). Swift fabrication of Ag nanostructures using a colloidal solution of Holostemma ada-kodien (Apocynaceae) - Antibiofilm potential, insecticidal activity against mosquitoes and non-target impact on water bugs. Journal of Photochemistry and Photobiology B-Biology, 181, 70-79. doi:10.1016/j.jphotobiol.2018.02.019
NO	Ashajyothi, C., Handral, H. K., & Kelmani, R. C. (2018). A Comparative In Vivo Scrutiny of Biosynthesized Copper and Zinc Oxide Nanoparticles by Intraperitoneal and Intravenous Administration Routes in Rats. Nanoscale Research Letters, 13. doi:10.1186/s11671-018-2497-2
NO	Backhaus, T. (2016). Environmental Risk Assessment of Pharmaceutical Mixtures: Demands, Gaps, and Possible Bridges. Aaps Journal, 18(4), 804-813. doi:10.1208/s12248-016-9907-0
YES	Baek, I. H., Kim, Y., Baik, S., & Kim, J. (2019). Investigation of the Synergistic Toxicity of Binary Mixtures of Pesticides and Pharmaceuticals on Aliivibrio fischeri in Major River Basins in South Korea. International Journal of Environmental Research and Public Health, 16(2). doi:10.3390/ijerph16020208
NO	Balkrishna, A., Sharma, N., Sharma, V. K., Mishra, N. D., & Joshi, C. S. (2018). Green synthesis, characterisation and biological studies of AgNPs prepared using Shivlingi (Bryonia laciniosa) seed extract. Iet Nanobiotechnology, 12(3), 371-375. doi:10.1049/iet-nbt.2017.0099
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NO	Banumathi, B., Vaseeharan, B., Ishwarya, R., Govindarajan, M., Alharbi, N. S., Kadaikunnan, S., . . . Benelli, G. (2017). Toxicity of herbal extracts used in ethno-veterinary medicine and green-encapsulated

	ZnO nanoparticles against Aedes aegypti and microbial pathogens. Parasitology Research, 116(6), 1637-1651. doi:10.1007/s00436-017-5438-6
NO	Benelli, G., Govindarajan, M., AlSalhi, M. S., Devanesan, S., & Maggi, F. (2018). High toxicity of camphene and gamma-elemene from Wedelia prostrata essential oil against larvae of Spodoptera litura (Lepidoptera: Noctuidae). Environmental Science and Pollution Research, 25(11), 10383-10391. doi:10.1007/s11356-017-9490-7
NO	Benelli, G., Govindarajan, M., Senthilmurugan, S., Vijayan, P., Kadaikunnan, S., Alharbi, N. S., & Khaled, J. M. (2018). Fabrication of highly effective mosquito nanolarvicides using an Asian plant of ethno-pharmacological interest, Priyangu (Aglaia elaeagnoidea): toxicity on non-target mosquito natural enemies. Environmental Science and Pollution Research, 25(11), 10283-10293. doi:10.1007/s11356-017-8898-4
NO	Benelli, G., Pavela, R., Drenaggi, E., & Maggi, F. (2019). Insecticidal efficacy of the essential oil of jambe (Acmella oleracea (L.) RK Jansen) cultivated in central Italy against filariasis mosquito vectors,.pdaus Chock for houseflies and moth pests. Journal of Ethnopharmacology, 229, 272-279. doi:10.1016/j.jep.2018.08.030
YES	Bi, R., Zeng, X. F., Mu, L., Hou, L. P., Liu, W. H., Li, P., . . . Xie, L. T. (2018). Sensitivities of seven algal species to triclosan, fluoxetine and their mixtures. Scientific Reports, 8. doi:10.1038/s41598-018-33785-1
YES	Bialk-Bielinska, A., Mulkiewicz, E., Stokowski, M., Stolte, S., & Stepnowski, P. (2017). Acute aquatic toxicity assessment of six anti-cancer drugs and one metabolite using biotest battery-Biological effects and stability under test conditions. Chemosphere, 189, 689-698. doi:10.1016/j.chemosphere.2017.08.174
YES	Bittner, L., Teixido, E., Seiwert, B., Escher, B. I., & Kluver, N. (2018). Influence of pH on the uptake and toxicity of beta-blockers in embryos of zebrafish, Danio rerio. Aquatic Toxicology, 201, 129-137. doi:10.1016/j.aquatox.2018.05.020
YES	Bohdziewicz, J., Dudziak, M., Kaminska, G., & Kudlek, E. (2016). Chromatographic determination and toxicological potential evaluation of selected micropollutants in aquatic environment-analytical problems. Desalination and Water Treatment, 57(3), 1361-1369. doi:10.1080/19443994.2015.1017325
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YES	Chen, H. H., Gu, X. H., Zeng, Q. F., & Mao, Z. G. (2019). Acute and Chronic Toxicity of Carbamazepine on the Release of Chitobiase, Molting, and Reproduction in Daphnia similis. International Journal of Environmental Research and Public Health, 16(2). doi:10.3390/ijerph16020209
YES	Chiffre, A., Clerandeau, C., Dwoinikoff, C., Le Bihanic, F., Budzinski, H., Geret, F., & Cachot, J. (2016). Psychotropic drugs in mixture alter swimming behaviour of Japanese medaka (Oryzias latipes) larvae above environmental concentrations. Environmental Science and Pollution Research, 23(6), 4964-4977. doi:10.1007/s11356-014-3477-4
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NO	Wang, Z., Kang, D. W., Chen, M., Wu, G. C., Feng, D., Zhao, T., . . . Liu, X. Y. (2018). Design, synthesis, and antiviral evaluation of novel hydrazone-substituted thiophene 3,2-d pyrimidine derivatives as potent human immunodeficiency virus-1 inhibitors. Chemical Biology & Drug Design, 92(6), 2009-2021. doi:10.1111/cbdd.13373
YES	Watanabe, H., Tamura, I., Abe, R., Takanobu, H., Nakamura, A., Suzuki, T., . . . Tatarazako, N. (2016). Chronic toxicity of an environmentally relevant mixture of pharmaceuticals to three aquatic organisms (alga, daphnid, and fish). Environmental Toxicology and Chemistry, 35(4), 996-1006. doi:10.1002/etc.3285
YES	Wei, S., Wang, F. H., Chen, Y. J., Lan, T., & Zhang, S. T. (2018). The joint toxicity effect of five antibiotics and dibutyl phthalate to luminescent bacteria (Vibrio fischeri). Environmental Science and Pollution Research, 25(26), 26504-26511. doi:10.1007/s11356-018-2720-9
YES	Wieczerzak, M., Kudlak, B., & Namiesnik, J. (2016). Study of the effect of residues of pharmaceuticals on the environment on the example of bioassay Microtox (R). Monatshefte Fur Chemie, 147(8), 1455-1460. doi:10.1007/s00706-016-1782-y
YES	Wu, M. N. N., Wang, X. C. C., & Ma, X. Y. Y. (2016). Phytotoxicity comparison of organic contaminants and heavy metals using Chlorella vulgaris. Desalination and Water Treatment, 57(44), 20809-20816. doi:10.1080/19443994.2015.1110537
NO	Xiong, J. Q., Govindwar, S., Kurade, M. B., Paeng, K. J., Roh, H. S., Khan, M. A., & Jeon, B. H. (2019). Toxicity of sulfamethazine and sulfamethoxazole and their removal by a green microalga, Scenedesmus obliquus. Chemosphere, 218, 551-558. doi:10.1016/j.chemosphere.2018.11.146
YES	Xiong, J. Q., Kurade, M. B., Kim, J. R., Roh, H. S., & Jeon, B. H. (2017). Ciprofloxacin toxicity and its co-metabolic removal by a freshwater microalga Chlamydomonas mexicana. Journal of Hazardous Materials, 323, 212-219. doi:10.1016/j.jhazmat.2016.04.073
YES	Xiong, J. Q., Miracle, M. B., & Jeon, B. H. (2017). Ecotoxicological effects of enrofloxacin and its removal by monoculture of microalgal species and their consortium. Environmental Pollution, 226, 486-493. doi:10.1016/j.envpol.2017.04.044
NO	Yamindago, A., Lee, N., Woo, S., Choi, H., Mun, J. Y., Jang, S. W., . . . Yum, S. (2018). Acute toxic effects of zinc oxide nanoparticles on Hydra magnipapillata. Aquatic Toxicology, 205, 130-139. doi:10.1016/j.aquatox.2018.10.008
YES	Ye, J., Du, Y. P., Wang, L. M., Qian, J. R., Chen, J. J., Wu, Q. W., & Hu, X. J. (2017). Toxin Release of Cyanobacterium Microcystis aeruginosa after Exposure to Typical Tetracycline Antibiotic Contaminants. Toxins, 9(2). doi:10.3390/toxins9020053
NO	Yeo, C. R., Yong, J. J., & Popovich, D. G. (2017). Isolation and characterization of bioactive polyacetylenes Panax ginseng Meyer roots. Journal of Pharmaceutical and Biomedical Analysis, 139, 148-155. doi:10.1016/j.jpba.2017.02.054
YES	Yokota, H., Taguchi, Y., Tanaka, Y., Uchiyama, M., Kondo, M., Tsuruda, Y., . . . Eguchi, S. (2018). Chronic exposure to diclofenac induces delayed mandibular defects in medaka (Oryzias latipes) in a sex-dependent manner. Chemosphere, 210, 139-146. doi:10.1016/j.chemosphere.2018.07.016
NO	Zahra, K., Yadav, S., Tanya, Jyoti, Deeksha, Sandeep, & Deepti. (2016). Assessment of acute toxicity of

