Risk-management tool for environmental prioritization of pharmaceuticals based on emissions from hospitals

Caterina Zillien[1, *], Cornelis van Loon[1], Marijn Gülpen[1], Kevin Tipatet[1], Birgit Hanssen[1], Henry Beeltje[2], Erwin Roex[3], Rik Oldenkamp[1, 4], Leo Posthuma[1, 5], Ad M.J. Ragas[1, 6]

[1] Radboud University, Department of Environmental Science, Institute for Water and Wetland Research, Faculty of Science, Radboud University, Nijmegen, the Netherlands

[2] TNO, Environmental Modelling, Sensing and Analysis, Utrecht, the Netherlands

[3] Deltares, Department of Subsurface and Groundwater Quality, Utrecht, the Netherlands

[4] Amsterdam Institute for Global Health and Development, Amsterdam, the Netherlands

[5] National Institute for Public Health and the Environment (RIVM), Centre for Sustainability, Environment and Health, Bilthoven, the Netherlands

[6] Open Universiteit, Faculty of Management, Science & Technology, Heerlen, the Netherlands

*Corresponding author at: Radboud University Nijmegen, Department of Environmental Science, Nijmegen, The Netherlands. Telephone: (+31) 24 365 32 81. Email address: C.Zillien@science.ru.nl (A.C. Zillien).

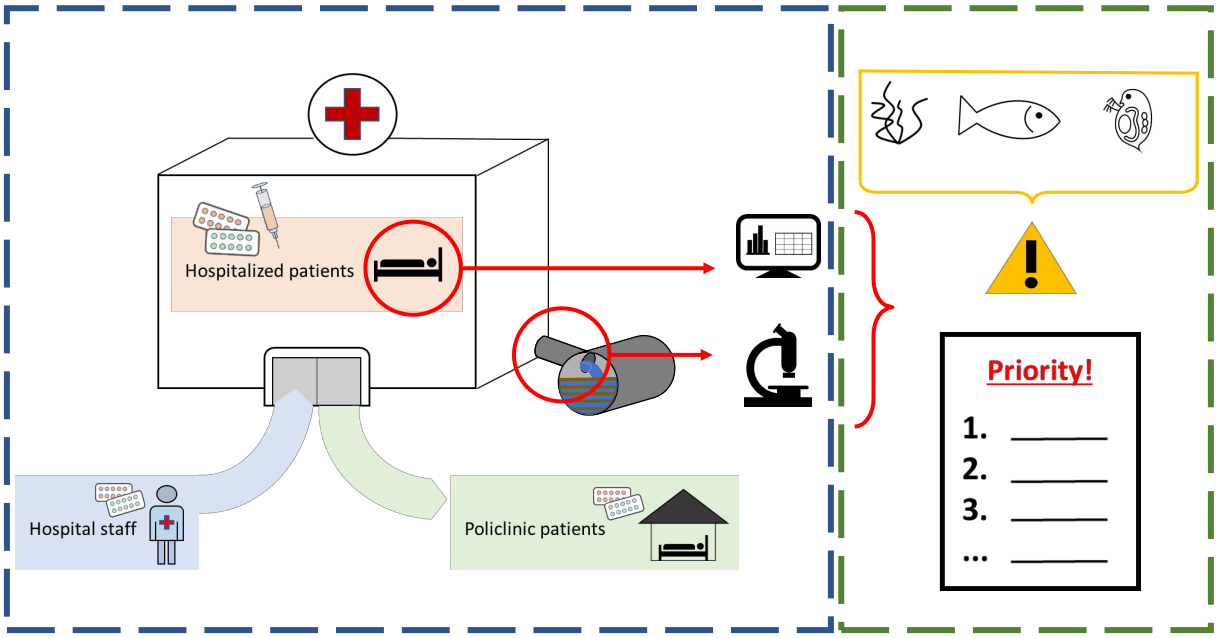
Abstract

Over the past decade, the health care sector has become increasingly aware of the impact of pharmaceutical emissions to the environment. Yet, it remains unclear which compounds are the most relevant to address and at what point emission control is most effective. This study presents a modelling framework to prioritize pharmaceuticals based on their relative risks for aquatic organisms, using purchase and prescription data from hospitals. The framework consists of an emission prediction module and a risk prioritization module. The emission prediction module accounts for three different routes of intake (oral, intravenous, rectal), for non-patient consumption, and for delayed at-home excretion due to relatively long half-lives or prescription durations of selected pharmaceuticals. We showcase the modelling framework with 16 pharmaceuticals administered at two Dutch academic hospitals. Predictions were validated with experimental data from passive sampling in the sewer system. With the exception of metformin, all predictions were within a factor of 10 from measurements. The risk prioritization module ranks each pharmaceutical based on its predicted relative risk for aquatic organisms. The resulting prioritization suggests that emission mitigation strategies should mainly focus on antibiotics and non-steroidal anti-inflammatory drugs (NSAIDs).

Highlights

- Pharmaceutical emissions were estimated from clinical purchase and prescription data
- Other required input data are mostly publicly available
- Predicted emissions were within factor 5 from measured emissions
- Painkillers were underestimated suggesting substantial consumption of OTC drugs
- Prioritization highlights risk of antibiotics and painkillers to aquatic organisms

Graphical abstract



1. Introduction

The presence of pharmaceuticals in surface waters can trigger adverse effects in ecosystems and humans. Antibiotic residues in the environment, for example, have been linked to increasing levels of antimicrobial resistance in bacteria, representing a potential global threat to the medical effect of commonly administered antibiotics (Duarte et al., 2018; Rizzo et al., 2013). Besides, an increasing number of publications on antidepressants suggests that behavioral changes in wildlife and aquatic species might occur at environmentally relevant concentrations (e.g., Ford and Fong, 2016). Yet, other pharmaceuticals have been reported to cause hormonal disorders in riverine fish leading to reproductive stress and hence endangering exposed populations (e.g. Tyler et al., 1998).

Due to rising life expectancies, growing populations and medical advancements, the consumption of pharmaceuticals is expected to further increase in the near future (aus der Beek et al., 2016; Oldenkamp et al., 2013). After intake, most pharmaceuticals are not entirely metabolized in the human body but can partially enter the sewer system via excretion. Currently applied technologies in wastewater treatment plants (WWTPs) remove pharmaceuticals to varying extents. Consequently, pharmaceuticals that are not completely removed, are discharged with the WWTP effluent into receiving water bodies. Pharmaceutical residues have not only been found in surface waters all over the world (e.g., Archer et al., 2017; Richmond et al., 2018), but increasingly also in groundwater sources and in drinking water (e.g., aus der Beek et al., 2016; Khan and Nicell, 2015; Moermond, 2016). This calls for strategies to reduce and if possible, prevent pharmaceutical emissions to the aquatic environment.

In an urban context, hospitals are often regarded as emission hotspots for pharmaceuticals (Herrmann et al., 2015; Verlicchi et al., 2014). Over the past years, the environmental awareness of hospitals has increased. Several initiatives currently promote more sustainable health care on a global scale (e.g. https://noharm.org/, http://www.healthierhospitals.org/). In the Netherlands, a new integrative strategy towards reducing pharmaceutical emissions to surface water was launched in 2016 (Dijksma, 2017; https://jamdots.nl/view/239/medicijnresten-uit-water). Since then, policy makers, pharmacists, drinking water companies, water authorities and hospital managers began to collaborate more closely to reduce the load of pharmaceuticals entering the surface water. Even though not legally compulsory, many hospitals consider on-site treatment measures to reduce their pharmaceutical emissions to the environment. Yet, it remains unclear which compounds are most relevant to mitigate and at what point emission control is most effective.

Measuring campaigns to assess hospital emissions are reactive, expensive and time-consuming. Instead, emission estimation models based on purchase and prescription data could represent a relatively simple method to estimate pharmaceutical emissions from hospitals (e.g. Le Corre et al., 2012). In combination with risk-based prioritization, pharmaceuticals can be ranked based on the risk they pose to aquatic organisms (Chèvre et al., 2013; Escher et al., 2011;). Compound prioritization is of crucial importance for several reasons: (1) monitoring campaigns could be fine-tuned to save costs, (2) hospital-specific shortlists of critical pharmaceuticals could be created to help identify the measures that are most effective in reducing risks, (3) hospitals can comprehensively quantify the environmental impact resulting from their pharmaceutical prescribing.

This study presents a generic framework to prioritize pharmaceuticals based on their relative risks for aquatic organisms due to hospital emissions. The framework consists of an emission estimation

module and a risk prioritization module, designed to be applicable in practice. The former uses purchase and prescription data from hospitals as input data, while the latter requires data on removal efficiencies of the selected pharmaceuticals for the respective WWTP. The framework was applied to estimate the emission of 16 pharmaceuticals at two Dutch academic hospitals (Radboudumc and Utrecht UMC), and to rank these pharmaceuticals based on predicted relative risks for aquatic organisms. The emission module was tested and validated in a case study, using measurement data collected by means of passive sampling in the sewer system.

