ENVIRONMENTAL AND SOCIO-ECONOMICAL ASSESSMENT OF MEASURES TO REDUCE PHARMACEUTICALS IN RIVERS

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DOCTORAL THESIS

ENVIRONMENTAL AND SOCIO-ECONOMICAL ASSESSMENT OF MEASURES FOR THE REDUCTION OF PHARMACEUTICALS IN RIVERS

Annex 1 - 4

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DOCTORAL PROGRAME IN WATER SCIENCE AND TECHNOLOGY

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WE DECLARE:

That the thesis "Environmental and socio-economical assessment of measures for the reduction of pharmaceuticals in rivers", presented by Vicent Pau Gimeno Melià to obtain a doctoral degree, has been completed under our supervision and meets the requirements to opt for an International Doctorate.

For all intents and purposes, we hereby sign this document.

Lluís Corominas Tabares   Joaquim Comas Matas

Girona, 17th of July of 2018

Universitat de Girona

ICRA Institut Català de Recerca de l'Aigua

DECLARATION OF AUTHORSHIP

I, Vicent Pau Gimeno Melià, declare that this thesis titled, “Environmental and socio-economical assessment of measures for the reduction of pharmaceuticals in rivers” and the work presented in it are my own. I confirm that:

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- Where I have consulted the published work of others, this is always clearly attributed.
- Where I have quoted from the work of others, the source is always given. With the exception of such quotations, this thesis is entirely my own work.
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- Where the thesis is based on work done by myself jointly with others, I have made clear exactly what was done by others and what I have contributed myself.

Signed:

Vicent Pau Gimeno Melià

Girona, 17th of July of 2018

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List of abbreviations and symbols

α: Percentage Removal of compound during ozonation and sand filtration

ϑ_h: Hydraulic retention time at a WWTP

7Q10: lowest 7-day average flow that occurs on average once every 10 years

AA-EQS: Annual Average - Environmental Quality Standard

AEMPS: Agencia Española de Medicamentos y Productos Sanitarios (Spanish Agency of Medicines and Medical Devices)

AF: Assessment Factor

API: Active Pharmaceutical Ingredient

AS: Activated Sludge

ATC: Anatomical Theraputic Chemical

BAFU: Bundesamt für Umwelt (Swiss Federal Office for the Environment)

CSTR: completely stirred reactor

DDD: Defined Daily Dose

DOC: Dissolved organic carbon

DREAM: Differential Evolution Adaptive Metropolis

E1: Estrone

E2: 17β-estradiol

EC: European Commission

ECDC: European Centre for Disease Prevention and Control

ECHA: European Chemicals Agency

EE2: 17α-ethynylestradiol

EMA: European Medicines Agency

EQS: Environmental Quality Standards

ERA: Environmental Risk Assessment

EU: European Union

F: Lumped factor that includes the fraction of the pharmaceutical parent compound that is excreted to toilets, discharged directly via sinks, washed off from skin or clothes and degraded in sewers.

HRT: Hydraulic Retention time in a river stretch

K_d: Solid–water distribution coefficient of a compound

k_{river}: Aggregated first order elimination rate of a compound in a stretch

k_{WWTP}: Aggregated pseudo-first order elimination rate of a compound in WWTPs

$L_{downstream,stretch}$: Load of compound at the downstream section of a river stretch

$L_{effluent}$: WWTP effluent loads of a compound

L_{inf}: WWTP influent load of a compound

$L_{stretch}$: Length of river stretch

$L_{upstream, stretch}$: Load of compound at the upstream section of a river stretch

LC-MS: Liquid chromatography–mass spectrometry

LIF: Läkemedelsindustriföreningen (Swedish Association of the Pharmaceutical Industry)

LOEC: Lowest Observed Effect Concentration

MAC-EQS: Maximum Acceptable Concentration - Environmental Quality Standard

MCMC: Markov Chain Monte Carlo

MFT: Microcontaminant Fate and Transport Model
NOEC: No Observed Effect Concentration
NSAID: Nonsteroidal anti-inflammatory drugs
NSGA: Non-dominated Sorting Genetic Algorithm
OECD: Organisation for Economic Co-operation and Development
OTC: Over The Counter
PAC: Powdered Activated Carbon
PDF: Probability Distribution Function
PE: Population Equivalent
PEC: Predicted Environmental Concentration
PNEC: Predicted No Effect Concentration
Qinf: WWTP influent flow
Qeff: WWTP effluent flow
$Q_{stretch}$**:** Stretch water flow
R^2: Nash & Sutcliffe goodness-of-fit index
RBA: River Basin Authorities
REACH: Registration, Evaluation, Authorisation and restriction of Chemicals
SPE: Solid Phase Extraction
SRC: Standard Regression Coefficients
v: Stretch water velocity
WWTP: Wastewater Treatment Plant
Xss: Mixed liquor suspendid solids concentration

List of publications

The following list contains the journal publications resulting from this doctoral thesis:

P. Gimeno, R. Marcé, Ll. Bosch, J. Comas, Ll. Corominas, 2017. Incorporating model uncertainty into the evaluation of interventions to reduce microcontaminant loads in rivers, Water Research, 124, 415-424

P. Gimeno, J. Severyns, V, Acuña, J. Comas, Ll. Corominas, 2018. Balancing environmental quality standards and infrastructure upgrade costs for the reduction of pharmaceutical loads in rivers, Water Research, 143, 632-641

Summary

Pharmaceuticals are inherently biologically active substances and ubiquitous water contaminants that have shown detrimental effects on aquatic organisms at low concentrations. The presence of pharmaceuticals in rivers is starting to be regulated by European and worldwide environmental legislations. Therefore, countries are starting to plan and implement measures (Wastewater treatment plants (WWTP) upgrades and source control) to reduce pharmaceutical concentrations in rivers. Decision-makers use models to predict the fate, removal and transport of pharmaceuticals in rivers and to evaluate the effectiveness of measures for the reduction of pharmaceutical concentrations at catchment scale. However, there is still large uncertainty around the processes driving the fate, removal and transport of pharmaceuticals in rivers which compromises decision-making. Moreover, the cost of implementing WWTP upgrades at catchment or national level can be daunting, hence the development of tools that optimize the upgrading costs are indeed required. In addition, there is little scientific information on the effectiveness of source control measures for the reduction of pharmaceutical concentrations at catchment scale.

Thus, the aim of this thesis is to provide decision-makers with modelling tools for the evaluation of measures (WWTP upgrades and source control) to reduce pharmaceutical concentrations in rivers. The modelling tools include uncertainty in the whole decision-making process.

The first section describes the development and calibration of a Microcontaminant Fate and Transport model for the estimation of pharmaceutical concentrations in rivers including uncertainty. The model was successfully calibrated and the uncertainty in the concentrations decreased after using Bayesian inference and measurements of diclofenac concentrations in WWTPs and rivers.

The second section deals with the influence that the model uncertainty has on the selection of WWTP upgrades designed to decrease pharmaceutical concentrations (i.e. diclofenac) in rivers. For this purpose, we evaluated different scenarios of model uncertainty and WWTP diclofenac removal efficiencies using the model developed in the first section. We concluded that the installation of tertiary treatments results in apparent reductions of diclofenac concentrations regardless of the uncertainty. However, apparent reductions after upgrading secondary treatments require lower uncertainty.

The third section shed light on the relationship between proposed Environmental Quality Standards (EQS) for pharmaceuticals (i.e. diclofenac) and the optimal cost of the WWTP upgrades at catchment level. For this purpose, we optimized the number of WWTPs requiring an upgrade for different EQS and uncertainty levels using multi-objective genetic algorithms and the model calibrated in the first section. We used minimization of costs and total EQS exceedance as the objective functions. We found that there is a non-linear relationship between EQS and the costs and, hence there is an optimal EQS that balances costs and ecosystem protection.

The fourth section illustrates the effect that source control measures (i.e. substitution of diclofenac by naproxen) have on the required WWTP upgrades for the reduction of pharmaceuticals in rivers. For this purpose, we optimized the number of WWTP upgrades for different levels in the consumption of diclofenac and naproxen, different EQS and uncertainty levels. We found that apparent reductions in the number of WWTP upgrades are achieved only when more than half of the diclofenac consumed is substituted by naproxen. However, we conclude that any substitution between pharmaceuticals requires a model-based evaluation because the substitution may be harmful for the environment under specific scenarios of EQS.

Finally, we discussed the factors that influence the selection of measures for the reduction of pharmaceuticals: uncertainty in the estimates of pharmaceutical concentrations, EQS setting, hydrological conditions and consumption of pharmaceuticals. Therefore, we recommend decision-makers to follow adaptive management of pharmaceuticals at catchment level in response to the changing factors that influence the selection of measures.

Resum

Els fàrmacs son substàncies biològicament actives intrínsecament i contaminants de l'aigua molt penetrants que han mostrat efectes perjudicials en organismes aquàtics a concentracions baixes. Legislacions ambientals en Europa i en la resta del món estan començant a regular la presència d'aquests productes en els rius. En conseqüència, alguns països estan començant a planificar i implementar mesures (millores en les EDARs i control de les fonts de la contaminació) per reduir les concentracions de fàrmacs en rius. Els responsables en la presa de decisions utilitzen model per a estimar el destí, l'eliminació i el transport de fàrmacs i per a avaluar l'efectivitat de les mesures orientades a reduir les concentracions d'aquests productes a nivell de conca. Malgrat això, encara existeix molta incertesa al voltant dels processos que descriuen el destí, l'eliminació i el transport de fàrmacs en rius, la qual cosa compromet la presa de decisions. A més, els costos d'implementar millores a les EDARs a nivell de conca o nacional pot ser aclaparant, per la qual cosa es requereix desenvolupar eines que optimitzen aquests costos A més, existeix poca informació científica sobre l'efectivitat de les mesures de control de les fonts per a la reducció de les concentracions de fàrmacs a nivell de conca.

Per tant, l'objectiu d'aquesta tesi és proporcionar eines de modelització als responsables en la presa de decisions per avaluar mesures (millores en les EDARs i control de les fonts de la contaminació) que reduïsquen les concentracions de fàrmacs en rius. Aquestes eines tenen en compte les incerteses en tot el procés de la presa de decisions.

La primera secció descriu el desenvolupament i la calibració d'un model per al destí i transport de microcontaminants que estima les concentracions de fàrmacs en rius, tenint en compte la incertesa. El model es va calibrar amb èxit i la incertesa en les concentracions va disminuir després d'utilitzar Inferència Bayesiana i mesures de concentracions de diclofenac en EDARs i rius.

La segona secció tracta sobre la influència que té la incertesa del model en la selecció de millores a realitzar en les EDARs i dissenyades per a disminuir les concentracions de fàrmacs (diclofenac, en particular) en rius. Per a aquest punt, avaluem diferents escenaris d'incertesa del model i diferents eficiències d'eliminació de diclofenac en les EDARs utilitzant el model anteriorment desenvolupat. Concloem que la instal·lació de tractaments terciaris dóna com a resultat reduccions evidents en les concentracions de diclofenac, independentment de la incertesa. No obstant això, es necessita menor nivell d'incertesa per a obtenir reduccions evidents després de millorar els tractaments secundaris.

La tercera secció posa llum sobre la relació entre les Normes de Qualitat Ambiental (NQA) propostes per a fàrmacs (diclofenac, en particular) i els costos òptims de les millores en les EDARs a nivell de conca. Per a aquest propòsit, optimitzem el nombre d'EDARs que requereixen una millora per a diferents NQAs i nivells d'incertesa utilitzant algoritmes genètics multi-objectius i el model desenvolupat en la primera secció. Com a funcions objectiu, considerem la minimització de costos i d'excedència total sobre les NQAs. Concloem que existeix una relació no lineal entre NCAs i costos i, per tant, existeix una NQA òptima que equilibra costos i protecció del medi ambient.