	cypermethrin and its mitigation by green tea extract in fresh water fishes, channa punctatus. Indo American Journal of Pharmaceutical Sciences, 3(4), 374-378.
NO	Zahra, S. S., Ahmed, M., Qasim, M., Gul, B., Zia, M., Mirza, B., & Ihsan-ul, H. (2017). Polarity based characterization of biologically active extracts of Ajuga bracteosa Wall. ex Benth. and RP-HPLC analysis. Bmc Complementary and Alternative Medicine, 17. doi:10.1186/s12906-017-1951-5
NO	Zaleska-Radziwill, M., Affek, K., & Doskocz, N. (2017). Ecotoxicological risk assessment of chosen pharmaceuticals detected in surface waters. Journal of Environmental Science and Health Part a-Toxic/Hazardous Substances & Environmental Engineering, 52(13), 1233-1239. doi:10.1080/10934529.2017.1356199
YES	Zanuri, N. B. M., Bentley, M. G., & Caldwell, G. S. (2017). Assessing the impact of diclofenac, ibuprofen and sildenafil citrate (Viagra (R)) on the fertilisation biology of broadcast spawning marine. Marine Environmental Research, 127, 126-136. doi:10.1016/j.marenvres.2017.04.005
NO	Zhang, H., Tian, Y., Kang, D. W., Huo, Z. P., Zhou, Z. X., Liu, H. Q., . . . Liu, X. Y. (2017). Discovery of uracil-bearing DAPYs derivatives as novel HIV-1 NNRTIs via crystallographic overlay-based molecular hybridization. European Journal of Medicinal Chemistry, 130, 209-222. doi:10.1016/j.ejmech.2017.02.047
YES	Zhang, L. L., Niu, J. F., & Wang, Y. J. (2016). Full life-cycle toxicity assessment on triclosan using rotifer Brachionus calyciflorus. Ecotoxicology and Environmental Safety, 127, 30-35. doi:10.1016/j.ecoenv.2015.12.043
NO	Zhang, Y. N., Wang, X. D., Yin, X. H., Shi, M. R., Dahlgren, R. A., & Wang, H. L. (2016). Toxicity Assessment of Combined Fluoroquinolone and Tetracycline Exposure in Zebrafish (Danio rerio). Environmental Toxicology, 31(6), 736-750. doi:10.1002/tox.22087
YES	Zhou, Z., Yang, J., & Chan, K. M. (2017). Toxic effects of triclosan on a zebrafish (Danio rerio) liver cell line, ZFL. Aquatic Toxicology, 191, 175-188. doi:10.1016/j.aquatox.2017.08.009
YES	Zhu, L. Y., Santiago-Schubel, B., Xiao, H. X., Hollert, H., & Kueppers, S. (2016). Electrochemical oxidation of fluoroquinolone antibiotics: Mechanism, residual antibacterial activity and toxicity change. Water Research, 102, 52-62. doi:10.1016/j.watres.2016.06.005
YES	Zivna, D., Plhalova, L., Chromcova, L., Blahova, J., Prokes, M., Skoric, M., . . . Svobodova, Z. (2016). The effects of ciprofloxacin on early life stages of common carp (Cyprinus carpio). Environmental Toxicology and Chemistry, 35(7), 1733-1740. doi:10.1002/etc.3317
NO	Zortea, T., dos Reis, T. R., Serafini, S., de Sousa, J. P., da Silva, A. S., & Baretta, D. (2018). Ecotoxicological effect of fipronil and its metabolites on Folsomia candida in tropical soils. Environmental Toxicology and Pharmacology, 62, 203-209. doi:10.1016/j.etap.2018.07.011
NO	Zuriaga, E., Lomba, L., German, B., Lanuza, P. M., Aldea, L., Ribate, M. P., . . . Giner, B. (2019). Ecotoxicity in Aliivibrio fischeri of Ibuprofen, Omeprazole and their Mixtures. Chemistry and Ecology, 35(2), 102-114. doi:10.1080/02757540.2018.1540608

TABLE S12: CRED scores evaluating the reliability and relevance of critical literature articles for their inclusion in the derivation of safe concentration in this study.