2. Materials and methods

2.1 Emission and prioritization framework

2.1.1 Emission estimation module

The aim of the emission module is to predict pharmaceutical emissions to the hospital wastewater (Equation 1). Using a mass balance approach, the total emission load of pharmaceutical *x* to the hospital wastewater $E_{HWW,x}$ (g year^{-1}) was assumed to originate from hospitalized patients $E_{p,x}$ (g year^{-1}) and staff working at the hospital $E_{np,x}$ (g year^{-1}).

$$E_{HWW,x} = E_{p,x} + E_{np,x} \quad (1)$$

The total emission load of pharmaceutical *x* from hospitalized patients, $E_{p,x}$ (g year^{-1}), (Equation 2) was then calculated by multiplying the mass of active pharmaceutical ingredient administered via intake route *i* (oral, intravenous, or rectal), $M_{x,i}$ (g year^{-1}), and the excretion fraction for that intake route $f_{exc,x,i}$ (dimensionless). As some patients are discharged from the hospital before their medication is finished or excretion has been completed, the emissions by hospitalized patients were corrected for the fraction of the medication excreted at home $f_{home,x,i}$ (dimensionless):

$$E_{p,x} = \sum_i ((M_{x,i} * f_{exc,x,i}) * (1 - f_{home,x,i})) \quad (2)$$

The fraction of the administered dose that is excreted as parent compound, $f_{exc,x,i}$, was calculated for all relevant intake routes. Since broad ranges are reported in literature and online databases (PubChem, 2019; DrugBank, 2018; Zorginstituut Nederland, 2019), we used the mean of the reported fractions per compound. A combined excretion fraction was calculated by adding the partial urinary and fecal excretion fractions for each intake route (Appendix A). For most pharmaceuticals, common prescription patterns were considered as described in the summary of product characteristics that are online available from the Dutch medicines evaluation board (https://www.cbg-meb.nl/).

When common prescription duration exceeds the average time of hospitalization, or when pharmaceuticals have a relatively slow body clearance, i.e. a relatively long elimination half-life ($t_{1/2}$), delayed excretion might cause a substantial part of hospital prescriptions to be emitted at-home into domestic instead of hospital wastewater. Therefore, at-home excretion was determined according to the respective dosing scheme and pharmacokinetic characteristics (see Appendix B1). For pharmaceuticals administered in multiple dosing routines, $f_{home,x,i}$ was calculated using the area-

under-the-curve method. For pharmaceuticals that are typically administered as single dose (e.g. contrast media), plasma concentration ratios were used (see Appendix B2).

Next to at-home excretion, pharmaceutical emission loads by non-patients $E_{np,x}$ (g year^{-1}) were estimated. Since both Radboudumc and Utrecht UMC are academic hospitals, the workforce consists of staff as well as students associated with the respective universities. Employment data were provided by the hospitals and expressed as full-time equivalents. Permanent staff was assumed to be aged 25-65 years and to spend 40 hours weekly at their workplace, while students were assumed to be aged 15-24 and to spend 32 hours weekly at the hospital. For non-patient emissions, only oral intake was included since we considered communal intravenous or rectal intake of pharmaceuticals unlikely.

To calculate the emission loads by the hospital staff and students (Equation 3), publicly available national prescription data (www.gipdatabank.nl) were used. We assumed the per capita consumption by staff and students at the hospital to be represented by the national per capita consumption of their respective age groups. As such, per capita consumption by age group *Ag* was calculated by multiplying the national number of items issued to that age group $N_{x,Ag,NL}$ with the mass of the active pharmaceutical ingredient (API) contained per dose D_x (g), and divided by the total number of Dutch citizens in the specific age group $P_{Ag,NL}$. Total annual consumption volumes by staff and students working at the hospital were subsequently calculated by multiplication with their population sizes $SP_{Ag,hospital}$. The resulting annual consumption by staff and students was then corrected for the time spent at the hospital f_{time} (dimensionless), and subsequently multiplied by the previously determined excretion fraction $f_{exc,x,oral}$ for oral intake. For detailed calculations see Appendix C.

$$E_{np,x} = \sum_{Ag=1}^{2} \left(N_{x,Ag,NL} * D_x * \frac{SP_{Ag,hospital}}{P_{Ag,NL}} * f_{time,Ag} \right) * f_{exc,x,oral} \quad (3)$$

2.1.2 Risk prioritization module

The aim of the risk prioritization module is to rank pharmaceuticals based on their relative risk for aquatic organisms, expressed as their risk quotients $RQ_{x,p}$. Hereto, predicted emission loads (g year^{-1}) had to be converted to concentrations per pharmaceutical C_x (ng L^{-1}), since the RQ_x is commonly defined as predicted (or measured) concentration divided by the predicted no-effect concentration of the respective pharmaceutical $PNEC_x$ (ng L^{-1}). To calculate C_x, the predicted emission loads to the respective hospital wastewater E_{HWWx} (g year^{-1}) were multiplied with the fraction of each pharmaceutical that is passing the WWTP $f_{pass,x}$ (dimensionless).In our case we used hereto 1 - observed removal efficiency during the sampling campaign (see Table 1). Subsequently, a factor of 10^9 was applied to convert the pharmaceutical load in the effluent from ng into kg. Assuming a constant daily dry weather flow Q_{DW} (L day^{-1}) for the respective WWWTP, the resulting effluent load was then divided by the annual dry weather discharge i.e. $Q_{DW} * 365\ days$ resulting in a conservative prediction of the yearly average effluent concentration C_x . This results in Equation 4:

$$RQ_{x,p} = \frac{C_x}{PNEC_x} = \frac{E_{HWWx} * f_{pass,x} * 10^9}{Q_{DW} * 365 * PNEC_x} \quad (4)$$

Table 1 - Observed WWTP removal efficiencies in percent during the sampling campaign in Nijmegen and Utrecht respective. If no removal percentage is reported, the compound was measured below the detection limit in both influent and effluent. Negative removal efficiencies indicate an increase of measured loads during treatment.

Observed WWTP removal efficiencies (%)		
Compound	*Nijmegen*	*Utrecht*
azithromycin	-10.8	0.9
carbamazepine	-42.0	-39.5
ciprofloxacin	96.1	91.4
cytarabine	-85.2	-1674.5
diclofenac	-43.4	-113.6
fluoxetine	-2.7	5.6
gemfibrozil	41.5	-166.7
ibuprofen	97.4	94.4
ifosfamide	-3.8	-
iomeprol	-64.3	-
iopromide	-	-57.2
metformin	90.5	99.0
metoprolol	-17.8	-21.9
naproxen	92.3	70.0
paracetamol	97.9	100.0
sulfamethoxazole	-12.4	34.7
trimethoprim	33.5	6.4

The PNEC values for the selected pharmaceuticals were obtained according to the assessment factor (AF) method (ECHA, 2017), and based on ecotoxicity data compiled from literature (SI 3). The AF method considers the amount of available toxicity data for a certain chemical compound for different species. The more toxicity data available for a wide range of species, the lower the assigned assessment factor. For example, if only one acute LC50 or EC50 value is available for each of the basic trophic levels (represented by fish, daphnia and algae), the value for the most sensitive species is divided by an assessment factor of 1000. In contrast, if chronic no-observed effect concentration (NOEC) values are available for at least three species representing three different trophic levels, the value for the most sensitive species is divided by an assessment factor of only 10. A detailed overview of all PNECs and safety factors used can be found in Appendix D.

2.1.3 Ranking strategies

The final RQ_xs were ranked for prioritization. The highest-ranking compounds thus either exert the highest potential environmental harm to aquatic organisms or entail the highest uncertainty regarding the related risk due to limited ecotoxicological data (i.e. translates into a high AF). Nonetheless, mitigation strategies are desirable in both cases: emissions should be mitigated if sufficient evidence proofs its risk to the aquatic environment. On the other side, emissions should be mitigated until it is sufficiently proven that a compound does not exert a considerable risk to the aquatic environment

(precautionary principle). Therefore, the ranking indicates on which compounds mitigation strategies by hospital should focus. In total three different ranking strategies were assessed for both hospitals.

The first strategy prioritizes the total emissions of a hospital into the HWW based on associated risks to the aquatic environment. Therefore, this strategy compares the predicted concentrations in HWW (Equation 1) with the measured concentrations in HWW (Equation 5). The predicted concentrations in the HWW consist of the emissions of hospitalized patients and the emissions of non-patients. Ranking 1 thus assesses the environmental risks resulting from the physical boundaries of the hospital (i.e. its wastewater outlet pipes).

The second strategy prioritizes emissions exclusively from hospitalized patients and thus represents the action range for a hospital for on-site measures. Hereto, the predicted concentrations corresponding to hospitalized patients (Equation 2) were compared to the measured concentrations. Since the measured concentrations also include emissions by non-patients, the measured concentrations were corrected by the relative contribution of non-patients (Equation 3). To assess the similarity of the rankings 1 and 2 between measured and predicted emissions, Spearman's rank correlation coefficients were calculated.

In a wider sense, hospitals may not only influence the emissions passing through their own HWW outlet, but also the share of emissions resulting from pharmaceuticals prescribed at hospital but consumed at home. Therefore, the third strategy prioritizes emissions by all hospital-associated patients based on related risks to the environment by comparing the predicted emissions by patients based on prescriptions (regardless if excretion occurs within the hospital or outside) to the measured emissions of hospitalized patients corrected for the relative contribution of non-patients. This last ranking indicates thus the action range by a hospital for measures on an urban scale.

2.2 Case study

2.2.1 Hospitals

To apply and showcase the developed model, two Dutch academic hospitals were approached. Radboudumc is one of two hospitals located in the city of Nijmegen, with a population of approximately 170,000 inhabitants in 2015 (Gemeente Nijmegen, 2019). Radboudumc counts more than 10,000 employees, about 2,700 students and 626 beds (Radboudumc, 2016). Utrecht UMC is one of three hospitals in the city of Utrecht, with a population of approximately 340,000 inhabitants in 2016 (Gemeente Utrecht, 2019). Utrecht UMC employs over 11,000 people, 3,700 students and counts 1,042 beds (UMC Utrecht, 2017). Both hospitals provided monthly purchase data (Radboudumc: May 2015; Utrecht UMC: April 2016) for the selected pharmaceuticals (Section 2.2.2), specified for oral, intravenous and rectal administration, which we extrapolated to annual consumption. In this, we assumed that pharmaceuticals purchased by a hospital are consumed within the month of purchase and exclusively by the patients of the respective hospital. We furthermore assumed both months to represent baseline months for an entire year as the purchased amounts per pharmaceutical in April and May are very close to the annual monthly means (see Appendix E). Over the counter pharmaceuticals (OTCs) were not considered, although their contribution was inevitably measured during the sampling campaign.