La quarta secció descriu l'efecte que tenen les mesures de control de les fonts (substitució de diclofenac per naproxen, en particular) en les millores de les EDARs requerides per a la reducció de fàrmacs en rius. A aquest efecte, optimitzem el nombre de millores per a diferents nivells en el consum de diclofenac i naproxen, diferents NQAs i nivells d'incertesa. Trobem que reduccions evidents en el nombre de millores s'aconsegueixen només quan més de la meitat del diclofenac consumit es substitueix per naproxen. No obstant això, concloem que qualsevol substitució entre fàrmacs requereix una avaluació basada en models ja que la substitució pot ser perjudicial per al medi ambient amb específiques NQAs.

Finalment, analitzem els factors que influeixen en la selecció de mesures per a la reducció de fàrmacs: la incertesa en les estimacions de les concentracions de fàrmacs, l'establiment de NQAs, la condició hidrològica i el consum de fàrmacs. Per tant, recomanem als responsables en la presa de decisions que seguisquen una gestió modulada contra els fàrmacs a nivell de conca, en resposta als factors canviants que influeixen en la selecció de les mesures.

Resumen

Los fármacos son sustancias biológicamente activas intrínsecamente y contaminantes del agua muy extendidos que han mostrado efectos perjudiciales en organismos acuáticos a bajas concentraciones. Legislaciones ambientales europeas y a escala mundial están empezando a regular la presencia de estos productos en los ríos. En consecuencia, algunos países están empezando a planificar e implementar medidas (mejoras en EDARs y control de la contaminación en origen) para reducir las concentraciones de fármacos en ríos. Los responsables en la toma de decisiones usan modelos para estimar el destino, la eliminación y el transporte de fármacos y para evaluar la efectividad de las medidas orientadas a reducir las concentraciones de estos productos a nivel de cuenca. Sin embargo, todavía existe una gran incertidumbre en torno a los procesos que describen el destino, la eliminación y el transporte de fármacos en ríos, lo que compromete la toma de decisiones. Además, el coste de implementar mejoras en las EDARs a nivel de cuenca o nacional puede ser abrumador, por lo que se requiere desarrollar herramientas que optimicen estos costes. Además, existe poca información científica sobre la efectividad de las medidas de control en origen para la reducción de las concentraciones de fármacos a nivel de cuenca.

Por lo tanto, el objetivo de esta tesis es proporcionar a los responsables en la toma de decisiones de herramientas de modelización que evalúen medidas (mejoras en las EDARs y control de la contaminación en origen) para reducir las concentraciones de fármacos en ríos. Estas herramientas tienen en cuenta las incertidumbres en todo el proceso de toma de decisiones.

La primera sección describe el desarrollo y la calibración de un modelo de destino y transporte de microcontaminantes que estima las concentraciones de fármacos en ríos, teniendo en cuenta la incertidumbre. El modelo se calibró con éxito y la incertidumbre en las concentraciones se redujo tras utilizar Inferencia Bayesiana y mediciones de concentraciones de diclofenaco en EDARs y ríos.

La segunda sección trata sobre la influencia que tiene la incertidumbre del modelo en la selección de mejoras a realizar en las EDARs y diseñadas para disminuir las concentraciones de fármacos (diclofenaco, en particular) en ríos. Para este propósito, evaluamos diferentes escenarios de incertidumbre del modelo y diferentes eficiencias de eliminación de diclofenaco en las EDARs utilizando el modelo anteriormente desarrollado. Concluimos que la instalación de tratamientos terciarios da como resultado reducciones evidentes en las concentraciones de diclofenaco, independientemente de la incertidumbre. No obstante, se necesita menor nivel de incertidumbre para obtener reducciones evidentes tras mejorar los tratamientos secundarios.

La tercera sección arroja luz sobre la relación entre las Normas de Calidad Ambiental (NCA) propuestas para fármacos (diclofenaco, en particular) y el coste óptimo de las mejoras en las EDARs a nivel de cuenca. Para este propósito, optimizamos el número de EDARs que requieren una mejora para diferentes NCAs y niveles de incertidumbre utilizando algoritmos genéticos

multi-objetivos y el modelo desarrollado en la primera sección. Como funciones objectivo, consideramos la minimización de costes y de excedencia total sobre NCAs. Concluimos que existe una relación no lineal entre NCAs y costes y, por lo tanto, existe una NCA óptima que equilibra costes y protección del medio ambiente.

La cuarta sección describe el efecto que tienen las medidas de control en origen (sustitución de diclofenaco por naproxeno, en particular) en las mejoras de las EDARs requeridas para la reducción de fármacos en ríos. Con este fin, optimizamos el número de mejoras para diferentes niveles en el consumo de diclofenaco y naproxeno, diferentes EQS y niveles de incertidumbre. Encontramos que reducciones evidentes en el número de mejoras se logran sólo cuando más de la mitad del diclofenaco consumido se sustituye por naproxeno. Sin embargo, concluimos que cualquier sustitución entre fármacos requiere una evaluación basada en modelos ya que la sustitución puede ser perjudicial para el medio ambiente con específicas NCAs.

Finalmente, analizamos los factores que influyen en la selección de medidas para la reducción de fármacos: la incertidumbre en las estimaciones de las concentraciones de fármacos, el establecimiento de NCAs, la condición hidrológica y el consumo de fármacos. Por lo tanto, recomendamos a los responsables en la toma de decisiones que sigan una gestión modulada contra los fármacos a nivel de cuenca, en respuesta a los factores cambiantes que influyen en la selección de las medidas.

1. Introduction

1.1 Sources, fate and toxicity of pharmaceuticals

Current and future use of pharmaceuticals

An active pharmaceutical ingredient (API or just pharmaceutical from now on) is a substance used in medicines intended to furnish pharmacological activity or to otherwise have direct effect in the diagnosis, cure, mitigation, treatment or prevention of disease, or to have direct effect in restoring, correcting or modifying physiological functions in human beings (World Health Organisation, 2009). About 3,000 active pharmaceutical substances are currently authorized in the EU, with a wide variability across Member States (Touraud et al., 2011). The number of new pharmaceuticals per year and the volume of medicines consumed in Europe have nearly doubled in the last decade (OECD Health Statistics, 2017) The increase was driven by the use of antimicrobials (ECDC, 2017) as well as pharmaceutical drugs related to ageing and chronic diseases (antihypertensives, cholesterol lowering drugs, antidiabetics, and antidepressants; OECD Health Statistics, 2017). Figure 1 shows the increase in the consumption of pharmaceuticals of 9 anatomical main groups (ATC groups) in 15 OECD countries from 2000 to 2016 (OECD Health Statistics, 2017). Cardiovascular pharmaceuticals showed the higher increase during this period (Figure 1). A similar trend in the consumption of pharmaceuticals is forecasted in 2050 following demographic projections in Europe (Aa et al., 2011).

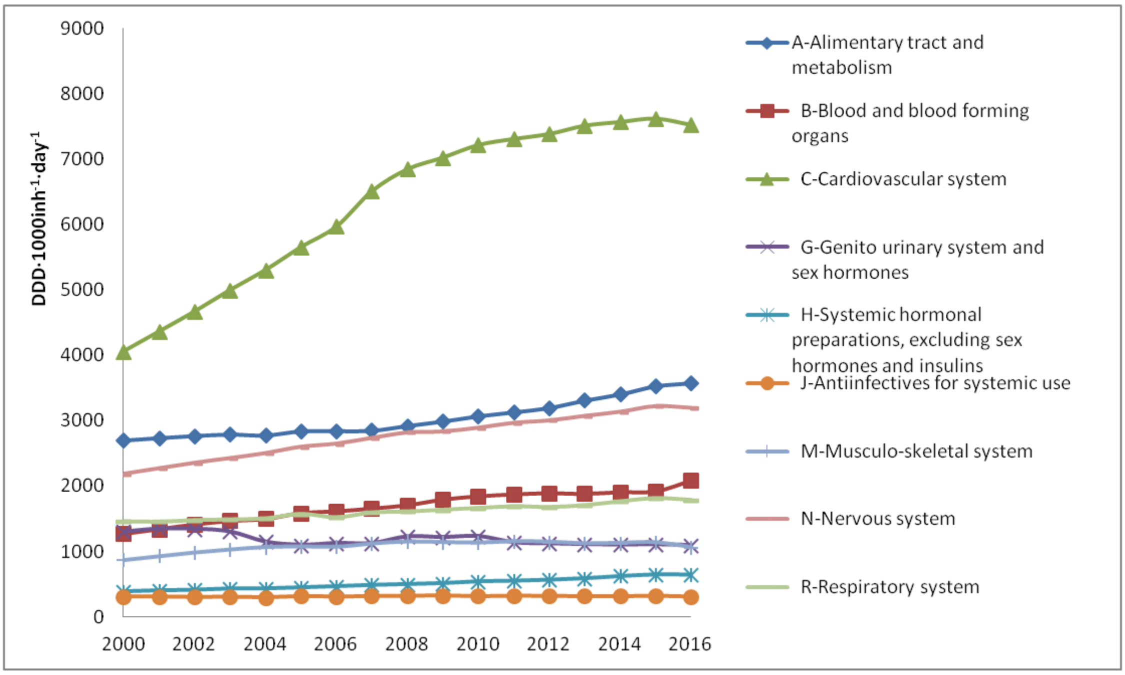


Figure 1. Total consumption of pharmaceuticals (DDD·1000inh^{-1}·day^{-1}) of 9 anatomical groups (A- Alimentary tract and metabolism, B - Blood and blood forming organs, C- Cardiovascular system, G- Genito-urinary system and sex hormones, H - Systemic hormonal preparations, excluding sex hormones and insulins, J - Antiinfectives for systemic use, M - Musculo-skeletal system, N - Nervous system and R - Respiratory system) in 15 OECD countries (Australia, Belgium, Czech Republic, Denmark, Estonia, Finland, Germany, Hungary, Iceland, Netherlands, Norway, Portugal, Slovak Republic, Spain and Sweden) from 2000 to 2016 (OECD Health Statistics, 2017)

Why are pharmaceuticals present in the environment?

Pharmaceuticals are consumed in hospitals or purchased in pharmacies either with a physician prescription or over-the-counter (OTC or without a prescription). These compounds are excreted with urine and feces either as an active substance (unchanged drug) or as a metabolite (Ternes, 1998) reaching the sewers. Pharmaceuticals may also be discharged to sewers by improper disposal via toilets and sinks. If drugs are administered topically, part of the parent compound can also be discharged after showering or along with the washing machine drainage (Bound & Voulvoulis, 2005; Osorio et al., 2014). Negligible removal of most of the pharmaceuticals is expected along the sewer pipes (Jelic et al., 2015) Therefore, pharmaceutical compounds reach the wastewater treatment plants (WWTPs) in concentrations that vary from few $ng \cdot L^{-1}$ to hundreds $\mu g \cdot L^{-1}$ (Daughton & Ternes, 1999). Figure 2 shows a sketch including the different sources of pharmaceuticals in Wastewater Treatment Plants (WWTPs).