Articles	Reliability	Relevance	Sufficient quality? [a]
Aderemi et al., (2018)	R1	C1	Yes
Ando et al., (2007)	R4	C2	No
Bayer et al., (2014)	R4	C4	No
Chen et al., (2019)	R1	C2	Yes
De Liguoro et al., (2009)	R2	C2	Yes
Di Poi et al., (2018)di Poi et al., (2018)	R1	C2	Yes
Dordio et al., (2011)	R3	C2	No
Eguchi et al., (2004)	R4	C1	No
Fabbri et al., (2014)	R3	C4	No
Godoy et al., (2018)	R1	C1	Yes
González-Pleiter et al., (2013)	R2	C2	Yes
Han et al., (2006)	R3	C1	No
He et al., (2013)	R2	C2	Yes
Jarvis et al., (2014)	R2	C3	No
Ji et al., (2012)	R2	C1	Yes
Jungmann et al., (2017)	R2	C2	Yes
Li et al., (2010)	R2	C2	Yes
Majewska et al., (2018)	R2	C1	Yes
Martins et al., (2012)	R2	C2	Yes
Ofoegbu et al., (2019)	R3	C3	No
Russo et al., (2018)	R2	C1	Yes
Yang et al., (2008)	R3	C1	No
Yokota et al., (2018)	R1	C1	Yes
Monika et al., (2011)	R4	C1	No
Zhu et al., (2014)	R2	C1	Yes
Zounková et al., (2007)	R4	C2	No

a Studies deemed of sufficient quality had to be assign reliability scores of R1 or R2, and relevance scores of C1 or C2.

Literature search string

The titles, abstracts, and keywords were screened using the following search string "(LC50* OR EC50* OR EC10* OR NOEC* OR "effect concentration") AND (aquatic* OR *water*) AND (*toxic*) AND (pharmaceutic* OR medicine* OR drug* OR ((amantadine OR *amant*) OR (carbamazepine OR carbamaz*) OR (ciprofloxacin OR ciproflox*) OR (cyclophosphamide OR c*clo*os*amid*) OR (diclofenac OR diclofenac*) OR (doxycycline OR dox*c*clin*) OR (erythromycin OR er*throm*cin*) OR (ethinylestradiol OR *ethinyl*estradiol) OR (iopamidol OR io*ami* OR "contrast agent") OR (metformin OR metformi* OR dimethylbiguanid* OR dimethylimidodicarbonimidic) OR (metoprolol OR "1-(Isopropylamino)-3-[4-(2-methoxyethyl)phenoxy]-2-propanol") OR (oxazepam OR "7-Chloro-3-hydroxy-5-phenyl-1,3-dihydro-2H-1,4-benzodiazepin-2-one") OR (phenazone OR phenazon* OR antipyrine OR "1,5-Dimethyl-2-phenyl-1,2-dihydro-3H-pyrazol-3-one") OR (sul*amethazine OR sul*adimidin* OR sul*adimethylpyrimidine) OR (valsartan))) NOT QSAR". At the time of the search, additional compounds besides the eight pharmaceuticals of interest in this study were included, retrieving a total of 233 publications. All these publications were screened in detail but only the ones containing information on the eight pharmaceuticals of interest in this study were used.

Species names

Harmonized according to most recent taxonomic nomenclature and corrected for misspellings.

Exposure type

"Chronic" or "acute" classification was primarily assigned according to the authors. If not explicitly mentioned, a decision was made according to the corresponding original methods article referenced (if readily available), or (inter)national chemical testing guidelines (e.g. OECD Test No. 201). Alternatively, the life span of the organism and the exposure duration was considered. In this regard, a 10% lifespan coverage threshold was applied as to decide whether to classify an exposure as chronic or acute(Suter II 2007). For example, Danio rerio lives on average 1 year in the wild; bioassays with exposure times higher than 10% of 365 days where tagged "chronic". Similarly, this threshold was applied in early development stage data under the assumption that exposure during this critical period can potentially exert long-term effects further in the lifecycle. If no exposure time, guideline or

protocol were provided, the values were conservatively classified as “acute”.

Effect code

If effects were not reported or unspecified, these were coded as “UND” (undetermined). Population effects reported as more than one effect like “Survival, reproduction and growth rate” were coded as “POP” (population). In the case of multiple effects in which one or more effects do not necessarily dictate the sustainability of a population, such as “Length, reproduction and survival”, were attributed the code “MUL” (multiple).

Endpoints

When authors did not explicitly use LOEC or NOEC terminology, the publications’ graphs were inspected to assign the corresponding concentration values according to the results of the statistical tests. In studies where single concentrations were tested, if effects were determined significant, that concentration was classified as “LOEC”. If not significant, a “<” was assigned. Highest concentrations tested showing no effects tagged by the authors as “NOEC” and assigned with “>” were recorded. If not explicitly classified by the authors, these values were coercively assigned “>” to distinguish from studies where both NOEC and LOEC were derived empirically.

Exposure duration

If several exposure times were given (e.g. interval, 176-301 days) associated with only one effect value, the highest time point is used (e.g. sampled at 8-60 days, only 60 days is accounted for).

Concentration units

Given the intent of this assessment, only aquatic exposure measured in weight of test substance per volume (e.g. mg/L) were included. All concentrations were converted to µg/L. Unit conversion from molar to µg/L was done using the molecular weight (MW) provided by authors, chemical manufacture company, PubChem (https://pubchem.ncbi.nlm.nih.gov/) or other relevant source. The CAS numbers were used to extract MW. If CAS was not disclosed then the substance name and the corresponding best match result was used.

Substance aggregation

Different forms or variations of a parent substance were aggregated (Table S13) to circumvent the scarcity of substance-specific effect data and pool compounds with analogous biological activity (e.g. metoprolol tartrate and metoprolol succinate) or metabolically related (e.g. carbamazepine and carbamazepine metabolite trans-10,11-dihydroxy-10,11-dihydrocarbazepine). Moreover, this aggregation prevents overly stringent data exclusion due to incomplete identification of the substance (e.g. missing CAS registry number).

TABLE S13: Grouping of pharmaceuticals.

Group	Compounds
Amantadine	amantadine
Carbamazepine	carbamazepine
	carbamazepine 10,11-epoxide
	trans-10,11-dihydroxy-10,11-dihydrocarbazepine
Ciprofloxacin	ciprofloxacin
	ciprofloxacin HCl
Cyclophosphamide	cyclophosphamide
	carboxycyclophosphamide
	keto-cyclophosphamide
	N-dechloroethyl-cyclophosphamide
Diclofenac	diclofenac
	diclofenac Na
Doxycycline	doxycycline
Erythromycin	erythromycin
	erythromycin phosphate
Ethinylestradiol	ethinylestradiol
	17α-ethinylestradiol
Iopamidol	iopamidol
Metformin	metformin
	metformin HCl
Metoprolol	metoprolol
	metoprolol tartrate
	metoprolol succinate
Oxazepam	oxazepam
Phenazone	phenazone
Sulfamethazine	sulfamethazine
	sulfadimidine
Valsartan	valsartan

Endpoint Aggregation

The aggregation of endpoints was done following established guidelines (ECHA, 2008) and according to their closest or equivalent toxicological effect response (Table S14). Aggregated endpoints are in the present study referred simply as 'endpoints'.