2.2.2 Substance selection

The pharmaceuticals were chosen in close consultation with both hospitals. Each pharmaceutical selected had to meet two criteria, i.e. it had to be (1) used by both hospitals, and (2) detectable using the passive samplers to enable validation of the model results. Furthermore, a group criterion was defined, i.e. (3) the selection had to cover a wide range of pharmaceutical classes. Since both hospitals used different iodinated contrast media, criterion 1 could not be met for this group and we decided to select two different iodinated contrast media, i.e. one for each hospital. The list of pharmaceuticals assessed is shown in Table 2.

Table 2 – Selection of pharmaceuticals included in case study. RUMC means Radboudumc, UUMC refers to Utrecht UMC.

Therapeutic group	Compound	CAS number
Antibiotics	Azithromycin	117772-70-0
	Ciprofloxacin	85721-33-1
	Sulfamethoxazole	723-46-6
	Trimethoprim	738-70-5
Antineoplastics	Cytarabine	147-94-4
	Ifosfamide	3778-73-2
Iodinated contrast media	Iomeprol (RUMC)	78649-41-9
	Iopromide (UUMC)	73334-07-3
Non-steroidal anti-inflammatory drugs (NSAID)	Diclofenac	15307-86-5
	Ibuprofen	15687-27-1
	Naproxen	22204-53-1
	Paracetamol	103-90-2
Anticonvulsants	Carbamazepine	298-46-4
Antidepressants	Fluoxetine	54910-89-3
Lipid regulators	Gemfibrozil	25812-30-0
Antihyperglycemics	Metformin	657-24-9
β-blockers	Metoprolol	37350-58-6

2.2.3 Field measurements

To validate the modelled emissions, loads of the selected pharmaceuticals were measured using passive samplers. Field measurements were conducted during the same month as indicated above for the respective hospitals, and extrapolated to annual emissions. In total 7 measuring locations were selected. Per measuring location, two adsorption samplers (Speedisk®) were placed. To calculate the

emission loads (Equations 5 and 6), we assumed an average sampling rate Rs per sampler of 50 ml day^{-1} which is consistent with experimental tests performed by Deltares (Smedes et al., 2013; unpublished results). Furthermore, the flow rate was measured at each sampling location so that wastewater loads could be calculated (Appendix F).

In Nijmegen, samplers were placed on May 20th 2015 and retrieved on June 1st 2015 covering a sampling duration of 12 days. They were placed at the two main outlets where wastewater effluent from Radboudumc enters the sewer, and at the influent and effluent points of the local WWTP. In Utrecht, samples were obtained similarly for a period of eight days from April 11th 2016 to April 19th 2016. In total, three locations were chosen for sampling: at the central collection point for all hospital effluent of the Utrecht UMC, and at the influent and effluent points of the local WWTP.

For transportation, the samplers were cooled and stored in glass jars. Upon arrival at the laboratory, the samples were stored in the dark at a temperature of -18° Celsius. Samplers were extracted with dichloromethane and ethanol. Extracts were dried over sodium sulphate and concentrated to a small volume. All extracts were stored in a dark environment at 1-5°C until further analysis.

The analysis was performed according to an internal protocol previously described in e.g. Kivits et al. (2018). The 17 analytes and internal standards were detected by an Agilent 1260 series high-performance liquid chromatographer using a 100 x 2.1 mm, 2.6 mm Kinetex column (Phenomenex, Utrecht, the Netherlands) coupled with an Agilent 6460 triple quadrupole LC/MS with Jetstream Electron Spray Ionisation (ESI) and multiple reaction monitoring (MRM). A sample volume of 5 mL was injected with a column temperature of 60 °C and a flowrate of 200 mL min^{-1}. The sample was eluted with a gradient of 1mM ammonium fluoride with 0.01% acetic acid in Milli-Q water (eluent A) and methanol (eluent B) and with flow rates of 0.5 mL min^{-1}. Eluent A was increased from 5% to 90% in 10 min and maintained for 3 min. After this it is decreased to 5% in 0.1 min and maintained for 1.9 min to complete the cycle of 15 min. Mass spectrometry was performed with a gas temperature of 350 °C and a flow rate of 7 L min^{-1}. Sheath gas temperature was set at 350 °C with a flow rate of 12 L min^{-1}. The capillary voltage was set at 3500 V. The target compounds were determined with one precursor ion and two product ions. For information about mass-to-charge ratios, retention times and ratios see SI 4. Calibration was done before measuring the samples with known amounts of the analytes in 9 steps with concentrations ranging between 0 and 50 ng mL^{-1}. The limit of detection (LOD) and limit of quantification (LOQ) of the analytes were determined with signal-to-noise ratios of 1:3 and 1:10 respectively. Average recoveries and concentrations for the LOD and LOQ are given in SI 4. The method resulted in values for LOQ ranging between 0.5 and 2.6 ng mL^{-1}.

The measured loads L_x (g) on the samplers were extrapolated to annual emission loads per pharmaceutical MEL_x (g $year^{-1}$) according to Equation 5. The load per sampler was divided by the sampling rate *Rs* (L day^{-1}) and multiplied by the average discharge of the respective outlet $\bar{Q}_{out}$ (L day^{-1}) during the sampling campaign. This resulted in the average daily emission load (g day^{-1}), which was divided by the sampling duration $T_{sampling}$ (days). This value was multiplied by 365 days, resulting in the annual emission per pharmaceutical (g $year^{-1}$). A sampling rate (*Rs*) of 0.05 liter day^{-1} was assumed for each sampler resulting in a total sampling volume of approximately one liter for each of the two case study locations. More detailed information on sampling locations and the exact calculations are provided in Appendix F.

$$MEL_x = \frac{L_x * \bar{Q}_{out} * 365}{R_s * T_{sampling}} \quad (5)$$

Like discussed in 2.1.2, also the measured emission loads had to be converted into concentrations MEC_x (ng L^{-1}) in order to perform the risk prioritization. Therefore, equation 4 was slightly adapted, by replacing E_{HWWx} with MEL_x:

$$RQ_{x,m} = \frac{MEC_x}{PNEC_x} = \frac{MEL_x * f_{pass,x} * 10^9}{Q_{DW} * 365 * PNEC_x} \quad (6)$$

2.2.4 Model parameterization

Pharmacokinetic data were used to determine excretion fractions and the at-home excretion fractions. The required data (absorption fractions, metabolism, elimination half-lives) were retrieved from following publicly accessible online databases:

- Dutch medicine evaluation board (https://www.cbg-meb.nl/)
- Dutch National Health Care Institute (www.farmacotherapeutischkompas.nl/)
- Drugs.com (www.drugs.com)
- DrugBank (www.drugbank.ca)

In case of missing or contradicting information, scientific literature was consulted. A detailed overview of the excretion fractions used and corresponding references is provided in Appendix A. The data and equations used to estimate at-home excretion can be found in Appendix B.

National consumption data, expressed as the defined daily doses (DDD), were used to estimate the non-patient consumption, and were retrieved from an online database maintained by the Dutch National Health Care Institute (www.gipdatabank.nl). Data on the number of staff and students of the hospitals were retrieved from the annual reports which were issued by the hospitals and that are publicly available on their respective homepages. A detailed overview of the data used and the corresponding calculations is provided in Appendix C.

Toxicological data to derive the PNEC values were retrieved from several online databases of which some are publicly accessible:

- US EPA Ecotox (cfpub.epa.gov/ecotox)
- Public data from REACH (echa.europa.eu)
- Wikipharma (www.wikipharma.org/api_data.asp),
- Dutch National Institute for Public Health and the Environment (e-TOX database, not public)
- German Environment Agency (ETOX, webetox.uba.de/webETOX/index.do)
- Ecotox Centre Eawag-EPFL (https://www.ecotoxcentre.ch/expert-service/quality-standards/proposals-for-acute-and-chronic-quality-standards/)

Data preparation for the ecotoxicological assessment was conducted according to van Vlaardingen and Verbruggen (2007). For all 16 pharmaceuticals, acute and chronic toxicity data for algae, fish and invertebrates were assessed, which are commonly used to represent the aquatic environment (ECHA, 2017). Also, different endpoints (EC50, LC50, NOEC and EC10) for these species were considered. The

lowest concentration for the most sensitive species reported was subsequently divided by the corresponding assessment factor, yielding the PNECs of the respective compounds.

To derive a chronic PNEC, EC10/LC10 and NOECs from chronic tests were used. ECx values where x is between 10 and 20 were divided by 2 to use them as chronic toxicity data (van Vlaardingen & Verbruggen, 2007). If the highest concentration in the test did not show any significant effect (i.e. no effect was detected) this was noted in the raw toxicity table with a greater than sign (>). These values are only included in the chronic toxicity table. If the value with the greater than sign is higher than the other available NOECs, this value was taken into account for the choice of the safety factor. EC50 and LC50 values from algae tests were used as acute values, whereas the NOEC value of the same test were considered to represent chronic values. For *Daphnia magna* and *Ceriodaphnia dubia*, it depends on the duration of the test whether values were considered acute or chronic. For both species, tests outcomes with an exposure time of 48 hours were considered acute values. Chronic values were obtained from tests with an exposure time of 21 days for *D. magna* and 7 days for *C. dubia*. Fish tests were commonly acute toxicity except for early life stage (ELS) tests. Acute L(E)C50 values were only used if sufficient chronic data was not available. A detailed description of the toxicity data, corresponding safety factors and resulting PNECs is provided in Appendix D.