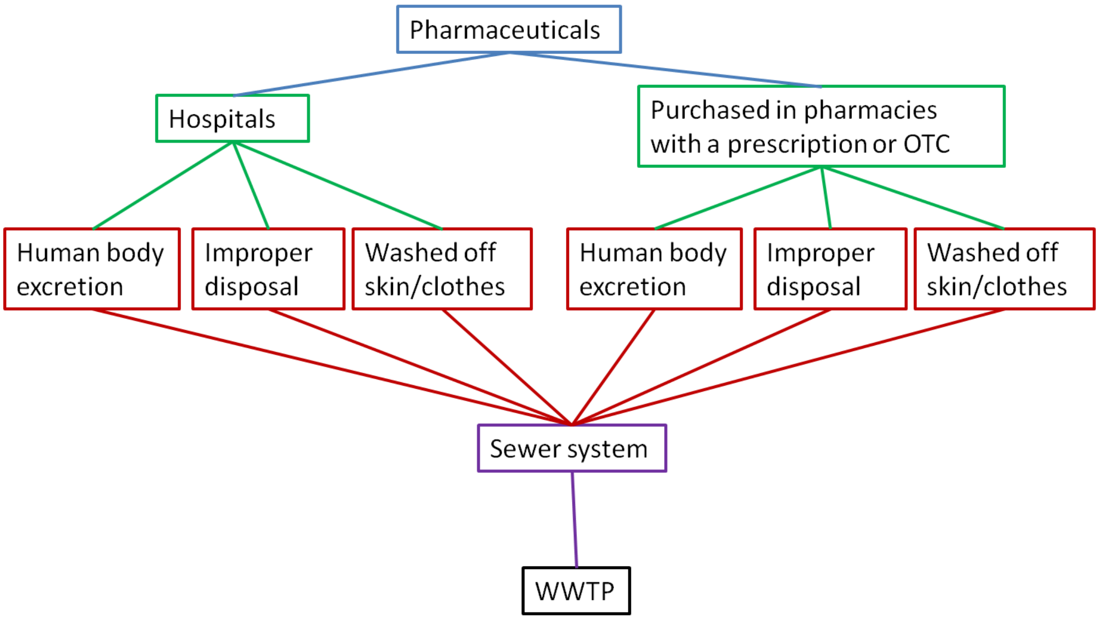


Figure 2. Sources of pharmaceuticals in WWTP influents.

The removal rate of pharmaceuticals during conventional WWTPs (conventional primary treatment followed by secondary activated sludge reactors) is compound-specific (Carballa et al., 2004). The main removal mechanisms in primary treatments are sorption onto coarse solids and sedimentation. A combination of biodegradation/biotransformation due to suspended biomass and sorption onto particles, flocs and sludge are the main removal mechanisms in secondary treatments (Ternes & Joss, 2006). The efficacy in removing pharmaceuticals by primary treatments is in general poor (Ternes & Joss, 2006). The removal rate in the activated sludge reactors varies significantly; for some compounds the removal is very high (e.g., ibuprofen is very well removed (removals rates greater than 90%; Joss et al., 2005) by biotransformation and norfloxacin is well removed (greater than 80%; Golet et al., 2003) by sorption onto sludge) but others are recalcitrant (e.g. erythromycin, azythromycin, diclofenac; Gros et al., 2010; Jelic et al., 2011). Thus, we expect the occurrence of pharmaceutical loads in our water bodies (i.e. rivers, lakes, seas) as well as in soils (Petrovic et al., 2003)

Environmental toxicity of pharmaceuticals

Pharmaceuticals are inherently biologically active substances. They are designed to be resistant to biodegradation because metabolic stability usually improves pharmacological action. However, this contributes to their environmental persistence (Ternes & Joss, 2006; Khetan & Collins, 2007; Petrovic et al. , 2009). Human pharmaceuticals are ubiquitous water contaminants that have shown detrimental effects on aquatic organisms at low environmental concentrations ($ηg·L^{-1}$-$µg·L^{-1}$; Huerta et al., 2015, Acuña et al., 2015b). Some ground-breaking examples were the collapse of a fish population at the Experimental Lakes Area in north-western Ontario (Canada) after exposure to a synthetic estrogen (Kidd et al., 2007) or alterations in fish behaviour after exposure to a psychoactive drug (Huerta et al., 2016). Furthermore, complex mixtures of pharmaceuticals and metabolites may interact and show concentration additivity (Altenburger et al., 2004; Brian et al., 2005). Indirect effects of veterinary pharmaceuticals may happen if they are transferred within the food web (Kümmerer, 2009). The most reported example was the decline of vulture populations in India due to feeding vultures with diclofenac-treated livestock (Oaks et al., 2004). Risks for human health due to environmental exposure to pharmaceuticals have been considered unlikely (Cunningham et al., 2009). Besides, wastewater is considered to be the main source of entry of antibiotic-resistant genes into the aquatic environment (along with manure and sludge). As a consequence, organisms that cause infections are becoming resistant to common prescribed antibiotic treatments resulting in prolonged illness and greater risk of death (Marti et al., 2013)

1.2 Legislation on pharmaceuticals in the environment

On one hand, an Environmental Risk Assessment (ERA) is required for all new marketing authorization applications for medicinal products (Directive 2001/83/EC, as amended; European Commission, 2001). ERA consists of 2 phases. The first phase estimates the exposure of the environment to the pharmaceutical substance by calculating Predicted Environmental Concentrations (PEC). In the second phase, an environmental fate and effect analysis is performed by comparing PECs and Predicted No Effect Concentrations (PNECs). PNECs are calculated by applying an assessment factor (AF) to the lowest no-observed-effect-concentration (NOEC) result from relevant long-term toxicity tests (European Medicines Agency, 2006)

On the other hand, the European Commission (2015) included three hormones (EE2, E2 and E1), diclofenac and three antibiotics (Erythromycin, Clarithromycin and Azithromycin) in the “watch list” of substances which require targeted monitoring across the EU. The “watch list” supports the prioritization process in future reviews of the Priority Substances Directive (Directive 2008/105/EC; European Commission, 2008). The Directive sets environmental quality standards (EQS) for the substances in surface waters (river, lake, transitional and coastal) as annual average concentrations (AA-EQS protection against prolonged exposure) and maximum acceptable concentrations (MAC-EQS protection against short term concentration peaks). While PNEC is just a part of a risk assessment, EQS is an overall threshold that protects all receptors and routes. However, the procedures for estimating AA-EQS (relevant for pharmaceuticals) and PNECs in surface waters (guidance REACH; ECHA, 2008) are the same (use of the same ecotoxicity data and assessment factors) so both values usually match (European Commission, 2011). The establishment of EQSs for Priority Substances results from a scientific process (based on ecotoxicological studies) and a political process (i.e. in the European Union (EU), amendments to the EQS Directive 2008/105/EC are negotiated in the European Council and the European Parliament; European Commission, 2012). Good chemical status is reached for a water body when it complies with the EQS for all the priority substances. Thus, European countries should implement measures (included in the River Basin Management Plans of the Water Framework Directive; European Commission, 2000) with the aim of achieving good chemical status in their water bodies. ***The assessment of measures for reducing the pharmaceutical loads in water bodies is the focus of this thesis***, as described in the objectives section.

Similarly to EU, USA implemented the Drinking Water Contaminant Candidate List and Regulatory Determination (USEPA, 2017) including one antibiotic (Erythromycin), three hormones (EE2, E2 and E1), nitroglycerin (treatment of systemic sclerosis) and quinoline (anti-malarial). Moreover, the Global Water Research Coalition (GWRC, 2008) developed a Priority List of 44 Pharmaceuticals Relevant for the Water Cycle. The Ecotox centre (2017) in Switzerland has proposed Environmental Quality Standards (EQS) for 20 pharmaceuticals and steroidal estrogens and 4 transformation products which will be added in the Annex 2 of the Swiss Water Protection Ordinance as numerical requirements for water quality. Sweden has developed an Environmental classification of pharmaceuticals by which pharmaceuticals companies assess and publish the environmental risks, degradation and bioaccumulation of their marketed substances in Sweden (available at www.fass.se; Carlsson et al., 2006).

Nevertheless, despite the regulatory efforts, the information regarding the environmental risk is not sufficient for the majority of pharmaceuticals currently on the EU market. This is because of the limited knowledge on environmental occurrence and the insufficient publically available data on the ecotoxicology (especially chronic exposure, ecotoxicity of mixtures) of many pharmaceuticals and their transformation products (European Commission, 2016c) Harmonizing the derivation of EQS for pharmaceuticals (e.g. diclofenac) among EU state members is currently being discussed within Expert Working Groups in the European Commission (Kase et al., 2011)

Challenge 1

Even though there are guidelines available on how to derive EQS for chemicals (European Commission, 2011), the approaches differ among countries and territories (European Commission, 2012; Ecotox centre, 2017). Taking diclofenac as an example, several EQSs have been proposed in Europe, ranging from 10 $ng \cdot L^{-1}$ (European Medicines Agency, 2006) to 100 $ng \cdot L^{-1}$ (European Commission, 2012). The selection of EQS should be fully consistent with the precautionary principle, but the economic implications (i.e. cost of the measures to reduce concentrations) surrounding the establishment of an EQS are not fully understood.

Our hypothesis is that there is a balance between EQS selection and the investment that needs to be considered in decision-making. For diclofenac in particular, the number of European river stretches exceeding a potential EQS increases exponentially as the EQS decreases from 100 $ng \cdot L^{-1}$ to 10 $ng \cdot L^{-1}$ (Figure 3, Johnson et al., 2013; Kehrein et al., 2015). We expect a similar relationship between the potential EQS and the corresponding investment to avoid EQS exceedance. ***The first challenge is to evaluate the relationship between the potential EQS for diclofenac and the investment required to avoid EQS exceedance.***

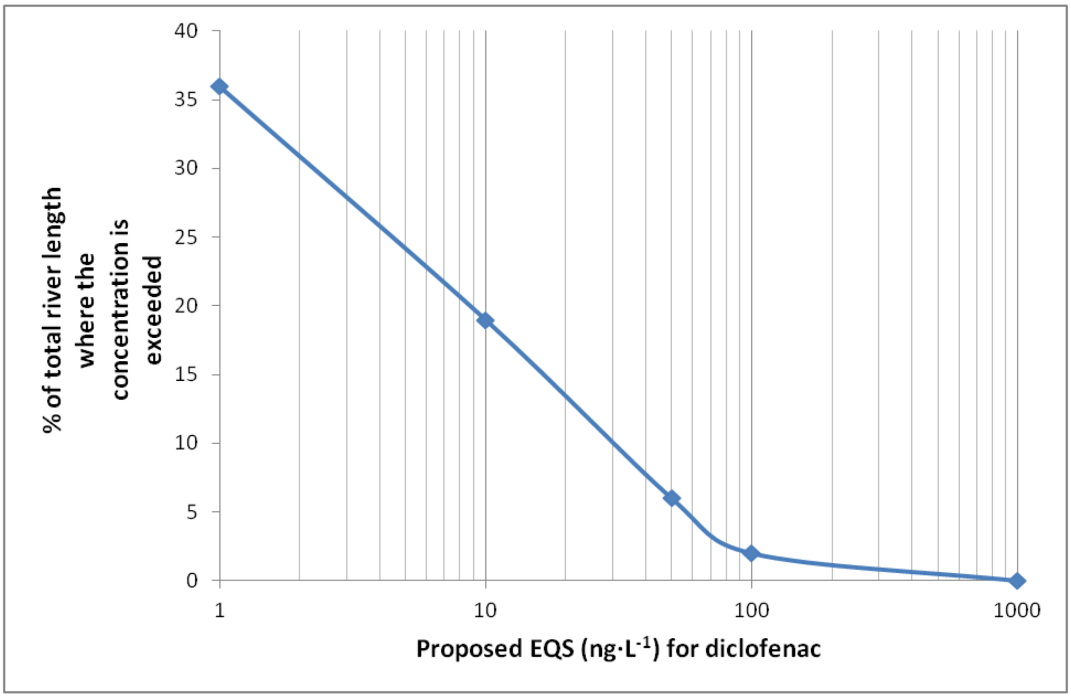


Figure 3. Percentages of total European river length where the concentrations of diclofenac exceed the proposed EQS. Extracted from Johnson et al. (2013).

1.3 Measures to reduce the discharge of pharmaceutical loads into rivers

Opportunities for reducing the input of pharmaceuticals into the aquatic environment are possible by taking advantage of several different approaches (Kümmerer, 2009; Kümmerer & Hempel, 2009; BAFU, 2009; Hillenbrand et al., 2014, Mulder et al., 2015)

On one hand, the removal of pharmaceuticals in conventional WWTPs can be enhanced by optimizing the operational parameters of the activated sludge process, for example, increasing the aeration time (Suarez et al., 2010), sludge age (Carballa et al., 2004) or the number of reactors in cascade (Joss et al., 2006). However, these actions do not completely remove most of the recalcitrant pharmaceuticals.