TABLE S14: Grouping of available endpoints in the database into aggregated chronic NOEC, chronic EC50, acute NOEC and acute EC50 endpoints. MATC was reverse calculated to obtain NOEC.

Chronic exposure		Acute exposure	
NOEC	EC50	NOEC	EC50
EC10	EC50	EC5	L(E)C50
EC5	ET50	EC10	EC20
IC10	IC50	LC10	EC25
IC5	LC50	MATC	EC50
LC01		NOEC	IC50
LC10		NOEL	LC50
MATC			MTC
NOAEC			
NOEC			
NOEL			

Predicted no effect concentration

TABLE S15: Chronic ecotoxicological effects on freshwater species. To derive predicted no effect concentrations (PNEC) for each substance a distinct assessment factor (AF) was applied to the most sensitive species and effect depending on the data available.

Substance	Taxa	Species	Effect	Concentration (µg/L)	AF	PNEC (µg/L)
Carbamazepine	insecta	Stenonema sp.	BEH	0.2	10	0.02
	crustacea	Daphnia similis	REP	0.3		
	algae	Chaetophora sp.	POP	2		
	crustacea	Daphnia pulex	REP	100		
	fish	Pimephales promelas	BEH	100		
	insecta	Chironomus riparius	DEV	164		
	fish	Oncorhynchus mykiss	GRO	180		

	crustacea	Ceriodaphnia dubia	REP	199		
	rotifera	Brachionus calyciflorus	REP/MOR	377		
	crustacea	Daphnia magna	REP/GRO	400		
	crustacea	Hyalella azteca	MOR	600		
	algae	Chlorella pyrenoidosa	POP	1000		
	algae	Scenedesmus acutus	POP	1000		
	algae	Raphidocelis subcapitata	POP	2046		
	insecta	Chironomus tentans	GRO	2600		
	fish	Oryzias latipes	BEH	6150		
	algae	Cyclotella meneghiniana	POP	10000		
	algae	Chlorella vulgaris	POP	11800		
	fish	Danio rerio	REP	12500		
Ciprofloxacin	fish	Lebistes reticulatus	GRO	780	10	78
	fish	Poecilia reticulata	GRO	780		
	algae	Raphidocelis subcapitata	POP	3006		
	crustacea	Daphnia magna	REP	3217		
Cyclophosphamide	crustacea	Ceriodaphnia dubia	POP	1250	10	125
	rotifera	Brachionus calyciflorus	POP	3394		
	algae	Raphidocelis subcapitata	POP	12500		
	fish	Danio rerio	MOR	13743785		
Diclofenac	mollusca	Dreissena ploymorpha	MOR	0.5	50	0.01
	fish	Oryzias latipes	DEV	7.29		
	fish	Danio rerio	GRO	10		
	fish	Oncorhynchus mykiss	REP/DEV/MOR	1084		
	algae	Raphidocelis subcapitata	GRO	25000		
	algae	Chlamydomonas reinhardtii	POP	32700		
Erythromycin	cyanobacteria	Anabaena sp.	POP	5	10	0.5
	algae	Raphidocelis subcapitata	POP	23		
	crustacea	Daphnia magna	GRO	11100		
	crustacea	Moina macrocopa	MOR/REP	50000		
	fish	Oryzias latipes	MOR	100000		
17α-Ethinylestradiol	fish	Gobiocypris rarus	REP	0.00018	50	3.6x10-6
	fish	Danio rerio	DEV	0.00069		
	fish	Rutilus rutilus	GRO	0.00071		
	fish	Syngnathus scovelli	DEV	0.001		
	fish	Salmo trutta	GRO	0.00208		
	fish	Gasterosteus aculeatus	DEV	0.00418		
	amphibia	Lithobates septentrionalis	GRO/DEV	0.005		
	amphibia	Lithobates clamitans	REP	0.0058		
	fish	Salvelinus	GRO	0.0063		

		namaycush				
	fish	Pimephales promelas	GRO/REP	0.008		
	fish	Oryzias latipes	REP	0.00669		
	mollusca	Bithynia tentaculata	GRO	0.009		
	mollusca	Radix balthica	GRO	0.009		
	fish	Cyprinodon variegatus	REP	0.009		
	fish	Alburnus tarichi	REP	0.01		
	amphibia	Xenopus tropicalis	DEV	0.0175		
	fish	Etheostoma caeruleum	DEV	0.02		
	mollusca	Potamopyrgus antipodarum	REP	0.025		
	fish	Syngnathus abaster	MOR	0.02655		
	fish	Poecilia reticulata	DEV/POP	0.05		
	mollusca	Lymnaea stagnalis	DEV	0.05		
	fish	Oncorhynchus mykiss	REP	0.05965		
	fish	Fundulus heteroclitus	MOR	0.1		
	crustacea	Gammarus pulex	POP	0.1		
	mollusca	Haitia pomilia	POP	0.1		
	fish	Tautogolabrus adspersus	MOR	0.1		
	mollusca	Marisa cornuarietis	REP	0.5		
	crustacea	Daphnia magna	REP	14		
	crustacea	Sida crystallina	DEV	32		
	crustacea	Acartia tonsa	DEV	46		
	crustacea	Hyalella azteca	GRO/MOR	70		
	insecta	Chironomus tentans	POP	88.32		
	crustacea	Ceriodaphnia reticulata	MOR	200		
	crustacea	Ceriodaphnia dubia	REP	500		
Metformin	crustacea	Daphnia similis	REP	4400	10	440
	crustacea	Ceriodaphnia dubia	REP	7900		
	fish	Pimephales promelas	DEV	10000		
	fish	Brachydanio rerio	DEV	11713		
	crustacea	Daphnia magna	REP/MOR	26593.859		
	algae	Raphidocelis subcapitata	POP	99749		
	cnidarian	Hydra attenuata	REP	701800		
Metoprolol	crustacea	Daphnia magna	REP	3100	10	310
	algae	Raphidocelis subcapitata	POP	6786		
	crustacea	Gammarus fossarum	REP	15000		
	protozoa	Tetrahymena pyriformis	GRO	21800		
	fish	Danio rerio	GRO	24000		

TABLE S16: Predicted no effect concentration estimations from literature and this study. Bold numbers indicate values uniquely calculated in this study.