3. Results and discussion

3.1 Predicted emission loads

Table 3 presents the annual predicted emission loads for Radboudumc and Utrecht UMC. Patients uncorrected refers to the extrapolation of clinical purchase data without correcting for at-home excretion. Hospitalized patients refers to annual emission loads corrected for at-home excretion calculated according to Equation 2, while non-patients refers to the contribution of hospital staff calculated according to Equation 3. The last column predicted HWW emissions sums the emission loads of hospitalized patients and emission loads from non-patients (Equation 1). Detailed calculations are provided in SI 1 (at-home excretion) and SI 2 (emission estimation).

Table 3 - Predicted emission loads for patients, hospitalized patients, non-patients and cumulative emission loads for Radboudumc (Nijmegen) and Utrecht UMC (Utrecht).Detailed calculations are provided in SI(2).

Radboudumc	**Patients, uncorrected (g/year)**	**Hospitalized patients (g/year)**	**Non-patients (g/year)**	**Predicted HWW emissions (g/year)**
azithromycin	894	358	145	502
carbamazepine	54	23	175	198
ciprofloxacin	7802	3429	318	3747
cytarabine	306	156	0	156
diclofenac	30	30	8	38
fluoxetine	0	0	14	14
gemfibrozil	104	104	55	159
ibuprofen	430	430	438	868
ifosfamide	216	212	0	212
iomeprol	1258596	377579	0	377579
iopromide	0	0	0	0

metformin	7392	7392	22796	30188
metoprolol	415	415	204	619
naproxen	774	464	428	893
paracetamol	14533	14533	318	14851
sulfamethoxazole	2175	538	76	614
trimethoprim	1428	250	9	259

Utrecht UMC	**Patients, uncorrected (g/year)**	**Hospitalized patients (g/year)**	**Non-patients (g/year)**	**Predicted HWW emissions (g/year)**
azithromycin	867	347	118	465
carbamazepine	232	137	155	291
ciprofloxacin	9291	4455	277	4732
cytarabine	216	110	0	110
diclofenac	36	36	7	42
fluoxetine	3	2	12	14
gemfibrozil	35	35	53	88
ibuprofen	819	819	376	1195
ifosfamide	218	218	0	218
iomeprol	0	0	0	0
iopromide	139201	41760	0	41760
metformin	14204	14204	23765	37969
metoprolol	318	318	201	519
naproxen	222	158	422	579
paracetamol	24172	24172	385	24557
sulfamethoxazole	2128	695	62	758
trimethoprim	1364	315	7	322

3.2 Measured emission loads

Table 4 presents the emission loads of the selected pharmaceuticals measured on the passive samplers after the sampling campaign of 12 days (Nijmegen) and 8 days (Utrecht) respectively. Per measuring location 2 adsorption samplers were placed, loads reported in Table 4 refer to cumulative sum of both samplers. The detection limit for all compounds is 10 ng.

Table 4 – Pharmaceutical loads measured on passive samplers after the field studies in Nijmegen and Utrecht. < indicates that the measured load was below the detection limit.

	Nijmegen				**Utrecht**		
Compound	Pit A/B (ng)	Pit C (ng)	Influent WWTP (ng)	Effluent WWTP (ng)	Central collection pit (ng)	Influent WWTP (ng)	Effluent WWTP (ng)
azithromycin	808	96	380	292	371	229	227
carbamazepine	267	253	653	644	266	494	689
ciprofloxacin	30282	939	995	27	827	116	10
cytarabine	289	242	177	228	<	17	293

diclofenac	694	190	418	416	233	195	417
fluoxetine	<	27	25	18	<	8	8
gemfibrozil	578	77	820	333	63	200	533
ibuprofen	3426	3411	5022	92	2833	3798	214
ifosfamide	1884	50	63	45	59	<	<
iomeprol	676396	227879	2185	2494	<	<	<
iopromide	582	656	<	<	68592	1348	2119
metformin	318	237	656	43	403	880	8
metoprolol	3545	1281	6008	4917	490	1194	1455
naproxen	7343	3281	5792	311	1382	1125	338
paracetamol	181747	46775	54654	780	37153	20726	<
sulfamethoxazole	5201	245	338	264	451	943	616
trimethoprim	4102	185	309	143	1098	128	120

Table 5 presents the relative contribution of hospital emissions to the influent of the respective municipal WWTP. Although the overall contribution of both hospitals is low (<2.5% for Utrecht UMC, <1.1% for Radboudumc), some pharmaceuticals contribute above average (ciprofloxacin, trimethoprim and ifosfamide [Nijmegen]) while contrast media contribute substantially (>29% and >34% respectively). The relative contribution (%) was calculated dividing the measured loads L_x (g) at the respective hospital outlet (in gram) by the measured loads at the respective WWTP inlet (SI 2) for each pharmaceutical individually as well as for the overall contribution of the hospitals (e.g. ∑ measured loads HWW / ∑ measured loads WWTP *100%).

Table 5 - Relative contribution (%) of hospital emissions to the influent of the respective municipal WWTP per pharmaceutical as well as cumulatively. Pharmaceuticals that contribute above the cumulative average are indicated in bold.

Compound	Utrecht UMC	Radboudumc
azithromycin	1.10	0.17
carbamazepine	0.37	0.05
ciprofloxacin	**4.86**	**2.28**
cytarabine	-	0.21
diclofenac	0.81	0.15
fluoxetine	0.00	0.07
gemfibrozil	0.22	0.06
ibuprofen	0.51	0.1
ifosfamide	-	**2.2**
iomeprol	-	**29.25**
iopromide	**34.55**	-
metformin	0.31	0.06
metoprolol	0.28	0.06
naproxen	0.83	0.13
paracetamol	1.22	0.30
sulfamethoxazole	0.32	**1.17**
trimethoprim	**5.83**	1.01