On the other hand, installing advanced treatment techniques at existing WWTPs have the potential to significantly remove both known and unknown substances (precautionary principle, European Commission, 2016a). Two technologies are mainly tested and implemented in full scale: the oxidation of chemicals with ozone and the adsorption onto activated carbon (Hollender et al., 2009, Reungoat et al., 2010, Margot et al., 2013). Specific substances are removed more efficiently by ozone but powdered activated carbon effectively removes a wider range of pollutants (Margot et al., 2013).The installation of a sand filter would also be needed to remove the toxic sub-products formed after ozonation and the remaining small PAC particles from the wastewater effluent (Mulder et al., 2015). However, the cost of implementing these technologies at catchment/national level can be daunting and require considerable additional energy requirements (Owen & Jobling, 2012; Johnson & Sumpter, 2015). For the capital and operating costs, Hillenbrand et al. (2014) estimated that the upgrade of all German WWTPs serving more than 5,000 population equivalent (PE) would cost approximately 1.3 billion € annually (3,013 WWTPs requiring an upgrade for a total of 82 M inhabitants in Germany). The Swiss Federal Office for the Environment (BAFU, 2012) estimated that the upgrade of the required 123 WWTPs would cost 1 billion € in total (0.12 billion € annually, for a total of 8.5 M inhabitants in Switzerland). Provisional estimates by the UK government showed that the upgrade of 1,360 WWTPs in England and Wales would cost between 32 and 37 billion € in total (Owen & Jobling, 2012).

The investment and operational costs of ozonation and activated carbon have been assessed by BAFU (2012), Hillenbrand et al. (2014) and Mulder et al. (2015) based on the full-scale practice in Germany and Switzerland. The resulting costs varied from 0.1 to 0.3 $€\cdot m^{-3}$, with ozonation being the cheapest technology for the removal of pharmaceuticals. However the final cost considerably depends on the amount of treated flow, the plant size, the characteristics of the treated secondary effluent and the existing local infrastructure (Mulder et al., 2015)

Source control of pharmaceuticals aims to reduce the emission of these substances at source. This includes the promotion of green pharmacy that is the design of more environmentally-benign products (Sanderson, 2011), lower dose prescriptions of drugs and prescription of drugs that are better removed in WWTPs (Daughton & Sue Ruhoy, 2013), public awareness campaigns on the purchase of more environmentally-benign OTC products (Interreg IV B Nopills project, 2015) or take-back schemes (Bound & Voulvoulis, 2005). However, the success of these measures can only be expected on the long-term and some of these (e.g. restrictions on the use of drugs) are controversial due to the unquestionable benefits of medicines (Eggen et al., 2014) Thus, end-of-pipe measures would be still necessary to prevent the discharge of pharmaceuticals to the environment (Eggen et al., 2014). In any case, source control measures need to be carefully designed between both Healthcare and Environmental Authorities (Kümmerer & Hempel, 2009). A good example of such collaboration was a pilot study conducted in the Netherlands in 2016 aimed to prescribe more environmentally-benign drugs. They found that diclofenac (drug poorly removed in conventional WWTPs) prescriptions could be reduced by 40% while naproxen (better removed in WWTPs compared to diclofenac) prescriptions increased by 50% (Grinten et al., 2016) Another example was the separate collection of Iodinated X-ray contrast media in 2 hospitals in Berlin. After the urine collection in the 5-month experiment, 5.2 kg of organic iodine could be kept away from the wastewater (Schuster et al., 2006).

Challenge 2

The management strategies for the reduction of pharmaceuticals at catchment level include a combination of source control (e.g. prescription of more environmentally-benign drugs) and end-of-pipe measures (e.g. upgrading WWTPs with a tertiary treatment). The importance of combining both management strategies for the reduction of pharmaceuticals has already been discussed in Eggen et al. (2014); Hillenbrand et al. (2014); van Wezel et al. (2017). The effectiveness of end-of-pipe measures has already been evaluated at a catchment level using model-based approaches (Kehrein et al., 2015; Ort et al., 2009). However, the effectiveness of source control measures in reducing the concentrations in freshwater ecosystems has been poorly addressed in literature. For instance, Hillenbrand et al. (2014) assessed the compliance with PNEC for diclofenac, ibuprofen and sulfamethoxazole in the Neckar river basin (Germany) when the total consumption (total amount that was purchased with a prescription and OTC in pharmacies) of these drugs decreases by 20% using MoRe (Modelling tool for the management of pollutant emissions in River Basins; Fuchs et al., 2017). They found that "20% less total consumption" did not contribute to a significant improvement of the water quality nor "20% less total consumption" on top of the upgrade of every WWTP with more than 50,000 PE. Only upgrading every WWTP larger than 10,000 PE (regardless of whether pharmaceuticals consumption decreases or not) resulted in reductions of concentrations below PNEC in almost the entire basin. However, Hillenbrand et al. (2014) did not justify which source control measure could result in a reduction of 20% in the total consumption nor evaluate the effect of higher reduction rates on the environment.

Our hypothesis is that larger reductions in the total consumption of pharmaceuticals could lead to significant reductions in the number of WWTP upgrades and enormous savings in the cost of these upgrades. So far, no study has assessed which reduction rate in the consumption would be required to significantly avoid WWTP upgrades nor the kind of source control measure that would achieve this reduction rate. Thus, ***the second challenge would be to evaluate the effect that source control measures have on the required end-of-pipe measures for the reduction of pharmaceuticals at catchment scale.***

1.4 Evaluation of measures to reduce pharmaceutical loads in rivers

Models of microcontaminant fate and transport (MFT) in wastewater treatment plants (WWTPs) and receiving rivers have been developed and used to assist decision-making in the field of water quality management (QUAL2E; USEPA, 1985, AQUASIM; Reichert, 1994, ChemCAN, Mackay et al., 1996; GREAT-ER, Feijtel et al., 1997, GWAVA, Dumont et al., 2012; PhAtE, Anderson et al., 2004; IUWS_MP model library, Vezzaro et al., 2014; SAGIS, Comber et al., 2013, among others; Table 1). These models have proven to be very useful in chemical risk assessments due to their relatively low complexity (Hollander et al., 2007). Concerning pharmaceuticals, MFT models have been applied to estimate exposure concentrations and their associated risks quotients for human health and the environment (Oldenkamp et al., 2013). They have been also used to conduct hot-spot analysis as the idenfification of river stretches with concentrations of pharmaceuticals exceeding PNECs/EQS. For instance, Johnson et al. (2013) assessed the number of river stretches in Europe exceeding proposed EQS for Ethinylestradiol, Estradiol, and Diclofenac using GWAVA. Finally, MFT models have been used to evaluate measures for the reduction of pharmaceutical river concentrations. For example, Kehrein et al. (2015) evaluated the effect of upgrading a WWTP with activated carbon and of redirecting secondary effluent to a neighbouring WWTP using GREAT-ER with the goal of reducing the diclofenac concentrations in the Ruhr river catchment (Germany). Hillenbrand et al. (2014) also used GREAT-ER to evaluate whether diclofenac concentrations decrease after upgrading every WWTP in the Neckar river catchment (Germany) and reducing the human consumption. Oldenkamp et al. (2014) compared the environmental and human health impacts of two alternative equivalent antibiotic prescriptions (ciprofloxacin and levofloxacin) in 3 European regions using a European exposure model (Oldenkamp et al., 2013)

Table 1. Scope of application of available Microcontaminant Fate and Transport models used for water quality management. Extracted from Aldekoa et al. (2015), Dumont et al. (2012) and Comber et al. (2013).

Model	Scope of application
QUAL2E	In-stream water quality model that simulates complex processes on the fate and transport of pollutants. Dynamic and spatial calculation of pollutant concentrations (large and small scale)
ChenCAN	Multi-media model. Calculation of pollutant concentration in different compartments (air, water, soil, sediment and biota). No spatial and temporal variability
AQUASIM	Multi-media model. Dynamic and spatial calculation of pollutant concentration in different compartments (water, soil, sediment and biota). Mostly used in Switzerland
IUWS_MP model library	Multi-media model. Integrated dynamic model that calculates MP emissions from urban areas at catchment scale
GREAT-ER	Risk assessment of chemicals. Steady state and spatial calculation of pollutant concentrations at catchment scale. Mostly used in Europe
PhATE	Risk assessment of chemicals. Steady state and spatial calculation of pollutant concentrations at catchment scale. Mostly used in USA
GWAVA	Assessment of changes in human water security and aquatic biodiversity. Dynamic and spatial calculation of pollutant concentrations at large scale (Europe)
SAGIS	Chemical Source Apportionment and water quality model. Dynamic and spatial calculation of pollutant concentrations at national scale (UK)

Due to the daunting costs of upgrading WWTP infrastructure for the removal of pharmaceuticals, national/regional water agencies have the responsibility of allocating resources effectively. Cost-effective allocation implies optimizing resources at catchment scale and can take advantage of MFT models. Such optimization approaches have already been demonstrated in the research field, as seen in Bishop & Grenney (1976), Udias et al. (2012), and Saberi & Niksokhan (2017), but are mostly applied to the reduction of conventional contaminants (organic matter, ammonia, nitrate, etc.).

Challenge 3

Such an optimization assessment has never been conducted for microcontaminants. Very few studies evaluated (and even less optimized) the implementation of strategies to decrease pharmaceutical concentrations in rivers below the EQSs; however, none of them conducted a proper economic assessment. For instance, (Ort et al., 2009) optimized the number of WWTPs (but not the cost) to be upgraded with ozone or activated carbon to avoid any exceedance of the diclofenac proposed EQS throughout all river catchments in Switzerland. Coppens et al.

(2015) prioritized the number of WWTPs (not optimizing or assessing the cost) to be upgraded in the Netherlands based on the impact of pharmaceutical emissions on drinking water and ecology.

Our hypothesis is that the daunting cost of the WWTP upgrades at catchment level would decrease by using multi-objective optimization. Thus***, the third challenge would be optimizing the number of WWTP upgrades and costs by minimizing the total amount of pharmaceutical that exceeds the proposed EQS in every river section and the total upgrading costs at catchment level.***

1.5 Uncertainty in the estimation of pharmaceutical loads in rivers

From a management perspective, uncertainty is the lack of exact knowledge, regardless of the source of this deficiency (Refsgaard et al., 2007). The uncertainty of MFT model outcomes needs to be estimated when they are utilized for decision support (Uusitalo et al., 2015). Pistocchi et al. (2010) observed that the high uncertainty in chemical emissions and physico-chemical behaviour in the environment makes realistic MFT model simulations difficult to obtain. Moreover, high levels of uncertainty compromise the usability of model outcomes for decision-making when evaluating different scenarios (Reichert & Borsuk, 2005; de Kort & Booij, 2007; Xu et al., 2007). No certain conclusion can be drawn if model prediction uncertainty is larger than the difference between simulation outcomes of different scenarios (Reichert & Borsuk, 2005) However, prediction uncertainties can be reduced by additional research and data collection and analysis (Loucks & Van Beek, 2005).