Substance	PNEC (ug/L)	References
17α-Ethinylestradiol	1.6x10-2, 1x10-4, 3.7x10-5, 3.5x10-5, 3.1x10-5, 2x10-5, 3.6x10-6, 3x10-8	1-9, 22
Carbamazepine	170, 130, 17, 10, 8, 2.6, 2.5, 2, 0.5, 0.4, 0.05, 0.02	1, 3, 5, 8-20
Ciprofloxacin	78, 0.5, 0.45, 0.089, 0.005	3, 5, 6, 9, 15, 21, 22
Cyclophosphamide	1120, 980, 560, 125	9, 13, 22
Diclofenac	50, 32, 31, 20, 10, 0.45, 0.1, 0.05, 0.02, 0.01	2, 3, 5, 6, 7, 8, 9, 13, 15, 18, 20, 22, 24, 23
Erythromycin	2, 0.5, 0.3, 0.2	3, 5, 6, 8, 9, 21
Metformin	1030, 1000, 780, 640, 440, 156, 100, 20, 13.45, 10, 4.2	3, 5, 7, 8, 9, 12, 14, 16, 17, 25-27
Metoprolol	310, 75, 64, 62, 58.3, 31, 8.6, 7.3, 3.2	3, 5, 8, 9, 12, 16, 17, 22, 28-30

1. van Vlaardingen et al., (2007). 2 van der Aa et al., (2011). 3. Oekotoxzentrum (2016a). 4. European Union (2011b). 5. NORMAN-network (2019). 6. Loos et al., (2018). 7. Vestel et al., (2016). 8. Agerstrand and Rudén (2010). 9. Perazzolo et al., (2010). 10. Triebskorn et al., (2007). 11. Heye et al., (2019). 12. Lif (2019). 13. Boxall et al., (2014). 14. Comber et al., (2018). 15. Frédéric and Yves (2014). 16. Moermond (2014). 17. Moermond and Smit (2016). 18. Ferrari et al., (2004). 19. Wenzel and Shemotyuk (2014). 20. Gheorghe et al., (2016). 21. AMR Industry Alliance (2018). 22. Grung et al., (2008). 23. Hoeger et al., (2005). 24. European Union (2011a). 25. Caldwell et al., (2019). 26. Oekotoxzentrum (2016b). 27. AstraZeneca (2017a). 28. Oekotoxzentrum (2016c). 29. AstraZeneca (2017b). 30. Murray-Smith et al., (2012).

Emission estimation

Five APIs (carbamazepine, ciprofloxacin, diclofenac, metformin and metoprolol) had a quantification frequency above 90 % in STP influent and were included in the model evaluation exercise. Figure 2 shows that the majority of the predicted influent loads (> 85 %) agree within a factor of 3 with loads derived from measured concentrations. Except for two outliers in the Netherlands, all data points were within a factor of 10 indicating an acceptable overall model performance (Figure S1). Country-specific evaluation reveals differences; influent loads show a small overestimation in Germany and the Netherlands (SSPBGER = 17 %, SSPBNL = 6 %). Erythromycin showed a quantification frequency of less than 50 % in both, German and Dutch STPs. Even though, when erythromycin concentrations below the LoQ were replaced by the LoQ value, i.e. the highest possible quantifiable concentration, influent loads for erythromycin in German STPs are highly overestimated by the model (SSPB = 296 %). Since all other processes (excretion patterns, in-sewer processes) were assumed equal in German and Dutch Vecht regions, erroneous German consumption volumes were most likely responsible for this bias. To bring the overestimation to an acceptable level German erythromycin consumption was adjusted by a factor of 0.5 (SSPB = 99 %) as to account for unknown influencing factors.

In the next step, predicted effluent loads were compared to data (Figure 3 and Figure S2). After STP removal, four APIs (carbamazepine, diclofenac, metformin and metoprolol) had a quantification frequency above 90 %. Overall, predictions of STP effluent loads agreed well with empirical data, showing good accuracy (ξeffluent = 64 %) and small underestimation (SSPBeffluent = -22 %). Ciprofloxacin loads were very largely overestimated (SSPB = 288 %) even when measured concentrations below the LoQ were replaced with the LoQ (Supplemental Data, S3). Adjusting ciprofloxacin emissions by a factor of 0.5 lead to an acceptable bias (SSPB = -94 %).