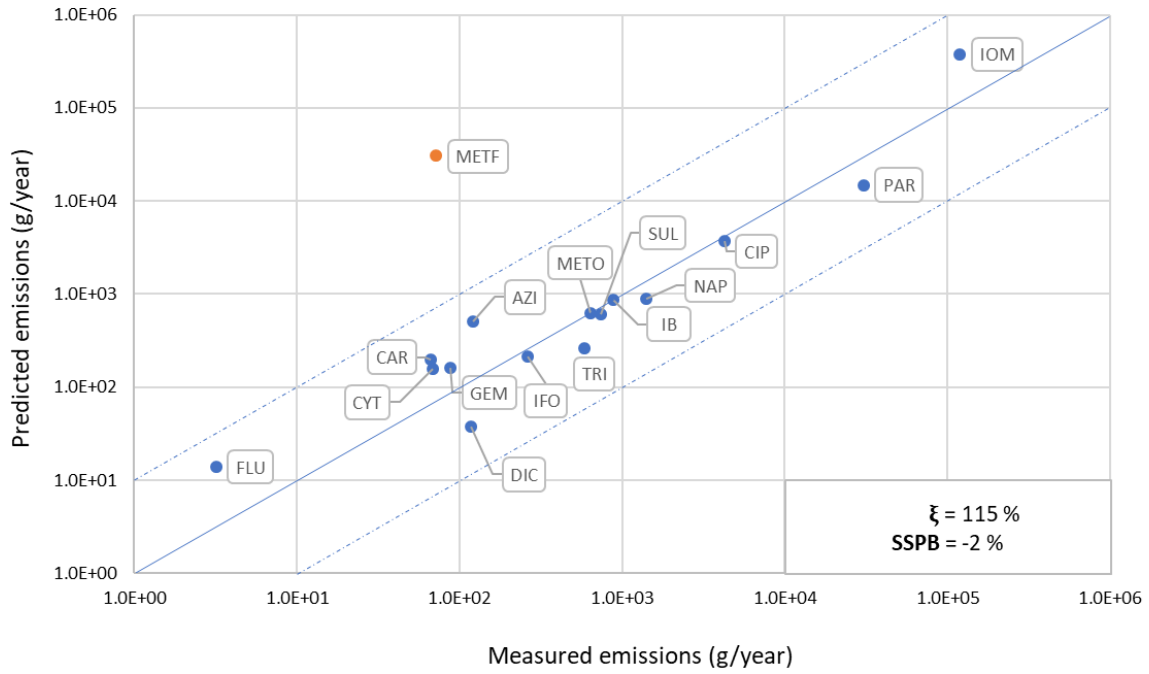
cumulative	***2.47***	**1.09**

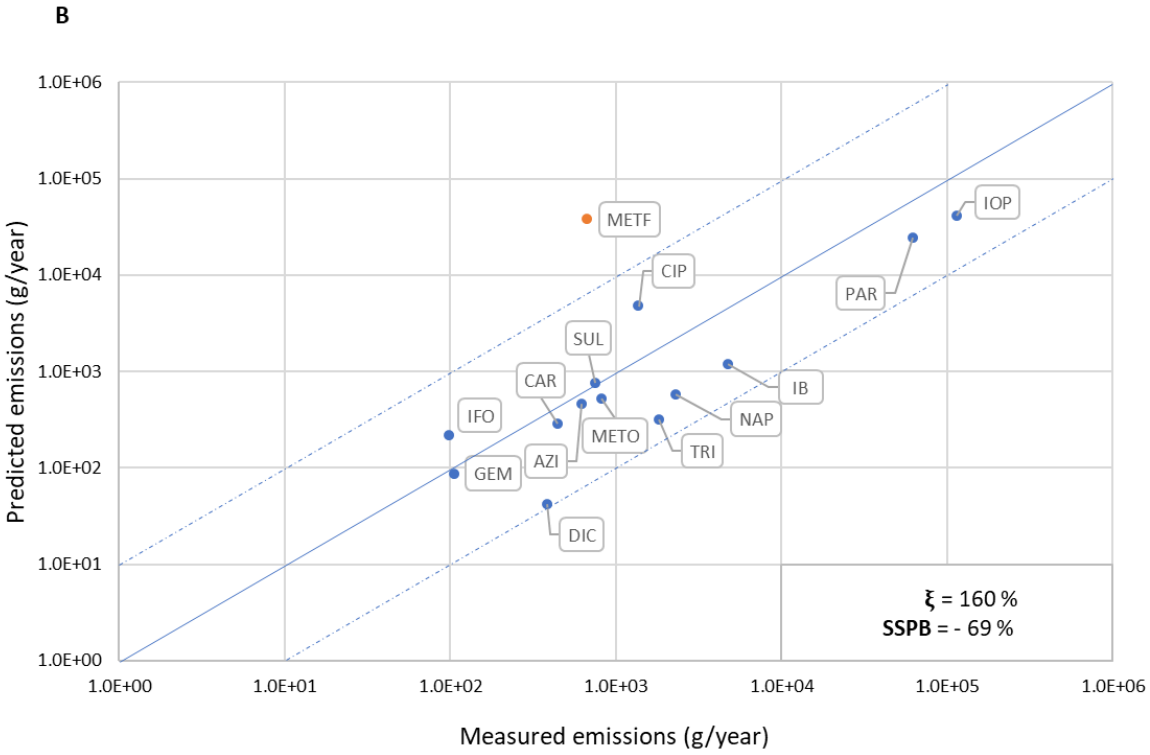
3.3 Comparing modelled and measured emission loads

Figure 1 presents the comparison between predicted emission loads ($E_{HWW,x}$) and measured emission loads (MEL_x) for both hospitals. The continuous line represents a $E_{HWW,x}/MEL_x$ ratio of 1, meaning that measured emission loads equal predicted emission loads. For both cases, most predicted emission loads are within a factor of 10 (dotted lines) of the measured emission loads. To assess the model performance, the median symmetric accuracy (ξ, Xi) and the symmetric signed percentage bias (SSPB) were calculated as described in Morley et al. (2018). Metformin was in both cases significantly overestimated, while diclofenac and trimethoprim were slightly underestimated in Utrecht (Figure 1B).

The hospitals use different contrast media; Radboudumc uses mainly iomeprol, while Utrecht UMC administers predominantly iopromide. Since iopromide was not purchased by Radboudumc in the selected period of time, iopromide does not appear in Figure 1A even though it was measured in low quantities (158g iopromide vs 119,618g iomeprol). Likewise, iomeprol was neither purchased nor measured at Utrecht UMC, and is therefore not depicted in Figure 1B. Furthermore, no $E_{HWW,x}/MEC_x$ ratio could be calculated for fluoxetine and cytarabine for Utrecht UMC, since these compounds were not detected in the HWW there.

A





386

387

388 *Figure 1 - Difference plot of predicted and measured emissions at Radboudumc (A) and Utrecht UMC (B). The continuous line*
389 *marks ideal ratio of 1 (predicted emission equals measured emission), dotted lines indicate a 10-fold deviation from it.*
390 *Abbreviations stand for azithromycin (AZI), carbamazepine (CAR), ciprofloxacin (CIP), cytarabine (CYT), diclofenac (DIC),*
391 *fluoxetine (FLU), gemfibrozil (GEM), ibuprofen (IBU), ifosfamide (IFO), iomeprol (IOM), iopromide (IOP), metformin (METF),*
392 *metoprolol (METO), naproxen (NAP), paracetamol (PAR), sulfamethoxazole (SUL) and trimethoprim (TRI). Model performance*
393 *indicators: median symmetric accuracy (ξ), symmetric signed percentage bias (SSPB).*

394 The presented emission model based on clinical purchase data predicts hospital emissions in both
395 cases fairly well ($\xi_{Nijmegen}$ = 115%, $\xi_{Utrecht}$ = 160%) even though emissions were rather underestimated
396 ($SSPB_{Nijmegen}$ = -2%, $SSPB_{Utrecht}$ = -69%). Overall, the model performed better for Nijmegen than for
397 Utrecht. This can be can be explained by the fact that UMC Utrecht is closely located to several other
398 healthcare institutions, such as a military hospital and two children hospitals that appear to discharge
399 via the same sewer pipe. Consequently, emissions from these institutions were measured but not
400 predicted, as purchase data were only obtained from Utrecht UMC but not from the surrounding
401 hospitals.

402 Metformin represents a clear outlier in both cases as its emissions appear highly overestimated.
403 Overestimation of metformin emissions was also reported in similar studies (e.g. Oosterhuis et al.,
404 2013) and could be explained by the relatively fast biodegradation to its transformation product
405 guanylurea. This appears likely when assuming that a "competent microbial community" is well-
406 established in the sewer system (Straub, 2013; Tisler and Zwiener, 2018). In our case, however, the
407 time from excretion in the hospital to the measured HWW outlet is rather short. Even if biodegradation
408 proceeded very fast, this could hardly result in such a large difference between predicted and observed
409 emission loads. It is therefore more likely that analytical errors lead to underestimation of the emission
410 loads, since metformin can only be determined semi-quantitatively using passive samplers (Macleod

et al., 2007; Moermond, 2016; Smedes et al., 2010). If metformin is excluded, the model performance improves slightly ($\xi_{Nijmegen}$ = 105%, $SSPB_{Nijmegen}$ = -3%; $\xi_{Utrecht}$ = 151%, $SSPB_{Utrecht}$ = -68%).

Furthermore, in both cases diclofenac was rather underestimated suggesting a substantial consumption of OTC-diclofenac by non-patients or considerable contribution of other dosage forms. Since the present study only considers the intake of the selected pharmaceuticals, other dosage forms like dermal application of creams and gels are neglected, even though the contribution to wastewater concentrations might be significant, especially in the case of diclofenac. Letzel et al. (2009) showed, for example, that dermal application of diclofenac contributes significantly to the measured loads in wastewater as 90-95% of the API is washed-off during showering.

3.4 Risk assessment and prioritization

Table 6 and 7 present the results of the first and second ranking strategies for Radboudumc and Utrecht UMC, respectively. In both cases, pharmaceuticals were excluded from the ranking if either not measured or not predicted. For Radboudumc, antibiotics score in all rankings in the top 3 based on predicted emissions. Furthermore, the first five ranking positions remain the same for both strategies. For Utrecht UMC, azithromycin and ciprofloxacin rank either 1 or 2, while diclofenac occupies rank 3 for both strategies. Ranking positions 3 to 6 remain the same for both strategies. Generally, NSAIDs score relatively high, even though the model underestimated measured loads. Likewise, selected contrast media scored along the midfield. The results suggest that mitigation strategies should especially focus on reducing the emissions of the antibiotics azithromycin, ciprofloxacin and sulfamethoxazole, as these pharmaceuticals represent the highest risk to aquatic organisms. The method used for this ranking assigns lower PNEC values to compounds that are either more toxic or on which not much toxicity data is available. This way, both toxicity (i.e. most sensitive endpoint) and uncertainty (i.e. magnitude of AF factor) are considered.

Relatively more ecotoxicity data were available for sulfamethoxazole, diclofenac and ibuprofen resulting in low application factors (i.e., of 10) while less ecotoxicity data were available and hence higher application factors (i.e., of 50-5,000) were applied for e.g. metoprolol, iomeprol or cytarabine Especially for ifosfamide very few ecotoxicity data was available resulting in the highest application factor of 10,000. For this latter group, performing additional ecotoxicity tests could result in a lower PNEC value and hence a lower estimated risk. However, performing ecotoxicity tests is often not considered as a potential risk reduction option by individual hospitals. Investing in ecotoxicity tests to optimize risk assessment could result in valuable insights that help to pinpoint priority compounds and adjust emission prevention measures accordingly.

443 *Table 6 - Prioritization of pharmaceuticals at Radboudumc (Nijmegen) based upon predicted and measured emissions and*
444 *RQs. Antibiotics are indicated in bold-print, NSAIDs in italic-print. The darker the background color, the better the ranks of*
445 *predicted and measured concentrations coincide. In ranking 2, fluoxetine is not listed as neither predicted nor measured after*
446 *correction for non-patient consumption.*

Ranking 1: Total emissions of Radboudumc into HWW					
pharmaceutical	predicted	RQ x,p (PEC/PNEC)	measured	RQ x,m (PEC/PNEC)	Assessment factor
azithromycin	1	3.30E-01	3	8.00E-02	50
ciprofloxacin	2	8.54E-02	2	9.67E-02	50
sulfamethoxazole	3	6.11E-02	4	7.34E-02	10
diclofenac	4	5.66E-02	1	1.76E-01	10
iomeprol	5	3.68E-02	7	1.16E-02	5000
ibuprofen	6	1.19E-02	6	1.20E-02	10
paracetamol	7	7.97E-03	5	1.63E-02	50
carbamazepine	8	5.86E-03	11	1.98E-03	10
metoprolol	9	5.02E-03	8	5.16E-03	1000
gemfibrozil	10	3.11E-03	12	1.72E-03	50
naproxen	11	2.12E-03	10	3.32E-03	50
trimethoprim	12	1.76E-03	9	3.96E-03	1000
fluoxetine	13	1.75E-03	13	4.04E-04	50
cytarabine	14	8.88E-04	14	3.90E-04	3000
metformin	15	1.49E-04	16	3.55E-07	10
ifosfamide	16	1.42E-05	15	1.76E-05	10000
Spearman's rho:	0.929				