Model Uncertainty comes from different sources: model structure, model parameters and input data (Figure 4). In each simulation, model uncertainty is propagated to the model outcomes. Regarding model parameters (the focus of this dissertation), three key parameters are identified in most of the MFT models currently in use (Alder et al., 2010; Aldekoa et al., 2013; Johnson et al., 2013; Kehrein et al., 2015; Grill et al., 2016): 1) the pharmaceutical consumption and metabolization, 2) the pharmaceutical removal rate in WWTPs, and 3) the pharmaceutical decay rate in rivers (Figure 4)

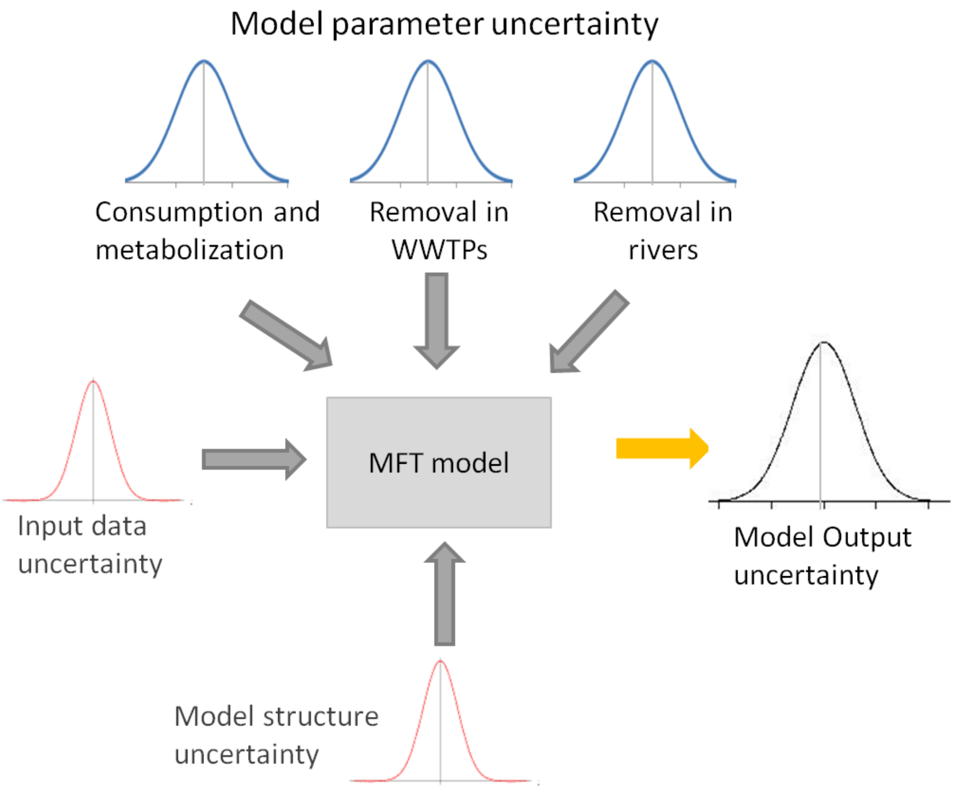


Figure 4. Sources of uncertainty in Microcontaminant Fate and Transport (MFT) models. The focus of this dissertation is on model parameter uncertainty.

Model parameter uncertainty can be incorporated in these models, e.g., by assuming probability distribution functions (PDFs) for the 3 key parameters, thereby resulting in simulation outcomes in the form of a PDF (Loucks & Van Beek, 2005). The definition of PDFs for these key model parameters is generally a crucial step in these assessments. They are normally built after collecting information from laboratory experiments or field measurements published in literature. However, these three key parameters exhibit large differences among different studies. For instance, percentages ranging from -36% to +30% are assumed for the consumption of antibiotics and a range from -90% to +90% is assumed for their human excretion (Verlicchi et al., 2014) Other studies consider a 50% uncertainty range for the combined parameter consumption and excretion of pharmaceuticals (Kehrein et al., 2015; Ort et al., 2009) The WWTP removal rates of specific compounds (e.g., ketoprofen and sulfamethoxazole) under the same wastewater treatment conditions (conventional activated sludge processes) can vary from 5 to 99% (Verlicchi et al., 2012), and the decay rates in rivers of some compounds (e.g., diclofenac) vary by up to 4 orders of magnitude (Boithias et al., 2013).

Challenge 4

Bayesian inference techniques have been successfully applied to estimate water quality parameters (phosphate, dissolved oxygen and ammonia) from a British catchment (Krueger, 2017), lake-sediment phosphorous model parameters in American creeks (Hantush & Chaudhary, 2014), first-oder decay rates of the river segments and ammonia loads in a chinese catchment (Liu et al., 2008), soil hydraulic parameters (Vrugt, 2016) and first-order decay rates in sewers for micropollutants (McCall et al., 2016). However, Bayesian inference has never been used to estimate the MFT key model parameters for the prediction of pharmaceutical concentrations in rivers. So far, uncertainty in MFT model has been addressed using simple Monte Carlo methods (Ort et al.,2009; Kehrein et al., 2015; Grill et al., 2016) assuming PDFs for the model parameters from literature.

Our hypothesis is that uncertainty in the key MFT model parameters would reduce using Bayesian inference techniques and measurements of pharmaceutical concentrations in WWTPs and rivers. Thus, ***the fourth challenge is the development and calibration of a MFT model for the estimation of pharmaceutical concentrations in rivers including Bayesian uncertainty analysis.***

Challenge 5

The large uncertainty in the MFT model parameters and predicted concentrations might lead decision makers to only select extreme interventions that drastically reduce (e.g., 95% reduction) pharmaceutical loads in rivers when compared to the reference situation. Thus, less ambitious, potentially cheaper interventions that can significantly reduce (e.g., 70% reduction) loads are discarded because of the large uncertainty in the predicted concentrations. What has never been addressed in the evaluation of strategies for pharmaceutical load reduction is whether changes in the PDFs of model parameters (e.g., due to more data becoming available for calibration or an increase in the scientific understanding of these parameters) influence the selection of interventions at WWTPs (e.g., secondary treatment upgrades or the installation of advanced tertiary treatments).

Our hypothesis is that existing knowledge on the model parameter values is not sufficient and biases the selection of WWTP upgrade interventions towards the most extreme alternatives that result in very large load reductions (e.g. installation of advanced tertiary treatments). Thus, ***the fifth challenge is to evaluate the influence that the magnitude of key model parameter uncertainties has on the selection of interventions designed to reduce the pharmaceutical loads in rivers.***

1.6 Thesis structure

This thesis is developed according to the following structure:

Chapter 1 introduces the sources, fate and toxicity of pharmaceuticals in the environment. Some key legislations leading to the protection of rivers from pharmaceuticals are described following a description of measures for the reduction of pharmaceuticals in rivers. Finally, we introduce the models available for the evaluation of measures and the sources of uncertainty in the models. We identified 5 research challenges throughout the introduction which lead to the objectives of this thesis (**chapter 2**)

A list with the specific objectives of this thesis is presented in **Chapter 2**. The specific objective 1 addresses the forth challenge, the specific objective 2 addresses the fifth challenge, the specific objective 3 addresses the first and third challenge and the specific objective 4 addresses the second challenge.

In **Chapter 3** the materials used are described and a general description of the methodology and the case study are presented.

Chapter 4 presents the main results and discussions obtained. **Sub-chapter 4.1** describes the development and calibration of the microcontaminant fate and transport model for the estimation of pharmaceutical concentrations including uncertainty (Specific objective 1). **Sub - chapter 4.2** describes a methodology to evaluate the influence of model parameter uncertainties on the selection of WWTP interventions designed to reduce the pharmaceutical loads in rivers (Specific objective 2). **Sub-chapter 4.3** evaluates the relationship between the potential EQS for diclofenac and the cost of the WWTP upgrades required to avoid EQS exceedance (Specific objective 3). In this Sub-chapter we describe the multi-objective optimization of the number of WWTP upgrades and costs for the reduction of pharmaceuticals in rivers at catchment level. Finally, **Sub-chapter 4.4** evaluates the effect of source control measures on the required end-of-pipe measures for the reduction of pharmaceuticals at catchment scale (Specific objective 4). Sub-chapters 4.1, 4.2 and 4.3 are edited versions of published peer-reviewed papers. The contents presented in sub-chapter 4.4 have been submitted in a peer reviewed journal to be considered for publication.

A general discussion is presented in **Chapter 5** considering all the outcomes presented in this dissertation, and also provides an outlook for future research.

Finally, **Chapter 6** presents the main conclusions of this thesis.

2. Objectives

The aim of this thesis is to evaluate management strategies (end-of-pipe and source control) for the reduction of pharmaceuticals in rivers including uncertainty in the whole decision-making process. Hence, in accordance with the challenges presented in the introduction, the specific objectives are fourfold:

1. To develop and calibrate a Microcontaminant Fate and Transport model for the estimation of pharmaceutical concentrations in rivers including uncertainty (challenge 4)

2. To evaluate the influence that the magnitude of key model parameter uncertainties has on the selection of WWTP interventions designed to reduce the pharmaceutical loads in rivers (challenge 5)

3. To evaluate the relationship between the potential EQS for diclofenac and the optimal cost of the WWTP upgrades required to avoid EQS exceedance (challenge 1 and 3)

4. To evaluate the effect that source control measures have on the required end-of-pipe measures for the reduction of pharmaceuticals at catchment scale (challenge 2)

3. Materials and methods

3.1 Study area

The study area is the Llobregat River basin, which is the second longest river in Catalonia (NE Iberian Peninsula). The main axis of the river extends 165 km from the Pyrenees to the Mediterranean, draining an area of 4,948 km^2, and has two main tributaries, the Cardener and Anoia Rivers. The hydrology of the Llobregat River is characterized by a highly variable flow that is strongly influenced by seasonal rainfall. The mean annual bulk precipitation is 670 mm, and it has an annual average bulk discharge of 693 hm^3. The basin includes 56 WWTPs (54 conventional activated sludge, 1 aerated lagoon and 1 membrane bioreactor; Table 2), which collect and treat wastewater from 1,100,000 inhabitants (Statistical Institute of Catalonia, 2016) and discharge to the Llobregat (Figure 5).

The Catalan Water Agency (Bernadette Catlla on 01.07.2015) provided daily values on the operational variables (i.e., Xss – Mixed Liquor Suspended Solids, ϑh – Hydraulic Retention Time, WWTP influent and effluent flows, Table 2) from 34 of the 56 studied WWTPs and we averaged the daily values of each WWTP for September 2010 (period when the sampling campaign for the measurements of diclofenac and naproxen concentrations in rivers and WWTPs was conducted). For the rest of the WWTPs with no data on the operational variables (22 of the 56), we assumed average operational conditions (justification in section 4.1.1.2). The Catalan Water Agency also provided the number of municipalities connected to each WWTP so the census population for each infrastructure in 2010 (Table 2) was obtained from the Statistical Institute of Catalonia (2016).