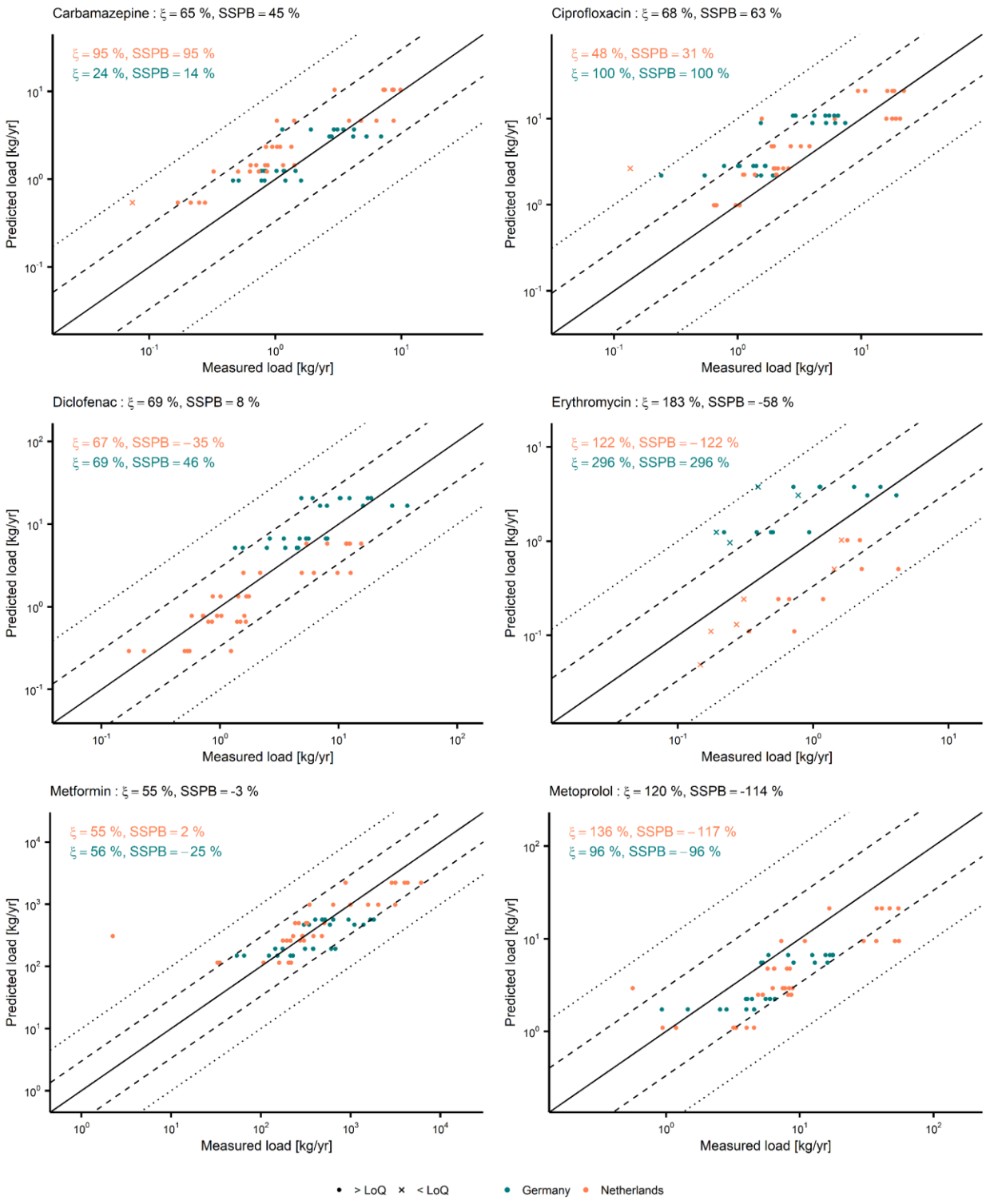

FIGURE S1: Predicted and measured STP influent loads of APIs with a detection frequency above 25 %. Dashed lines indicate the 1:3 and 3:1 ratios, dotted lines indicate the 1:10 and 10:1 ratios. All APIs were measured 25 times in German and 34 times in Dutch STPs. Concentrations below the LoQ are processed as LoQ. Actual concentrations are therefore lower and measures (ξ, SSPB) should be taken with care for substances with many concentrations below the LoQ, i.e. erythromycin.

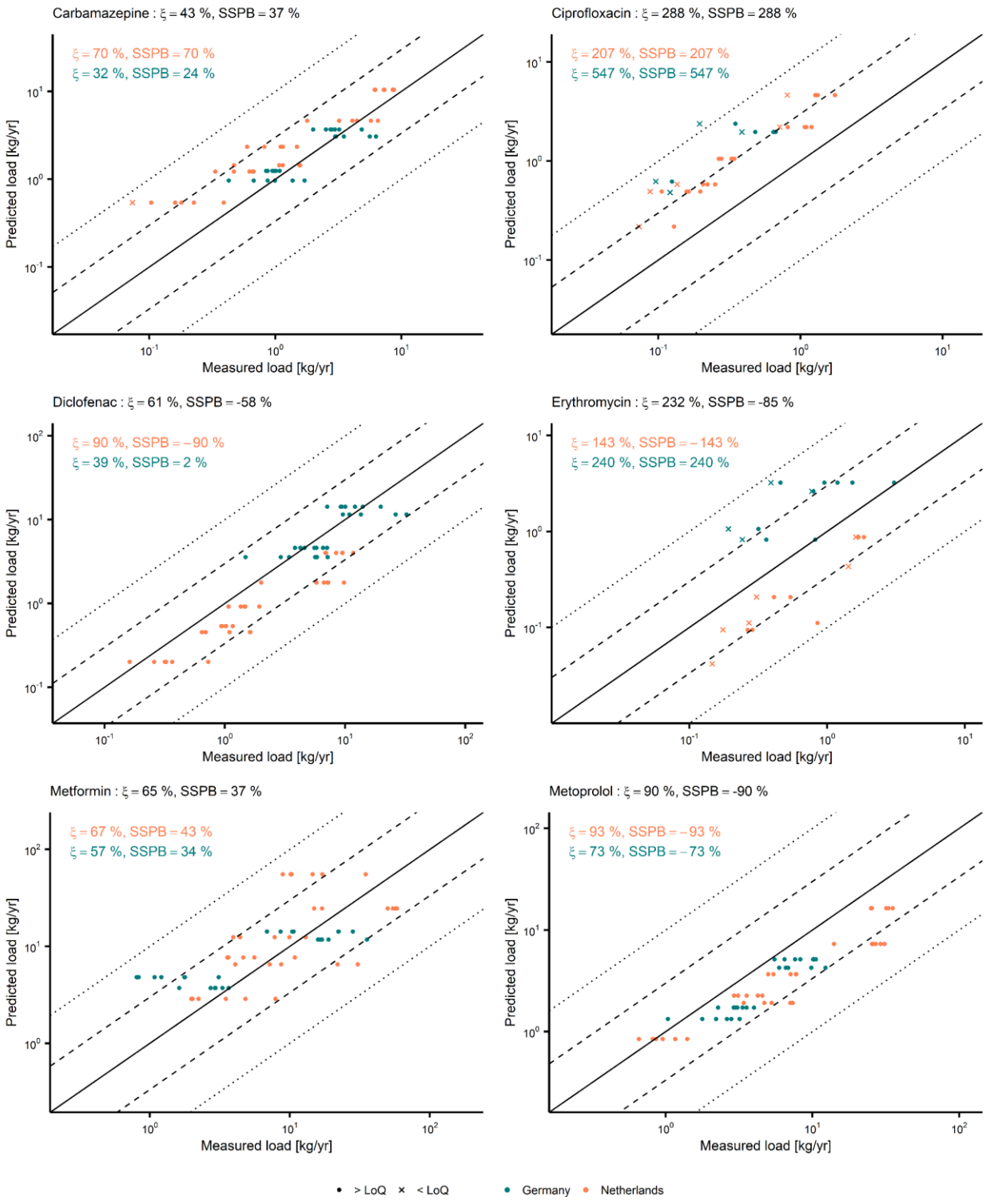

FIGURE S2: Predicted and measured STP effluent loads of APIs with a detection frequency above 25 %. Dashed lines indicate the 1:3 and 3:1 ratios, dotted lines indicate the 1:10 and 10:1 ratios. All APIs were measured 25 times in German and 33 times in Dutch STPs. Concentrations below the LoQ are processed as LoQ. Actual concentrations are therefore lower and measures (ξ, SSPB) should be taken with care for substances with many concentrations below the LoQ, i.e. ciprofloxacin and erythromycin.