447

Ranking 2: Action range for on-site measures by Radboudumc					
pharmaceutical	predicted	RQ x,p (PEC/PNEC)	measured	RQ x,m (PEC/PNEC)	Assessment factor
azithromycin	1	2.35E-01	4	5.69E-02	50
ciprofloxacin	2	7.82E-02	2	8.84E-02	50
sulfamethoxazole	3	5.35E-02	3	6.43E-02	10
diclofenac	4	4.53E-02	1	1.41E-01	10
iomeprol	5	3.68E-02	6	1.16E-02	5000
paracetamol	6	7.79E-03	5	1.60E-02	50
ibuprofen	7	5.90E-03	7	5.96E-03	10
metoprolol	8	3.36E-03	9	3.46E-03	1000
gemfibrozil	9	2.03E-03	11	1.12E-03	50
trimethoprim	10	1.70E-03	8	3.82E-03	1000
naproxen	11	1.10E-03	10	1.73E-03	50
cytarabine	12	8.88E-04	12	3.90E-04	3000
carbamazepine	13	6.69E-04	13	2.26E-04	10
metformin	14	3.66E-05	15	8.70E-08	10

ifosfamide	15	1.42E-05	14	1.76E-05	10000
Spearman's rho:	0.943				

448

449 *Table 7 - Prioritization of pharmaceuticals at Utrecht UMC based upon predicted and measured emissions and RQs. Antibiotics*
450 *are indicated in bold-print, NSAIDs in italic-print. The darker the background color, the better the ranks of predicted and*
451 *measured concentrations coincide. Cytarabine, fluoxetine, iomeprol and paracetamol are not listed as either not measured or*
452 *entirely removed in WWTP.*

Ranking 1: Total emissions of Utrecht UMC into HWW					
pharmaceutical	predicted	RQ x,p (PEC/PNEC)	measured	RQ x,m (PEC/PNEC)	Assessment factor
azithromycin	1	3.26E-01	2	4.32E-01	50
ciprofloxacin	2	2.83E-01	4	8.21E-02	50
diclofenac	3	1.13E-01	1	1.03E+00	10
sulfamethoxazole	4	5.22E-02	5	5.16E-02	10
ibuprofen	5	4.19E-02	3	1.65E-01	10
carbamazepine	6	1.01E-02	8	1.54E-02	10
gemfibrozil	7	9.35E-03	9	1.12E-02	50
naproxen	8	6.37E-03	6	2.52E-02	50
metoprolol	9	5.19E-03	10	8.13E-03	1000
trimethoprim	10	3.68E-03	7	2.08E-02	1000
iopromide	11	4.09E-04	11	1.11E-03	100
metformin	12	2.26E-05	13	3.99E-07	10
ifosfamide	13	1.68E-05	12	7.53E-06	10000
Spearman's rho:	0.896				

453

Ranking 2: Action range for on-site measures by Utrecht UMC					
pharmaceutical	predicted	RQ x,p (PEC/PNEC)	measured	RQ x,m (PEC/PNEC)	Assessment factor
ciprofloxacin	1	2.66E-01	4	7.73E-02	50
azithromycin	2	2.43E-01	2	3.22E-01	50
diclofenac	3	9.51E-02	1	8.66E-01	10
sulfamethoxazole	4	4.79E-02	5	4.74E-02	10
ibuprofen	5	2.87E-02	3	1.13E-01	10
carbamazepine	6	4.75E-03	7	7.21E-03	10
gemfibrozil	7	3.68E-03	10	4.40E-03	50
trimethoprim	8	3.60E-03	6	2.04E-02	1000
metoprolol	9	3.18E-03	9	4.98E-03	1000
naproxen	10	1.73E-03	8	6.87E-03	50
iopromide	11	4.09E-04	11	1.11E-03	100
ifosfamide	12	1.68E-05	12	7.53E-06	10000
metformin	13	8.47E-06	13	1.49E-07	10

Spearman's rho:	0.901

To assess the similarity of the rankings, the Spearman's rank correlation coefficient was determined for all four rankings. The coefficients are 0.929 (ranking 1) and 0.943 (ranking 2) for Radboudumc, and 0.898 (ranking 1) and 0.901 (ranking 2) for Utrecht UMC suggesting a strong positive correlation. Overall, this suggests that prioritization based upon clinical purchase and prescription data is a viable instrument for hospitals to assess their environmental impact.

Table 8 presents the outcome of the third ranking strategy for Radboudumc (above) and Utrecht UMC (below). Like in the previous rankings, the antibiotics azithromycin, sulfamethoxazole and ciprofloxacin score the highest, followed by iomeprol (Radboudumc) and diclofenac (Utrecht UMC) while other NSAIDs score along the midfield. Especially the case of trimethoprim (position 6 in Table 5 instead of position 10 and 11 in Table 3 and 4) highlights the relatively high risk that antibiotics pose to the aquatic environment. The results of ranking 3 confirm therefore that, also on an urban scale, a reduction of antibiotic emissions would be prioritized to protect aquatic ecosystems.

This means that the implementation of possible measures by hospitals to protect the aquatic environment should primarily focus on these compounds, while not neglecting solutions to reduce the emissions of other compounds when those would be easy to implement. For this ranking, no Spearman's rank correlation coefficient was determined since the ranking compares only predicted emissions.

Table 8 - Comparison of the prioritization of pharmaceuticals based on the urban impact of both hospitals. Antibiotics are indicated in bold-print, NSAIDs in italic-print. The darker the background color, the better coincide the ranks between predicted and measured concentrations.

Ranking 3: Action range for measures on urban scale by Radboudumc					
pharmaceutical	prescriptions	RQ (PEC/PNEC)	hospitalized patients	RQ (PEC/PNEC)	Assessment factor
azithromycin	1	5.88E-01	4	5.69E-02	50
sulfamethoxazole	2	2.16E-01	3	6.43E-02	10
ciprofloxacin	3	1.78E-01	2	8.84E-02	50
iomeprol	4	1.23E-01	6	1.16E-02	5000
diclofenac	5	4.53E-02	1	1.41E-01	10
trimethoprim	6	9.72E-03	8	3.82E-03	1000
paracetamol	7	7.79E-03	5	1.60E-02	50
ibuprofen	8	5.90E-03	7	5.96E-03	10
metoprolol	9	3.36E-03	9	3.46E-03	1000
gemfibrozil	10	2.03E-03	11	1.12E-03	50
naproxen	11	1.84E-03	10	1.73E-03	50
cytarabine	12	1.74E-03	12	3.90E-04	3000
carbamazepine	13	1.59E-03	13	2.26E-04	10
metformin	14	3.66E-05	15	8.70E-08	10
ifosfamide	15	1.45E-05	14	1.76E-05	10000
Ranking 3: Action range for measures on urban scale by Utrecht UMC					
pharmaceutical	prescriptions	RQ (PEC/PNEC)	hospitalized patients	RQ (PEC/PNEC)	Assessment factor
azithromycin	1	6.07E-01	2	3.22E-01	50
ciprofloxacin	2	5.55E-01	4	7.73E-02	50
sulfamethoxazole	3	1.47E-01	5	4.74E-02	10
diclofenac	4	9.51E-02	1	8.66E-01	10
ibuprofen	5	2.87E-02	3	1.13E-01	10
trimethoprim	6	1.56E-02	6	2.04E-02	1000
carbamazepine	7	8.05E-03	7	7.21E-03	10
gemfibrozil	8	3.68E-03	10	4.40E-03	50
metoprolol	9	3.18E-03	9	4.98E-03	1000
naproxen	10	2.44E-03	8	6.87E-03	50
iopromide	11	1.36E-03	11	1.11E-03	100
ifosfamide	12	1.68E-05	12	7.53E-06	10000
metformin	13	8.47E-06	13	1.49E-07	10

3.5 Model applicability

The presented emission estimation model and prioritization framework should be suitable to provide hospitals with sufficient exploratory information to prioritize potential emission reduction measures.

Both modules of the presented framework require a limited amount of relatively simple input data. To extrapolate from expected loads of pharmaceuticals to concentrations, data on the flow rate of the HWW effluent are required. The prioritization module requires data on removal efficiencies per pharmaceutical as well as PNEC values. If no real-time measuring data for the specific WWTP is available, average removal efficiencies reported in literature can be used. The latter, however, might compromise the accuracy of the predictions. A screening-level but comprehensive overview of the pharmaceutical emissions of a hospital can still be provided. The most limiting factor regarding the model applicability is likely the derivation of the PNEC values due to the lack of ecotoxicity data. Many substances, especially substances on the market before 2006 (so-called legacy substances) have very limited or no ecotoxicity data at all. Furthermore, selecting and assessing the quality of these ecotoxicity tests requires basic knowledge on environmental risk assessment. Besides, cleaning of collected ecotoxicity data remains a tedious and time-consuming task.

3.6 Limitations

3.6.1 Emission estimation model

Regarding the emission model, three main limitations come to the fore. Firstly, this study considers only excretion of the parent compounds but ignores formation and effects of metabolites. After intake of a pharmaceutical, part of the API is metabolized by the human body. During this process, several metabolites can be formed in differing quantities. Depending on the specific half-life of the compound, the entire intake dose is ultimately excreted; partially as metabolites and partially as parent compound mostly via urine and feces.