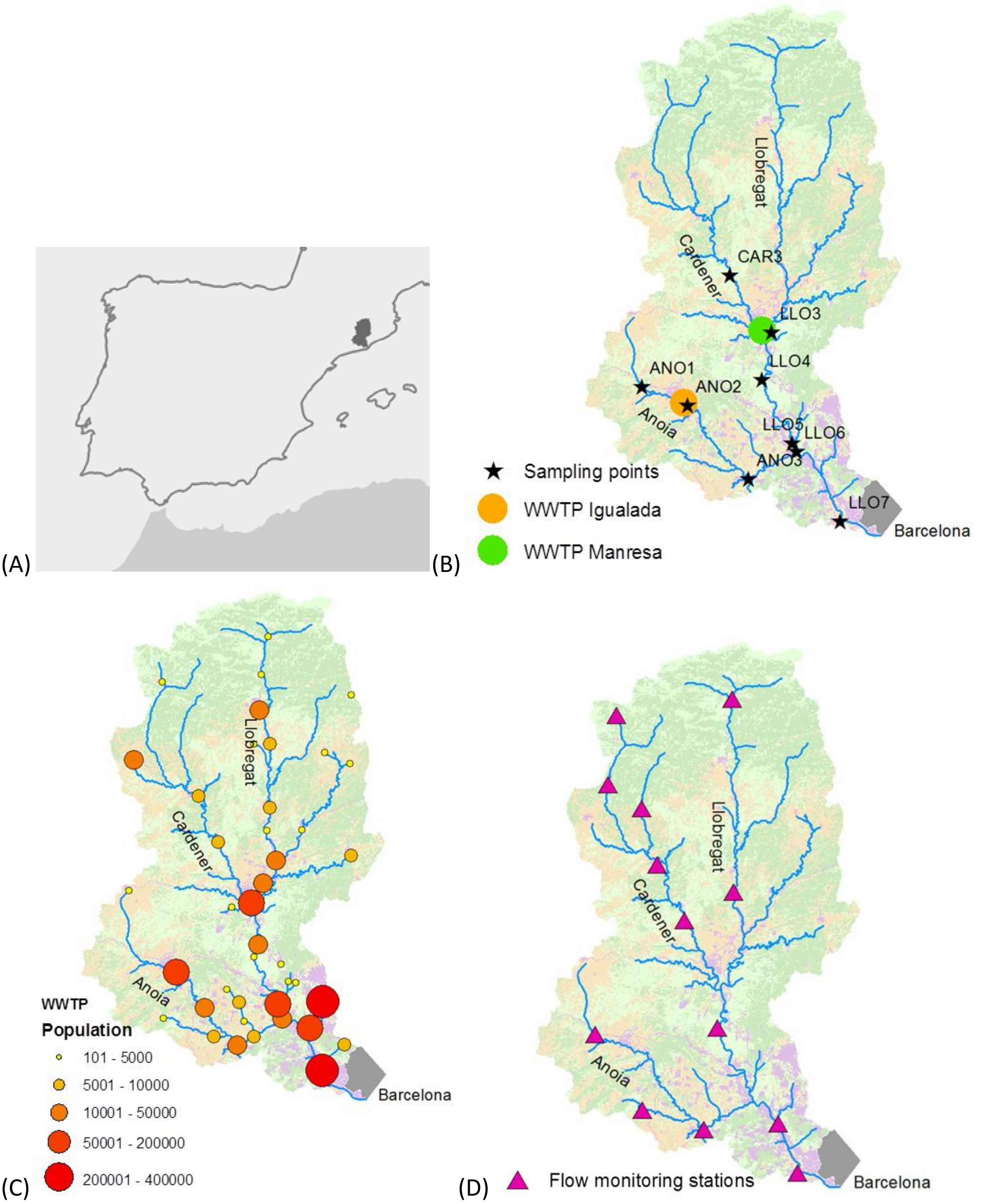


Figure 5 (A) Location of the Llobregat basin on the Iberian Peninsula (B) locations and WWTPs where sampling campaigns for the measurements of pharmaceutical concentrations were conducted in September 2010 (ANO1, ANO2, ANO3, CAR3, LLO3, LLO4, LLO5, LLO6 and LLO7, the Igualada WWTP (influent and effluent) and the Manresa WWTP (influent and effluent) (C) Location of WWTPs discharging to the Llobregat River. WWTPs are ranked (orange and red circles) based on census population served (Statistical Institute of Catalonia, 2016) (D) Location of flow monitoring stations in the Llobregat river basin. Llobregat catchment background map and coordinates of WWTPs and monitoring stations were provided by the Catalan Water Agency

Table 2. Characteristics and operational variables of the WWTPs discharging to the Llobregat river basin. These values represent average conditions for September 2010.

id	Θh (days)	Xss ($mg \cdot L^{-1}$)	Qinf ($m^3 \cdot d^{-1}$)	Qeff ($m^3 \cdot d^{-1}$)	Population	Type of treatment	Name
1	19.93	950	74.8	74.8	187	Activated Sludge	Castellar de N'Hug
2	0.30	1,645	1,926.7	1,926.7	3,385	AS	Baga
3	1.10	508	49.9	49.9	104	AS	Sant Corneli de Cercs
4		2,106.3	413.3	413.3	1,222	AS	Cercs
5	0.59	2,323.8	5,491.2	5,491.2	17,161	AS	Berga
6			1,647.5	1,647.5	5,067	AS	Gironella
7	9.84	1,557.5	123.7	123.7	1,583	AS	Casserres
8			612	612	4,333	AS	Puig-Reig
9	1.70	1,974.0	973	973	6,455	AS	Navas
10			740	740	3,204	AS	Balsareny
11	3.10	960	97	97	303	AS	Alpens
12	1.50	2,730	452	452	1,202	AS	Olost
13	1.10	1,949	800	800	2,739	AS	Prats de Llucanes
14	0.96	2,278	335	335	2,336	AS	Avinyo
15	2.83	2,640	2,509	2,509	12,544	AS	Sallent-Artus
16			1,846	1,846	5,713	AS	Moiß
17	0.86	2,284	4,957	4,957	21,219	AS	Sant Fruitos-Navarcles-Sant Pedor
18	3.06	2,012	463	463	3,760	AS	Pont de Vilomara
19			80	80	271	AS	La Coma
20	2.86	1,693	303	303	1,077	AS	Sant Llorenc de Morunys
21	1.48	1,908.5	2,842	2,430	10,060	AS	Solsona
22			30	30	102	AS	Riner (Freixinet)
23	1.94	2,538.8	577.3	577.3	5,182	AS	Cardona
24			30	30	57	AS	Riner (Su)
25	1.81	1,372	1,855	1,855	6,359	AS	Suria
26	0.76	2,520.2	29,205.3	29,205.3	89,651	AS	Manresa
27	1.88	1,690	512.2	512.2	3,078	AS	Sant Salvador de Guardiola
28	2.07	3,292.5	2,359.5	2,359.5	16,163	AS	Castellbel i el Vilar
29	0.58	1,902.5	2,595	2,595	3,027	AS	Monistrol
30			193.5	193.5	2,743	AS	Hostalet de Pierola
31	0.53	2,863.3	16,564	16,564	63,227	AS	Abrera
32			495.5	495.5	2,812	AS	Vacarisses
33			1,553.4	1,553.4	3,863	AS	Viladecavalls (S.E)
34			275.3	275.3	3,405	AS	Viladecavalls (S.O)
35			150	150	381	Aereated Lagoon	Sant Marti Sesgueioles
36	1.50	4,265	694	694	3,611	AS	Calaf
37	3.60	716	120	120	1,164	AS	Sant Marti de Tous
38	1.18	3,993	17,947	17,947	65,046	AS	Igualada
39			357	357	1,007	AS	Carme

40	0.44	2,050	6,645.7	6,645.7	12,973	AS	Capellades
41	0.98	1,450	4,291	4,291	14,576	AS	Piera
42		4,255	400	400	1,922	AS	Sant Joan de Mediona
43		3,220	1,257	1,257	5,952	AS	Riudebitlles
44		3,058	116.6	116.6	676	AS	Subirats (Ordal)
45		9,115	148.4	148.4	558	AS	Subirats (Sant Pau d'Ordal)
46		14,080	20.6	20.6	101	AS	Subirats (Els Casots)
47		9,713	3,243	2,098	12,323	AS	Sant Sarduni d'Anoia
48	0.88	2,664	982	982	6,945	AS	Gelida
49	1.00	2,171.5	1,362	1,362	8,295	AS	Masquefa
50	1.08	4,138	192	192	2,416	AS	Sant Llorenç de Hortons
51	0.38	2,603	6,526	6,508	34,144	AS	Martorell
52	0.27	3,248.3	35,154.1	35,154.1	195,948	AS	Terrasa (AS)
53	0.79	3,883.9	6,191.9	6,191.9	34,579.1	MBR	Terrasa (MBR)
54	0.29	4,243	22,265	22,265	149,673	AS	Rubi
55	0.58	6,755	865	865	5,491	AS	Vallvidrera
56	0.49	3,980	44,922	44,922	215,753	AS	Sant Feliu de Llobregat

3.2 Model substances

3.2.1 Diclofenac

Diclofenac is a common non-steroidal anti-inflammatory drug. The average defined daily dose (DDD) for diclofenac used as anti-inflammatory and anti-rheumatic in adults is 0.1 grams for any administration route (oral, parenteral or rectal; World Health Organisation, 2007). It is dispensed in pharmacies with a prescription or over-the-counter (OTC) in the form of pills, eye drops, suppositories or a gel. Diclofenac not only enters the sewer system in the urine and faeces after human body excretion but is also washed off of skin and clothes or disposed of improperly via sinks and toilets (Bound & Voulvoulis, 2005; Osorio et al., 2014). This drug is characterized as persistent in WWTPs, as only 29% is on average removed in conventional activated sludge processes (Verlicchi et al., 2012). Therefore, we expect to find high concentrations of this compound in river sections that are directly downstream of WWTP effluents. In the river, diclofenac is considered non-persistent because it is easily reduced by phototransformation (Acuña et al., 2015a). Diclofenac has been shown to bioaccumulate in fish and invertebrates (Huerta et al., 2015) at environmentally relevant concentrations and to potentially pose harmful effects on non-target aquatic organisms at higher concentrations (Acuña et al., 2015a). Thus, diclofenac has been included in the EU “Watch list” of priority substances under the Water Framework Directive (European Commission, 2015). The EQS proposed in Europe for diclofenac range from 10 $\eta g \cdot L^{-1}$ (European Medicines Agency, 2006) to 100 $\eta g \cdot L^{-1}$ (European Commission, 2012)

3.2.2 Naproxen

Naproxen is also a non-steroidal anti-inflammatory and anti-rheumatic drug. The average defined daily dose (DDD) for naproxen used as anti-inflammatory and anti-rheumatic in adults is 0.5 grams (5 times higher than diclofenac; World Health Organisation, 2007). It is dispensed in pharmacies with a prescription or OTC in the form of pills. Among the nonsteroidal anti-inflammatory drugs (NSAID), naproxen is associated with the lowest cardiovascular risks but increases gastrointestinal side effects (Baigent et al., 2013). Naproxen is excreted unchanged in urine and feces by 5-7%. However, the human body also excretes between 66 and 92% of glucuronide conjugates (Vree et al., 1993). These conjugates are easily hydrolysable, increasing the concentration of the naproxen parent compound in sewers (Carballa et al., 2008; Khan & Ongerth, 2004). Naproxen is better removed by biodegradation in conventional WWTP compared to diclofenac. An average removal of 73% was identified by Verlicchi et al. (2012) and Petrie et al. (2014). In the river, naproxen is also easily reduced by phototransformation (Acuña et al., 2015b), although sorption onto solids (Lin et al., 2006) and biotransformation (Radke et al., 2010) have been suggested as the removal drivers under light absence. Naproxen has low potential for bioaccumulation (LIF, 2005). However, chronic exposure to naproxen, especially its phototransformation products, causes the growth inhibition on crustaceans at low concentration ($\mu g \cdot L^{-1}$; Isidori et al., 2005). The EQS proposed in Europe for naproxen are also higher than diclofenac since they range from 640 $\eta g \cdot L^{-1}$ (LIF, 2005) to 1,700 $\eta g \cdot L^{-1}$ (Ecotox centre, 2017)

3.2.3 Total consumption (purchased with a prescription and Over-the-counter) of diclofenac and naproxen

IQVIA (2018) provided the yearly total amount (kg) of diclofenac and naproxen that the wholesalers and the manufacturers supplied directly to pharmacies and hospitals in Spain from 2006 to 2016. We assumed that all amount supplied to the pharmacies was sold to customers in the same year and that the customers consumed 100% of the medicines. Hence, the values include the total amount of drug purchased with a prescription and OTC. We standardized the amount of pharmaceutical purchased into $DDD \cdot 1000inh^{-1} \cdot day^{-1}$ (Figure 6) using the average DDD for diclofenac and naproxen (0.1 and 0.5 g respectively; World Health Organisation, 2007) and the population in Spain from 2006 to 2016 (World Bank, 2018)

3.2.4 Prescribed consumption of diclofenac and naproxen

AEMPS (2014, 2017) provided the yearly amount of diclofenac and naproxen that was prescribed in Spain as a $DDD \cdot 1000inh^{-1} \cdot day^{-1}$ and was reimbursed by the Spanish National Health system from 2006 to 2016. We assume that all amount prescribed by physicians was sold in pharmacies with a prescription and 100% consumed by customers in the same year. The difference between the total and the prescribed amount gives an estimation of the diclofenac and naproxen purchased OTC in Spain every year (Figure 6).