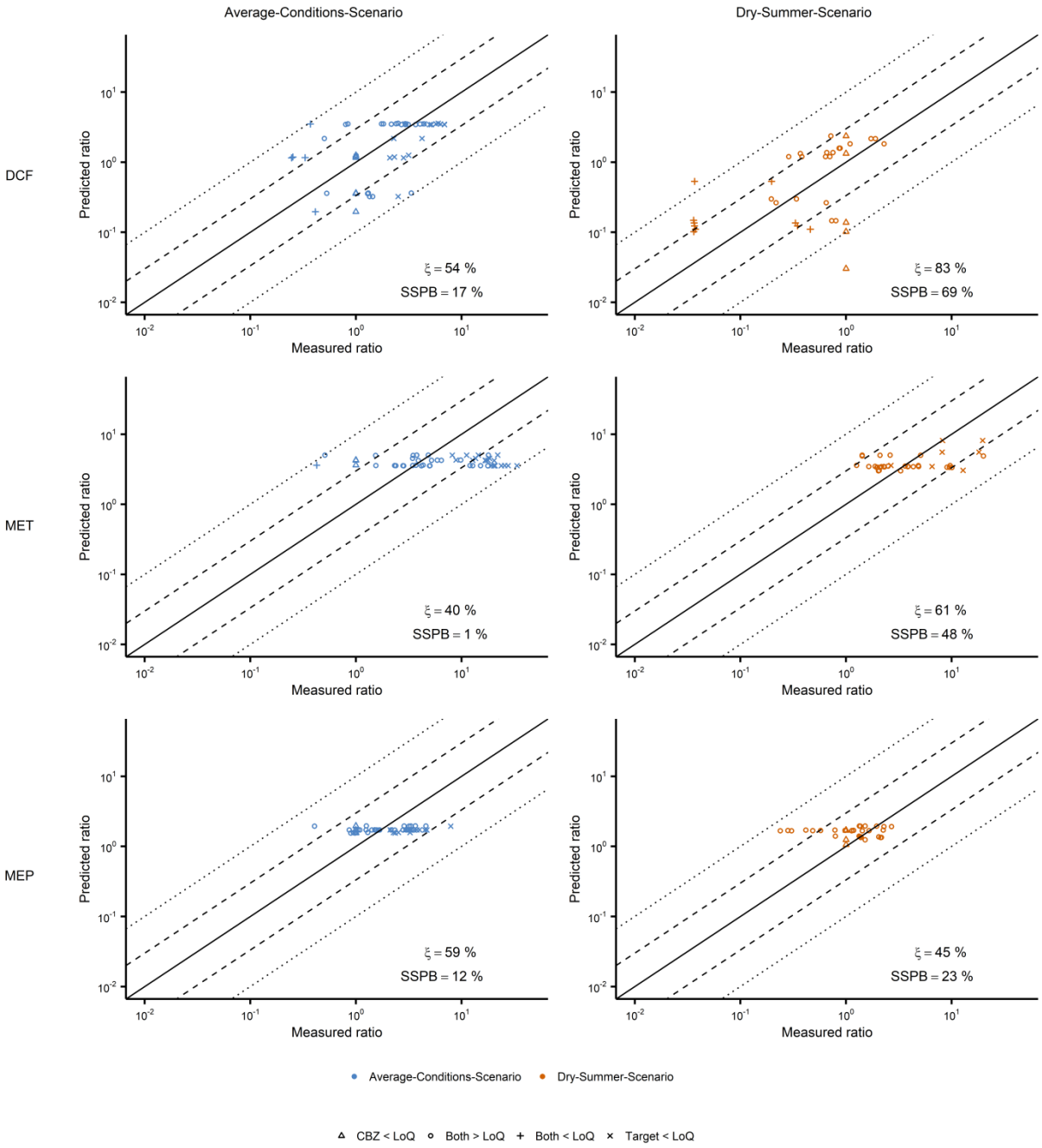

FIGURE S3: Predicted and measured benchmark ratios of diclofenac, metformin and metoprolol at monitoring sites in the whole Vecht catchment. Dashed lines indicate the 1:3 and 3:1 ratios, dotted lines indicate the 1:10 and 10:1 ratios. Measures were calculated including predicted-measured pairs where both, the target compound and carbamazepine concentrations, were above the LoQ.

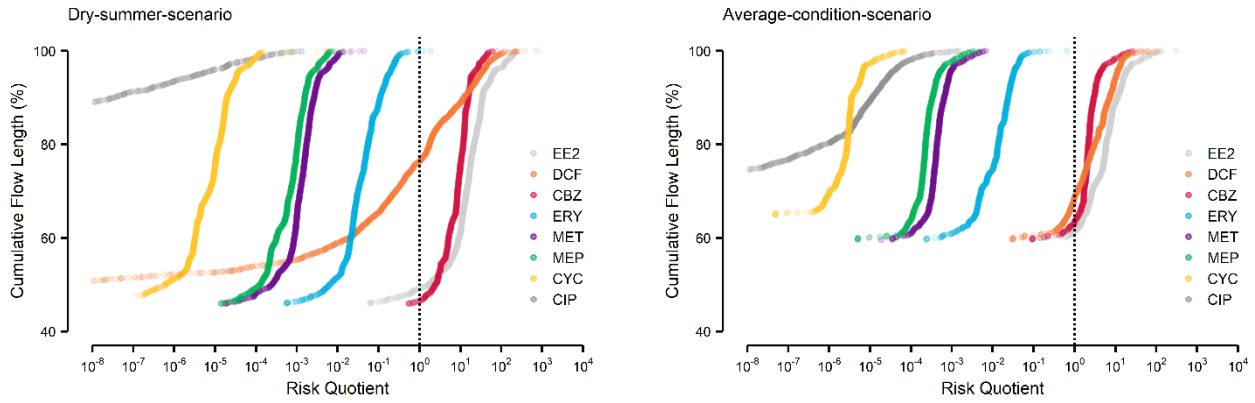

FIGURE S4: Percentage of the Vecht catchment flow length at risk of environmental pharmaceutical pollution. Vertical black dashed line indicates the safe threshold RQ = 1, i.e. predicted environmental concentrations equal to the predicted no chronic effect concentration. Risk quotients below 10-8 are not depicted in this figure. The Y-axis minimum value was set to 40% since more than 40% of the flow length have RQ = 0. Each point depicts a water stream segment of ≤ 2 km. CBZ, carbamazepine; CIP, ciprofloxacin; CYL, cyclophosphamide; DFC, diclofenac; ERY, erythromycin; EE2, 17α-ethinylestradiol; MET, metformin; MEP, metoprolol.

TABLE S17: Water volume percentage and flow length percentage of the Vecht River catchment vulnerable to different ranges of active pharmaceutical ingredients' (API) risk quotients (RQ). CBZ, carbamazepine; CIP, ciprofloxacin; CYL, cyclophosphamide; DFC, diclofenac; ERY, erythromycin; EE2, 17α-ethinylestradiol; MET, metformin; MEP, metoprolol.

		Average-condition-scenario					Dry-summer-scenario				
	API	[0, 0]	(0, 0.1]	(0.1, 1]	(1, 10]	(10, +∞)	[0, 0]	(0, 0.1]	(0.1, 1]	(1, 10]	(10, +∞)
Water volume (%)	EE2	9			65	25	2		1	9	87
	CBZ	9		1	89		2			66	32
	CIP	9	91				3	97			
	CYC	12	88				2	98			
	DCF	9		23	63	4	2	37	34	23	3
	ERY	9	91				2	91	7		
	MET	9	91				2	98			
	MEP	9	91				2	98			
Flow length (%)	EE2	59		1	27	11	46		3	12	39
	CBZ	59		3	35	2	46		1	29	24
	CIP	59	40				48	52			
	CYC	65	35				48	52			
	DCF	59	1	8	26	6	46	19	11	12	11
	ERY	59	40				46	43	11		
	MET	59	40				46	54			
	MEP	59	40				46	54			