As the formation of metabolites is highly variable and subject to complex chemical reactions, many differing estimates are reported in literature. Furthermore, conflicting statements exist on the contribution of metabolites to the environmental risk. Some studies argue aquatic toxicity of most metabolites is lower as compared to the respective parent compound (e.g. Escher et al., 2011) while other studies report a greater toxicity for metabolites than for parent compounds (e.g. Schulze et al., 2010). Consequently, assessing the formation and effects of metabolites was considered beyond the scope of the present study. This implies that the risk assessment module likely underestimates the total risk originating from a parent compound, as the toxic contribution by its metabolites is neglected leading to a non-conservative environmental risk assessment. More research is recommended to bring more clarity to this ongoing academic debate.

Secondly,the emission estimation model does not account for in-sewer transformation and degradation processes that might affect the compounds (both parent compound as well as metabolites). This could potentially lead to an overestimation of pharmaceutical concentrations and thus to a conservative emission estimation. However, several studies suggest that the effect of in-sewer processes on pharmaceuticals is limited mainly due to the rather short retention time in the sewer system (e.g. Jelic et al., 2014; O'Brien et al., 2017).

Thirdly, the non-patients' emissions estimated in the present study only include staff and working students, but not visitors. Visitors of hospitalized patients might contribute substantially to non-patient emissions even though spending only short periods of time at the hospital as compared to working staff. To the best of our knowledge, no data on annual numbers of visitors or average visit durations are recorded for any of the selected hospitals. Furthermore, due to the lack of data on OTCs sales or consumption, non-patient emissions are based solely on national prescription data.

3.6.2 *Environmental risk assessment*

In this study, only 16 pharmaceuticals were considered out of more than 1300 pharmaceutical products for human use which are registered within the EU (European Commission, 2019). It is admittedly questionable how representative a ranking on such a small sample size is. Therefore, we would like to mention explicitly that the presented ranking is relative to the present compound selection. Including more or other compounds could have resulted in distinct ranking positions for the single compounds. However, we demonstrated that the method functions well and therefore we do not expect major issues when upscaling the presented framework to a larger sample size. Moreover, even though the sample size was small, some general tendencies became apparent, for example, that antibiotics represent a higher aquatic risk than other groups of pharmaceuticals. This underlines the importance of reducing antibiotic emissions to the environment.

One general drawback of current risk assessment is that it does not account for potential mixture toxicity. There is general agreement that mixtures might be more toxic than the summed effects of each of the components, with aggregated responses being potentially slightly modified by synergistic processes (Kortenkamp et al., 2009). Furthermore, the long-term effects of chronic exposure of aquatic organisms to pharmaceuticals are still largely unknown. A recent study published by Richmond et al. (2018) suggests that some pharmaceutical residues can accumulate in benthic insects and biomagnify along the food web. A growing body of literature attributes behavioral changes as well as reproductive alterations resulting from long-term exposure to low concentrations of micro pollutants including pharmaceuticals (Ford and Fong, 2016; Tyler et al., 1998). However, current risk assessments do not yet account for these behavioral changes and reproductive effects.

3.6.3 *Model reliability*

As with all kinds of predictions or models, the present one is also subject to a certain degree of uncertainty. In our case, three main sources contribute to the overall uncertainty. Firstly, an important source of uncertainty is the estimation of excretion factors used to predict pharmaceutical emissions to HWW. Excretion factors reported in literature and online databases fall within a relatively wide range suggesting large variability in pharmaceutical excretion from person to person depending on several factors like age, diet, disease and combined intake of pharmaceuticals. The uncertainty regarding excretion factors is pharmaceutical-specific: while for some pharmaceuticals (e.g. contrast media) excretion factors are around 90%, for other pharmaceuticals (e.g. diclofenac, metoprolol, ibuprofen) merely 1% of the intake is excreted. Deviations in low excretion factors will have a much larger impact on emission estimates than deviations in high excretion factors. If 2% of the ibuprofen intake was excreted instead of 1% the emission estimation of ibuprofen would double, whereas an excretion factor of 91% instead of 90% for iomeprol would carry much less weight for the emission estimation. Likewise, uncertainty around half-life data affects the emission estimation for at-home excretion.

Secondly, regarding the conducted risk assessment, substantial uncertainty originates from the assessment factors applied which range from 10-10,000 depending on the number of ecotoxicological data available. In case of low data availability, PNECs might overestimate the risk of a pharmaceutical because of the high assessment factor. In case of high data availability (thus many different species tested), a low assessment factor is applied. In this case, however, there is still a risk that another species, which was not considered in the effect assessment, might be substantially more sensitive than

the least sensitive species considered. This has also implications for the prioritization, where the position of a pharmaceutical in the ranking depends on two estimated variables, i.e. the predicted environmental concentration (PEC) and the predicted no-effect concentration (PNEC), which are both subject to uncertainty. As described previously, our predicted concentrations hardly deviate more than a factor of 10 from measured concentrations. The derivation of PNECs, however, is much more uncertain. The PNEC of diclofenac, for example, can differ by a factor of 2000 depending on the endpoints chosen. If histopathological changes in fish are considered a population-relevant endpoint as suggested by Schwaiger et al. (2004) and Triebskorn et al. (2007), a much lower (conservative) PNEC of $5*10^{-5}$ mg/L is derived leading to a relatively high position for diclofenac in the ranking. If these studies are ignored because of variations in experimental setup or differing diagnostic interpretations of ecotoxicity test data (Wolf et al., 2014), a much higher (less conservative) PNEC of 0.1 mg/L is derived. Consequently, diclofenac would have scored position 16 instead of position 1 in ranking 1 (Tabel 6, right column). In this study, we used the more conservative PNEC value.

4. Conclusions

This study demonstrated that prioritization based upon clinical purchase and prescription data is a viable instrument for hospitals to assess their environmental impact. Expensive and laborious measuring campaigns might thus not always be necessary to decide at what point mitigation measures could be most effective.

The presented emission estimation model predicts pharmaceutical emissions from hospitals fairly accurately. Predicted emissions deviate mostly within a factor of 10 from measured emissions. NSAIDs are generally underestimated which is probably caused by the consumption of over the counter drugs by non-patients which was not included in our emission model.

Results from prioritizing pharmaceuticals indicate that azithromycin and ciprofloxacin represent the highest risk to aquatic organisms in relation to the substance selection of this study. Similarly, non-steroidal anti-inflammatory drugs (NSAIDs) scored relatively high even though the emission of this pharmaceutical group is underestimated in both cases. Emission mitigation strategies by hospitals could therefore focus their efforts primarily on reducing antibiotic and NSAID emissions.

Both modules of the presented framework require a limited amount of relatively simple input data. Therefore, this study provides health care managers with a useful and pragmatic tool to acquire sufficient exploratory information on hospital emissions for prioritizing potential emission reduction measures.

Acknowledgements

The authors would like to thank Frans Russel, Jos Henderik, Eric Mimmel, Nicole Vink - van Kimmenade, Anke Bouwmans, Cora Klaver, Kees Kramers, Nanneke Meijer, Hein van Onzenoort, Bas van Vlijmen and Jan Stegeman from Radboudumc in Nijmegen as well as Esther Willemsen, Danny Broekhuizen, Bernard Vos and Anne Manders from UMC Utrecht in Utrecht for their help regarding data collection and practical information. Furthermore, we thank Esther Schoutsen from Zorginstituut Nederland for helping us with the data collection.

This project was funded by the Netherlands Organization for Scientific Research (NWO) domain TTW under the grant agreement number 62003388 (SUSPECt).

606 The authors declare no conflict of interest.

607

608 **Supplementary information**

609 (Appendix) – Describing methods and calculations to determine excretion fractions, half-lives and at-
610 home excretion, non-patient emissions, PNECs, and data on field measurements.

611 (SI 1) - Excel presenting calculations on pharmaceutical half-lives and at-home excretion.

612 (SI 2) - Excel presenting calculations on emission estimation and prioritization.

613 (SI 3) – Excel presenting overview of ecotoxicological data used to derive PNECs.

614 (SI 4) – Detailed results from measuring campaign and chemical analysis

615 **References**

616 Archer, E., Wolfaardt, G.M., van Wyk, J.H., 2017. Pharmaceutical and personal care products (PPCPs)
617 as endocrine disrupting contaminants (EDCs) in South African surface waters. Water SA 43,
618 684–706. https://doi.org/10.4314/wsa.v43i4.16

619 aus der Beek, T., Weber, F.A., Bergmann, A., Hickmann, S., Ebert, I., Hein, A., Küster, A., 2016.
620 Pharmaceuticals in the environment-Global occurrences and perspectives. Environ. Toxicol.
621 Chem. 35, 823–835. https://doi.org/10.1002/etc.3339

622 Chèvre, N., Coutu, S., Margot, J., Wynn, H.K., Bader, H.-P., Scheidegger, R., Rossi, L., 2013. Substance
623 flow analysis as a tool for mitigating the impact of pharmaceuticals on the aquatic system.
624 Water Res. 47, 2995–3005. https://doi.org/10.1016/j.watres.2013.03.004

625 Dijksma, S.A.M., 2017. Kamerbrief staatssecretaris van infrastructuur en milieu.
626 https://doi.org/10.1007/s11156-014-0484-y

627 Duarte, D.J., Oldenkamp, R., Ragas, A.M.J., 2018. Modelling environmental antibiotic-resistance gene
628 abundance: A meta-analysis. Sci. Total Environ. 659, 335–341.
629 https://doi.org/10.1016/j.scitotenv.2018.12.233

630 ECHA, 2017. Guidance on information requirements and Chemical Safety Assessment Chapter R.7a:
631 Endpoint specific guidance. https://doi.org/10.2823/337352

632 Escher, B.I., Baumgartner, R., Koller, M., Treyer, K., Lienert, J., McArdell, C.S., 2011. Environmental
633 toxicology and risk assessment of pharmaceuticals from hospital wastewater. Water Res. 45,
634 75–92. https://doi.org/10.1016/j.watres.2010.08.019

635 European Commission, 2019. Union Register of medicinal products for human use [WWW
636 Document]. URL http://ec.europa.eu/health/documents/community-register/html/register.htm
637 (accessed 3.6.19).