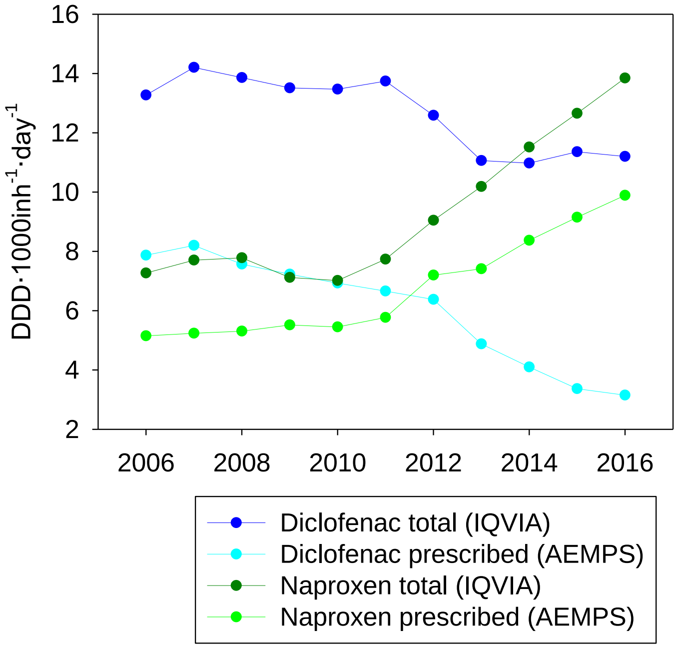


Figure 6. Total and prescribed consumption of diclofenac (dark and light blue) and naproxen (dark and light green) in Spain from 2006 to 2016.

The total and prescribed consumption of diclofenac decreased from 2011 in Spain because of a recommendation by the European Medicines Agency for the decrease in the number of diclofenac prescriptions in patients with high cardiovascular risk (European Medicines Agency, 2012, 2013). Instead, naproxen consumption increased from 2011 to compensate for the reduction in the diclofenac use (AEMPS, 2017, figure 2).

3.2.5 Monitored concentrations of diclofenac and naproxen in WWTPs and river

Within the framework of the project SCARCE (Consolider-Ingenio 2010 CSD2009-00065), grab samples were collected at 9 sites along the Llobregat River (Figure 5) on three consecutive days in September 2010. The sampling sites were those established by the Catalan Water Agency to evaluate the chemical and ecological status of rivers according to the Water Framework Directive (European Commission, 2000; Figure 5 (B)). In the same month, 24-h composite samples were collected in the influents and effluents of the Igualada and Manresa WWTPs (Figure 5 (B)). The samples were collected flow-proportional with a sampling frequency of one sample per hour. These samples were analysed using a multi-residue analytical method based on LC-MS/ MS after SPE, as described by Aldekoa et al. (2013) for river samples and by Osorio et al. (2014) for WWTP samples. Table 3 and Table 4 contain the diclofenac and naproxen concentrations measured at these locations.

Table 3. Concentrations of diclofenac measured in monitoring points along the Llobregat River and in the influents and effluents of the Igualada and Manresa WWTPs.

Monitoring points	Concentration of diclofenac ($ng \cdot L^{-1}$)
ANO1	6
ANO2	129
ANO3	51
CAR3	5
LLO3	10
LLO4	13
LLO5	18
LLO6	16
LLO7	62
WWTP Igualada influent	293.68
WWTP Igualada effluent	232.63
WWTP Manresa influent	333.68
WWTP Manresa effluent	200.53

Table 4. Concentrations of naproxen measured in monitoring points along the Llobregat River and in the influents and effluents of the Igualada and Manresa WWTPs.

Monitoring points	Concentration of naproxen ($ng \cdot L^{-1}$)
ANO1	20
ANO2	51
ANO3	38
CAR3	3
LLO3	10
LLO4	17
LLO5	41
LLO6	38
LLO7	50
WWTP Igualada influent	1,763.16
WWTP Igualada effluent	49.56
WWTP Manresa influent	2,017.54
WWTP Manresa effluent	166.67

3.3 Model calibration: Bayesian inference approach

When no observations of diclofenac and naproxen concentrations are available, the uncertainty of MFT model parameters can be propagated to the model outcomes (diclofenac and naproxen concentrations) using Monte Carlo techniques (Ort et al., 2009; Kehrein et al., 2015; Grill et al., 2016). When observations are available, the MFT model parameters can be calibrated using frequentist or probabilistic approaches (Gallagher & Doherty, 2007). The frequentist approach provides the most likely estimates of the MFT model parameters along with confidence intervals by minimizing an objective function (i.e. minimization of Root Mean Square Error; Aldekoa et al., 2015). If the modeller has some prior knowledge on the MFT model parameters, probabilistic approaches, such as Bayesian inference approach, can provide the calibrated (or posterior) probability distributions of MFT model parameters instead of a fixed estimate. McCall et al. (2016) estimates kinetic degradation constant in sewers for microcontaminants (pharmaceuticals and illegal abuse drugs) using experimental data and Bayesian inference. Since observations of diclofenac and naproxen are available in the Llobregat basin and prior parameter probability distributions can be obtained from other studies (Ort et al., 2009; Kehrein et al., 2015; Grill et al., 2016) or experimental data, we selected Bayesian inference to calibrate the MFT model parameters. Furthermore, uncertainty may be reduced by using probabilistic approaches compared to frequentist approaches (Gallagher & Doherty, 2007) which is relevant for the development of the objective 2 of this thesis.

The defined prior parameter distributions are updated using a likelihood function resulting in the posterior (or calibrated) distributions (Figure 7). Hence, the predicted concentrations match the measured concentrations when simulating the model with the posterior parameter distributions (Figure 7)

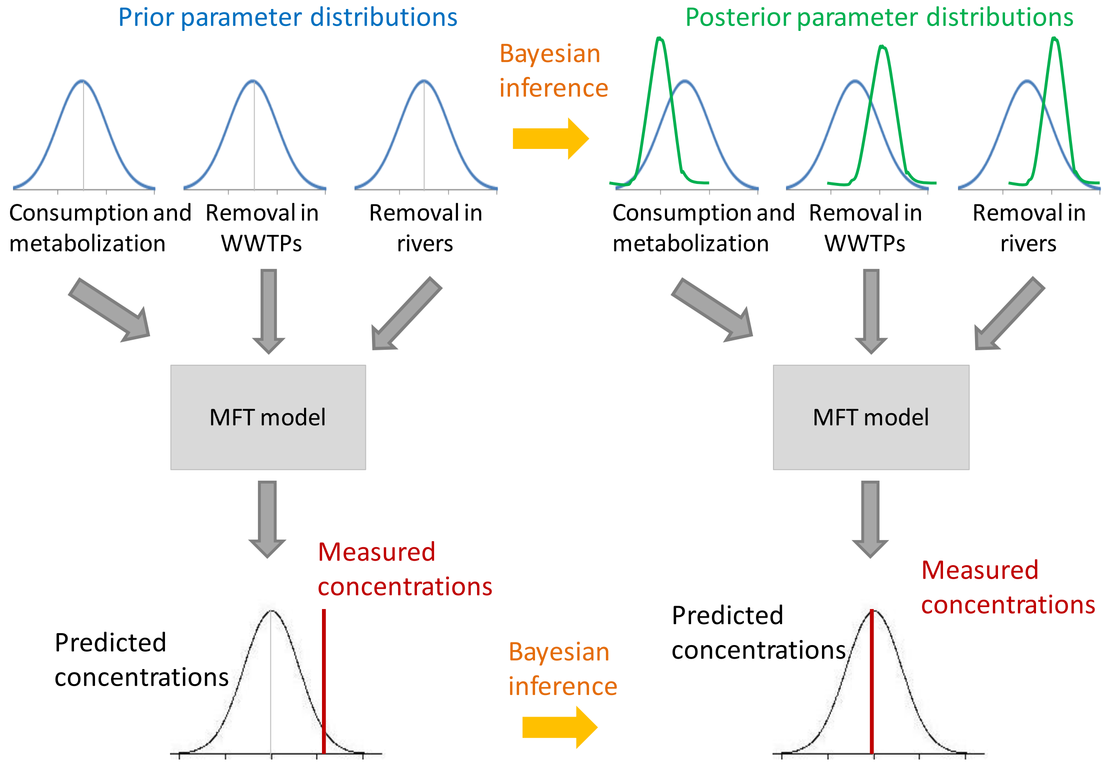


Figure 7. Prior parameters distributions and posterior parameter distributions after Bayesian inference. The predicted concentrations match the measurements when simulating the model with the poterior distributions

The posterior distributions are calculated based on Bayes' theory (Equation 1; Bayes, 1763):

$$p(x|\tilde{Y}) = \frac{p(x) \cdot p(\tilde{Y}|x)}{p(\tilde{Y})} \qquad \text{(Eq. 1)}$$

where $p(x)$ and $p(x|\tilde{Y})$ represent the prior and posterior parameter distributions, respectively, and $p(\tilde{Y}|x)$ represents the likelihood function (distance function between the model simulations and the corresponding observations). The distribution of observations $p(\tilde{Y})$ acts as a normalization constant (scalar) so that the posterior distribution integrates to unity.

For this calibration, we used the MATLAB toolbox and the DiffeRential Evolution Adaptive Metropolis (DREAM) algorithm developed by Vrugt et al. (2008; 2009) following the recently published manual (Vrugt, 2016). The DREAM algorithm is a Markov Chain Monte Carlo (MCMC) simulation method. MCMC draws samples from a target distribution which after a sequence of iterations (simulations) will converge to the posterior distribution. DREAM uses the Metropolis algorithm (Metropolis et al., 1953) as the sampling approach and multiple trajectories (Multi-chain) running in parallel to explore the posterior target distribution. The number of Markov chains and the number of generations are established by trial-and-error ensuring the convergence to the posterior distribution. The convergence is evaluated through the R-statistic (Gelman & Rubin, 1992) which has to remain below 1.2 for each parameter within the number of function evaluations.

The selection of the likelihood function can be made based on whether the measurement error of the observations (data used to calibrate the model parameters) is known or not. In our study, the measurement error is unknown so Vrugt (2016) suggests using the Gaussian likelihood function of equation 2 (measurement error integrated out)

$$p(\tilde{Y}|x) = -\frac{n}{2} \times \log\{\sum_{t=1}^{n} e_t(x)^2\} \qquad \text{(Eq.2)}$$

$e_t(x)$ signifies the residuals (difference between model predictions and observations) and n represents the number of observations.

3.4 Model variables optimization: Non-dominated Sorting Genetic Algorithm-II (NSGA-II)

Multi-objective optimization methods search for a set of trade-off optimal solutions, instead of one optimal solution, which is known as the set of Pareto-optimal solutions. Classical multi-objective optimization methods aggregate the objectives into a single objective function (e.g. Weighted Sum Method, Cohon, 1978). However, these methods require many simulations to find the Pareto-optimal solutions and some solutions cannot be found using a single objective function (Deb, 2002). Genetic algorithms can deal simultaneously with a set of possible solutions and explore them over the entire search space. The Non-dominated Sorted Genetic Algorithm II (NSGA-II; Deb, 2002) is among the most commonly used multi-objective global optimization method with numerous successful applications in watershed management (Fu et al., 2008; Montserrat et al., 2017; Nikoo et al., 2011). Hence, the NSGA-II was selected as the optimization method to identify the optimal number of WWTPs requiring an upgrade within a catchment when two objective functions (minimization of upgrading costs and minimization of EQS exceedance for pharmaceuticals) are involved.