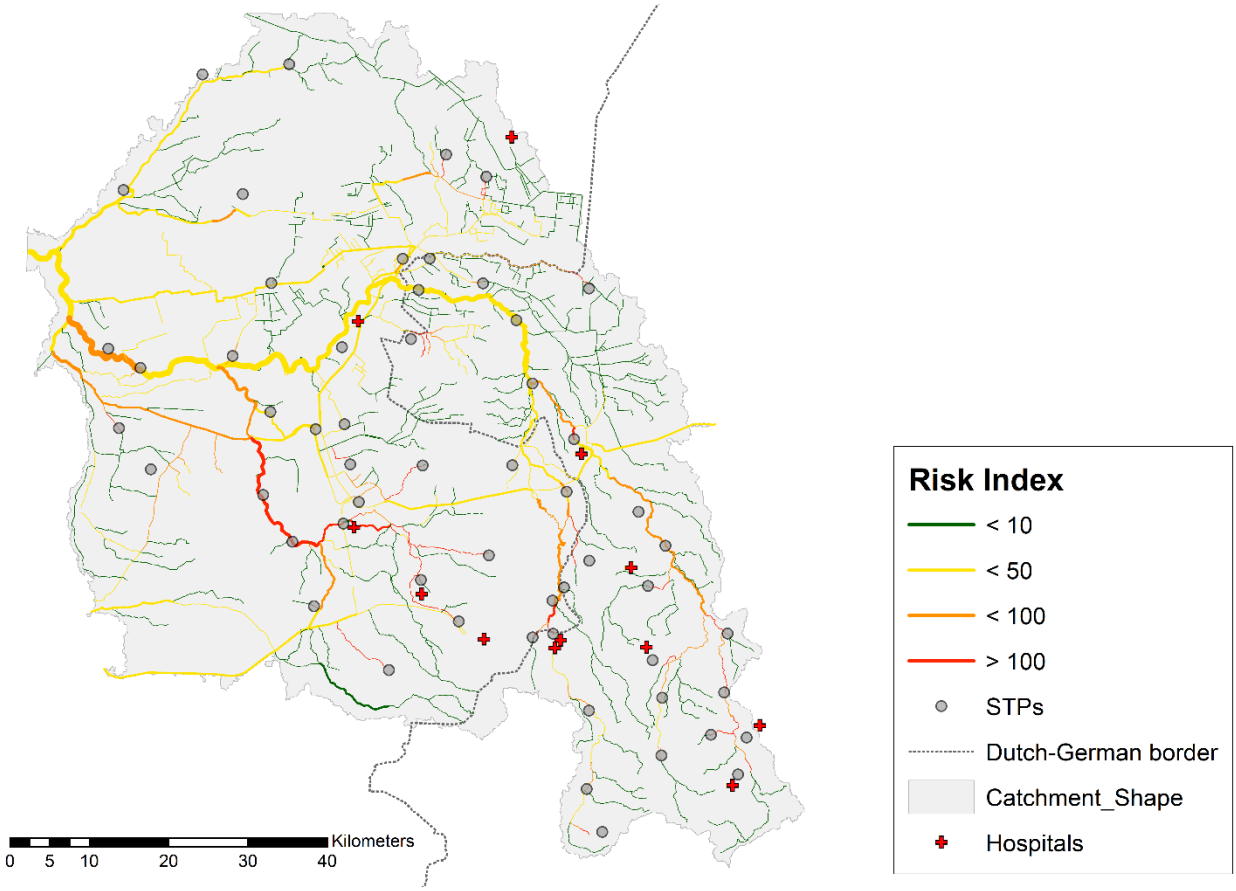

FIGURE S5: Risk index map of the Vecht River catchment during a typical dry-summer-scenario. Dashed line demarks the German-Dutch border.

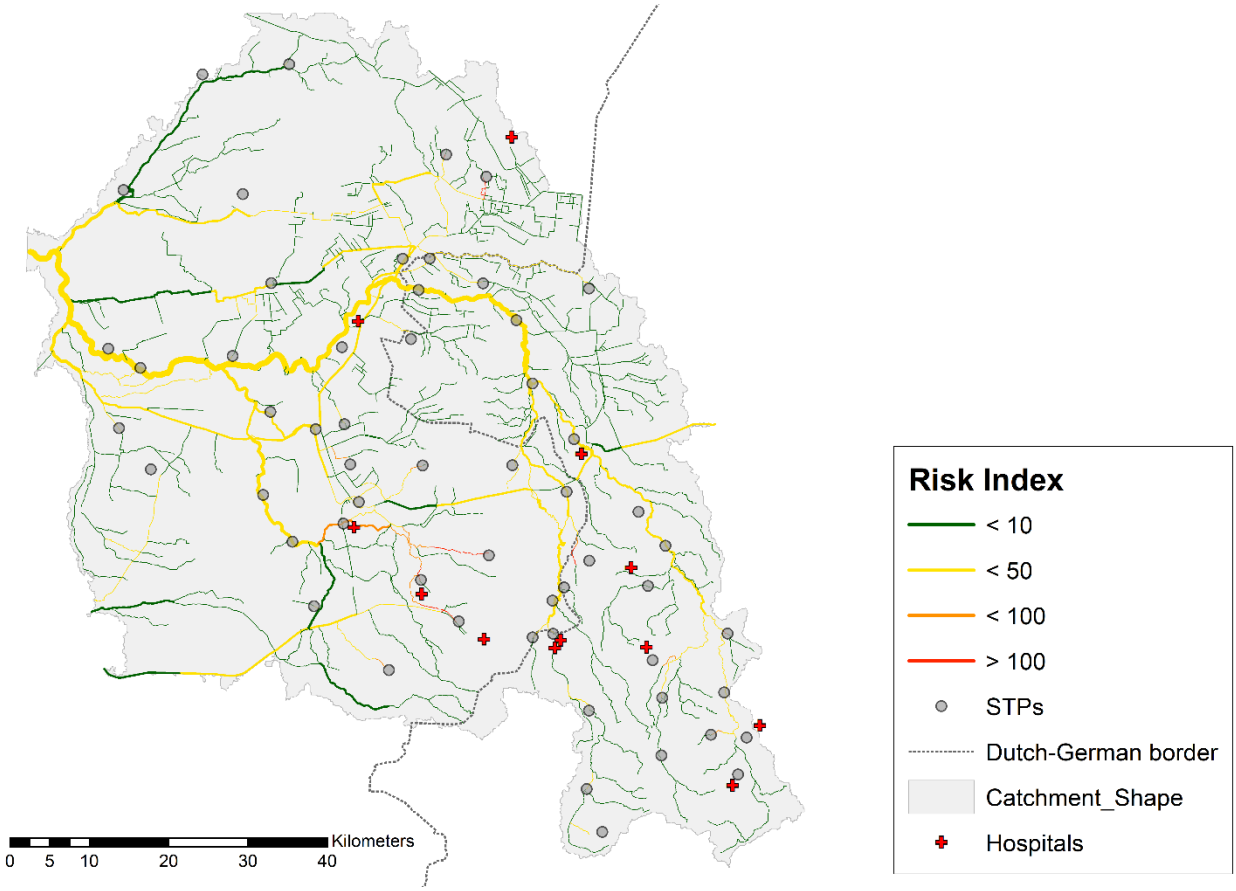

FIGURE S6: Risk index map of the Vecht River catchment during a typical average-condition-scenario. Dashed line demarks the German-Dutch border.

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