638 Ford, A.T., Fong, P.P., 2016. The effects of antidepressants appear to be rapid and at environmentally
639 relevant concentrations. Environ. Toxicol. Chem. 35, 794–798. https://doi.org/10.1002/etc.3087

640 Gemeente Nijmegen, 2019. Bevolkingscijfers - Gemeente Nijmegen | Tableau Public [WWW
641 Document]. URL

https://public.tableau.com/profile/gemeentenijmegen#!/vizhome/Bevolkingscijfers/Bevolking (accessed 3.13.19).

Gemeente Utrecht, 2019. WistUdata | Gemeente Utrecht - Totaal aantal inwoners [WWW Document]. URL https://wistudata.nl/jive?presel_code=p635804133201299301 (accessed 3.13.19).

Herrmann, M., Olsson, O., Fiehn, R., Herrel, M., Kümmerer, K., 2015. The significance of different health institutions and their respective contributions of active pharmaceutical ingredients to wastewater. Environ. Int. 85, 61–76. https://doi.org/10.1016/j.envint.2015.07.020

Jelic, A., Rodriguez-Mozaz, S., Barceló, D., Gutierrez, O., 2014. ScienceDirect Impact of in-sewer transformation on 43 pharmaceuticals in a pressurized sewer under anaerobic conditions 8. https://doi.org/10.1016/j.watres.2014.09.033

Khan, U., Nicell, J., 2015. Human Health Relevance of Pharmaceutically Active Compounds in Drinking Water. AAPS J. 17, 558–585. https://doi.org/10.1208/s12248-015-9729-5

Kim S, Chen J, Cheng T, Gindulyte A, He J, He S, Li Q, Shoemaker BA, Thiessen PA, Yu B, Zaslavsky L, Zhang J, B.E., 2019. About [WWW Document]. https://doi.org/10.1093/nar/gky1033

Kivits, T., Boers, H.P., Beeltje, H., van Vliet, M., Griffioen, J., 2018. Presence and fate of veterinary antibiotics in age-dated groundwater in areas with intensive livestock farming 241, 988–998. https://doi.org/10.1016/j.envpol.2018.05.085

Kortenkamp, A., Backhaus, T., Faust, M., 2009. State of the Art Report on Mixture Toxicity. Report Contract N, 1–391. https://doi.org/http://ec.europa.eu/environment/chemicals/pdf/report_Mixture%20toxicity.pdf

Le Corre, K.S., Ort, C., Kateley, D., Allen, B., Escher, B.I., Keller, J., 2012. Consumption-based approach for assessing the contribution of hospitals towards the load of pharmaceutical residues in municipal wastewater. Environ. Int. 45, 99–111. https://doi.org/10.1016/j.envint.2012.03.008

Letzel, M., Metzner, G., Letzel, T., 2009. Exposure assessment of the pharmaceutical diclofenac based on long-term measurements of the aquatic input. Environ. Int. 35, 363–368. https://doi.org/10.1016/j.envint.2008.09.002

Macleod, S.L., Mcclure, E.L., Wong, C.S., 2007. Laboratory Calibration and Field Deployment of the Polar Organic. Environ. Toxicol. Chem. 26, 2517–2529. https://doi.org/10.1897/07-238.1

Moermond, C., 2016. Geneesmiddelen en waterkwaliteit.

Morley, S.K., Brito, T. V., Welling, D.T., 2018. Measures of Model Performance Based On the Log Accuracy Ratio. Sp. Weather 16, 69–88. https://doi.org/10.1002/2017SW001669

O'Brien, J.W.O., Phillip, A., Banks, W., Novic, A.J., Mueller, J.F., Jiang, G., Ort, C., Eaglesham, G., Yuan, Z., Thai, P.K., 2017. Impact of in-Sewer Degradation of Pharmaceutical and Personal Care Products (PPCPs) Population Markers on a Population Model. https://doi.org/10.1021/acs.est.6b02755

Oldenkamp, R., Huijbregts, M.A.J., Hollander, A., Versporten, A., Goossens, H., Ragas, A.M.J., 2013.

680 Spatially explicit prioritization of human antibiotics and antineoplastics in Europe. Environ. Int.
681 51, 13–26. https://doi.org/10.1016/j.envint.2012.09.010

682 Oosterhuis, M., Sacher, F., ter Laak, T.L., 2013. Prediction of concentration levels of metformin and
683 other high consumption pharmaceuticals in wastewater and regional surface water based on
684 sales data. Sci. Total Environ. 442, 380–388. https://doi.org/10.1016/j.scitotenv.2012.10.046

685 Radboudumc, 2016. Radboudumc Jaardocument 2014.

686 Richmond, E.K., Rosi, E.J., Walters, D.M., Fick, J., Hamilton, S.K., Brodin, T., Sundelin, A., Grace, M.R.,
687 2018. A diverse suite of pharmaceuticals contaminates stream and riparian food webs. Nat.
688 Commun. 9, 4491. https://doi.org/10.1038/s41467-018-06822-w

689 Rijksoverheid, n.d. Medicijnresten uit water [WWW Document]. URL
690 https://jamdots.nl/view/239/medicijnresten-uit-water (accessed 2.7.19).

691 Rizzo, L., Manaia, C., Merlin, C., Schwartz, T., Dagot, C., Ploy, M.C., Michael, I., Fatta-Kassinos, D.,
692 2013. Urban wastewater treatment plants as hotspots for antibiotic resistant bacteria and
693 genes spread into the environment: A review. Sci. Total Environ. 447, 345–360.
694 https://doi.org/10.1016/j.scitotenv.2013.01.032

695 Schulze, T., Weiss, S., Schymanski, E., von der Ohe, P.C., Schmitt-Jansen, M., Altenburger, R., Streck,
696 G., Brack, W., 2010. Identification of a phytotoxic photo-transformation product of diclofenac
697 using effect-directed analysis. Environ. Pollut. 158, 1461–1466.
698 https://doi.org/10.1016/j.envpol.2009.12.032

699 Schwaiger, J., Mallow, U., Ferling, H., 2004. Bayerisches Landesamt für Wasserwirtschaft Abteilung
700 Gewässerökologische Forschung Ökotoxikologische Auswirkungen von Arzneimitteln
701 Langzeitwirkungen bei Fischen Endbericht.

702 Smedes, F., Bakker, D., De Weert, J., 2010. The use of passive sampling in WFD monitoring.

703 Smedes, F., Beeltje, H., Jonker, C., 2013. Onderzoek en veldpilot van passive sampling met partitie-
704 en adsorptie- samplers.

705 Straub, J., 2013. An Environmental Risk Assessment for Human-Use Trimethoprim in European
706 Surface Waters. Antibiotics 2, 115–162. https://doi.org/10.3390/antibiotics2010115

707 Tisler, S., Zwiener, C., 2018. Formation and occurrence of transformation products of metformin in
708 wastewater and surface water. Sci. Total Environ. 628–629, 1121–1129.
709 https://doi.org/10.1016/j.scitotenv.2018.02.105

710 Triebskorn, R., Casper, H., Scheil, V., Schwaiger, J., 2007. Ultrastructural effects of pharmaceuticals
711 (carbamazepine, clofibric acid, metoprolol, diclofenac) in rainbow trout (Oncorhynchus mykiss)
712 and common carp (Cyprinus carpio). Anal. Bioanal. Chem. 387, 1405–1416.
713 https://doi.org/10.1007/s00216-006-1033-x

714 Tyler, C.R., Jobling, S., Sumpter, J.P., 1998. Endocrine disruption in wildlife: A critical review of the
715 evidence. Crit. Rev. Toxicol. 28, 319–361. https://doi.org/10.1080/10408449891344236

716 UMC Utrecht, 2017. Jaardocument UMC Utrecht 2016 165.

van Vlaardingen, P.L.A., Verbruggen, E.M.J., 2007. Guidance for the derivation of environmental risk limits within the framework of' International and national environmental quality standards for substances in the Netherlands' (INS). Revision 2007.

Verlicchi, P., Al Aukidy, M., Jelic, A., Petrović, M., Barceló, D., 2014. Comparison of measured and predicted concentrations of selected pharmaceuticals in wastewater and surface water: A case study of a catchment area in the Po Valley (Italy). Sci. Total Environ. 470–471, 844–854. https://doi.org/10.1016/j.scitotenv.2013.10.026

Wishart, D.S., Feunang, Y.D., Guo, A.C., Lo, E.J., Marcu, A., Grant, J.R., Sajed, T., Johnson, D., Li, C., Sayeeda, Z., Assempour, N., Iynkkaran, I., Liu, Y., Maciejewski, A., Gale, N., Wilson, A., Chin, L., Cummings, R., Le, D., Pon, A., Knox, C., Wilson, M., 2018. DrugBank 5.0 [WWW Document]. Nucleic Acids Res. https://doi.org/10.1093/nar/gkx1037

Wolf, J.C., Ruehl-Fehlert, C., Segner, H.E., Weber, K., Hardisty, J.F., 2014. Pathology working group review of histopathologic specimens from three laboratory studies of diclofenac in trout. Aquat. Toxicol. 146, 127–136. https://doi.org/10.1016/j.aquatox.2013.10.033

Zorginstituut Nederland, 2019. Farmacotherapeutisch Kompas [WWW Document]. URL https://www.farmacotherapeutischkompas.nl/ (accessed 3.7.19).