The NSGA-II procedure is shown in Figure 8. Firstly, a combined population of 2N solutions ($R_t = P_t + Q_t$) is formed. Then the population R_t is sorted and ranked (F_1, F_2, F_3,...,F_l) descending according to non-domination (none of both solutions is better than the other with respect to every objective). To choose exactly N population solutions, the solutions of the last rank (F_l) are sorted using the crowding distance (index that measures how far each solution is to the maximum and minimum value of every objective function). The new population P_{t+1} is used to create a new population Q_{t+1} (offspring) by selection, crossover and mutation of the solutions in P_{t+1}. Initially, the first parent population P_0 is created randomly.

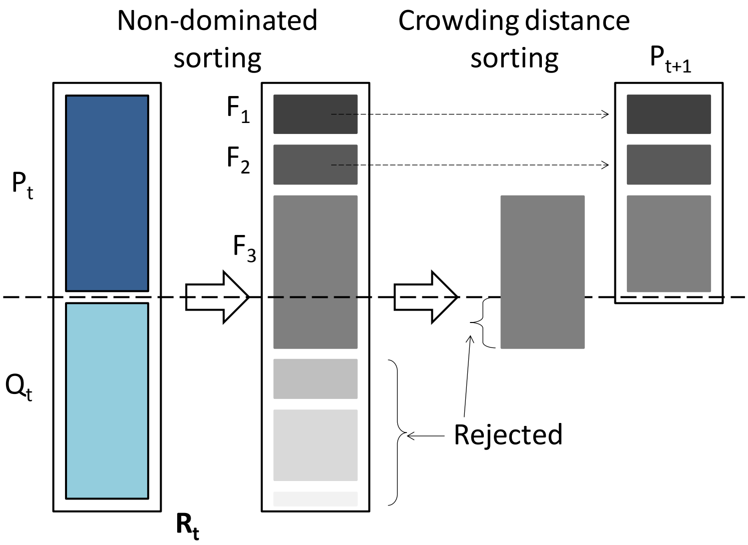


Figure 8. NSGA-II procedure. Extracted from Deb et al. (2002).

The NSGA-II algorithm was developed in Matlab. Regarding the NSGA-II parameters, we selected the population size and the number of generations following a "trial and error" approach and ensuring that we evaluate the extreme objective function values (minimum cost and maximum EQS exceedance, and maximum cost and minimum EQS exceedance). For further details about the NSGA-II development, we refer to Deb et al. (2002).

3.5 Matlab

Matlab is a numerical computing sotware developed by MathWorks. Matlab allows data analysis, develop algorithms and create mathematical models. Matlab has its own programming language that expresses matrix and array mathematics directly (Mathworks, 2018).

We used Matlab R2009b (Version 7.9.0.529, license number 161051) to develop the code of the Microcontaminant Fate and Transport model, to calibrate the model from Bayesian inference (code available from Vrugt, 2016), to simulate the predicted concentrations from the MFT model and to optimize the number of WWTP requiring an upgrade (NSGA-II code; Deb et al., 2002).

4. Results and discussion

4.1 Development and calibration of a Microcontaminant Fate and Transport model for the estimation of pharmaceutical loads in WWTPs and rivers.

Models of microcontaminant fate and transport in wastewater treatment plants (WWTPs) and rivers have been developed and used to assist decision-making in the field of water management. These models come with parameter uncertainties that must be properly estimated and incorporated into the decision-making process.

In this chapter, we develop a customized Microcontaminant Fate and Transport (MFT) model. The tool consists of three sub-models: 1) a substance-human consumption and excretion model, which estimates pharmaceutical loads that reach the influents of WWTPs; 2) a WWTP model, which estimates the effluent loads; and 3) a river model, which estimates the loads in every river stretch. The key MFT model parameters are F, k_{WWTP} and k_{river}

The uncertainty in the key MFT model parameters (probability distributions) is propagated to the model outcomes. Thus, the model predicts the loads of pharmaceuticals in WWTPs and in rivers including uncertainty. In this chapter, we take diclofenac as the target compound and the Llobregat river as the case study. The model was calibrated using Bayesian inference and observations of diclofenac concentrations in WWTPs and in rivers. This chapter shows that the calibrated model accurately (R^2=0.95) predicts the diclofenac loads in WWTPs and rivers. Moreover, the uncertainty in the loads after calibration significantly decreased compared to the uncertainty before calibration.

Redrafted from:

P. Gimeno, R. Marcé, Ll. Bosch, J. Comas, Ll. Corominas, 2017. Incorporating model uncertainty into the evaluation of interventions to reduce microcontaminant loads in rivers, Water Research, 124, 415-424

4.1.1 Methodology

4.1.1.1 Development of MFT model

We have developed a MFT model that describes the fate and removal of diclofenac along the entire Llobregat catchment under steady-state conditions. The tool integrates 3 sub-models: 1) a substance-human consumption, excretion and in-sewer degradation model; 2) a WWTP model; and 3) a river model (Figure 9).

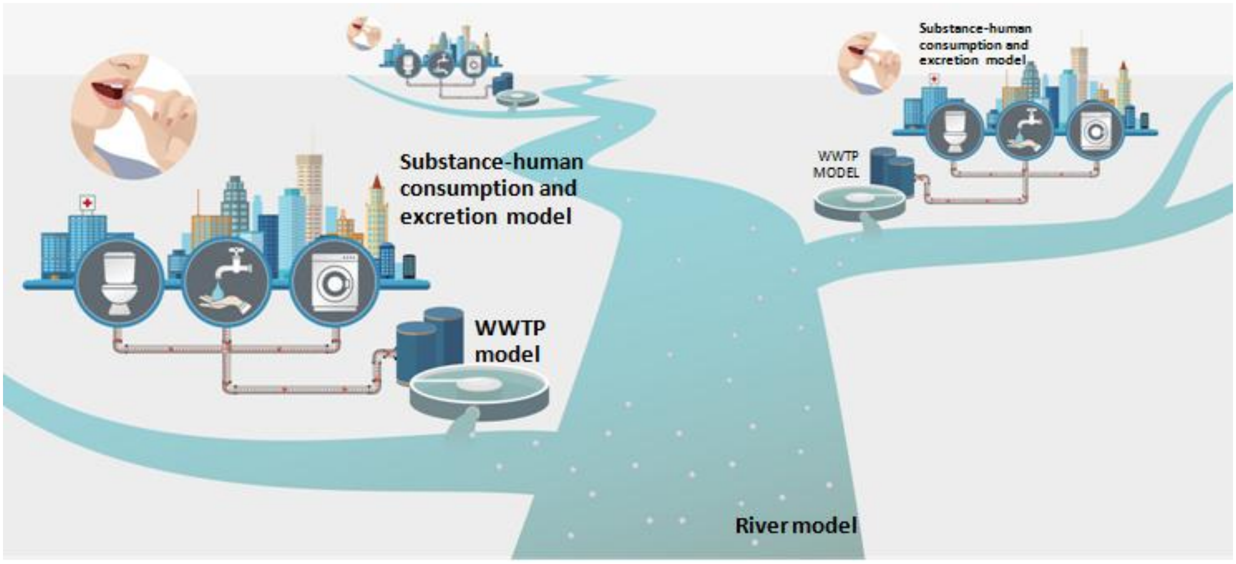


Figure 9. Submodels that compose the Microcontaminant Fate and Transport Model: Substance-human consumption and excretion model, WWTP model and River model

1. Substance-human consumption and excretion model (Equation 3)

$$L_{inf} = Sales \times F \times Census\ population \qquad \text{(Eq. 3)}$$

This sub-model estimates the pharmaceutical loads that reach the influents of WWTPs. L_{inf} represents the WWTP influent loads ($g \cdot d^{-1}$), *Sales* represents the total consumption of diclofenac (in hospitals and the amount sold in pharmacies located in the Llobregat catchment) for each person per year ($g \cdot d^{-1} \cdot person^{-1}$). F is a lumped factor (unitless) that includes the fraction of the diclofenac parent compound that is excreted to toilets, discharged directly via sinks, washed off from skin or clothes and degraded in sewers. *Census population* represents the number of inhabitants residing in households connected to a WWTP.

2. WWTP model (Equation 4)

$$L_{effluent} = L_{inf} \times \frac{1}{(1 + k_{WWTP} \times X_{ss} \times \vartheta_h)} \qquad \text{(Eq. 4)}$$

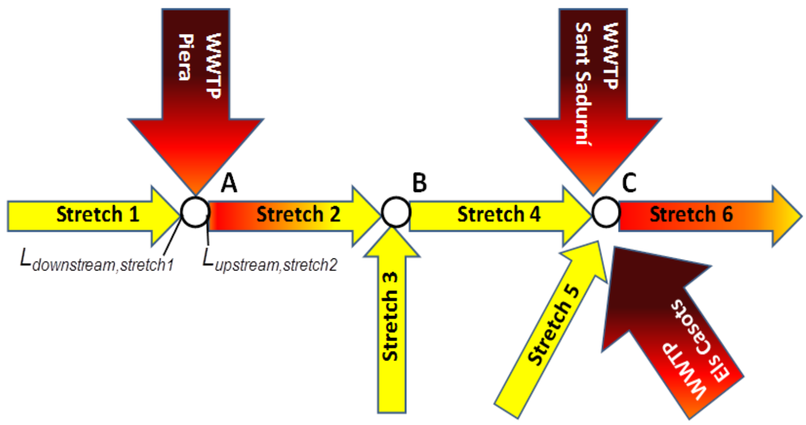
This sub-model estimates the degradation of diclofenac in WWTPs and, therefore, the effluent loads. We calculated the effluent load of each WWTP – $L_{effluent}$ ($g \cdot d^{-1}$) – based on the expression proposed in Joss et al. (2006). Thus, the diclofenac removal in a single completely stirred reactor (CSTR, with n=1) is described with pseudo-first-order kinetics in steady state. L_{inf} ($g{\cdot}d^{-1}$) is the diclofenac load in the influent of the WWTP, X_{ss} ($g_{ss}{\cdot}L^{-1}$) is the suspended solids concentration, ϑ_h (d) is the hydraulic retention time of the WWTP, and k_{WWTP} ($L{\cdot}g_{ss}^{-1}{\cdot}d^{-1}$) is the reaction rate constant that incorporates processes by which diclofenac is degraded (biodegradation, adsorption, volatilization, and photolysis). We do not expect significant reductions in diclofenac in the pre-treatment and sedimentation steps by adsorption to solids due to its low log K_d (Carballa et al., 2004); thus, the removal of diclofenac by these processes is not considered.

3. River model (Equations 5 and 6)

$$L_{downstream,stretch} = L_{upstream,stretch} \times e^{-HRT \times k_{river}} \qquad \text{(Eq. 5)}$$

$$HRT = \frac{L_{stretch}}{v} \qquad \text{(Eq. 6)}$$

Diclofenac elimination in rivers is described by first-order removal. $L_{upstream,\ stretch}$ ($g{\cdot}d^{-1}$) is calculated by the mass balance of diclofenac loads at each point defined in the river network. Thus, $L_{upstream,\ stretch}$ ($g{\cdot}d^{-1}$) is the result of the sum of every $L_{effluent}$ ($g{\cdot}d^{-1}$) discharging within the stretch and the $L_{downstream,stretch}$ ($g{\cdot}d^{-1}$) calculated from upstream stretches. Figure 10 shows a river network section with a detailed balance of diclofenac loads. *HRT* (s) is defined as the hydraulic retention time of a stretch and is calculated by the length $L_{stretch}$(m) and water velocity v ($m{\cdot}s^{-1}$) in that segment. The parameter k_{river} (s^{-1}) is the reaction rate constant that represents natural diclofenac degradation in rivers. We calculate concentrations by dividing the calculated load by the water flow of each stretch.



Mass balance in A: $L_{upstream,stretch2} = L_{effluent,WWTP\_Piera} + L_{downstream,stretch1}$

Mass balance in C: $L_{upstream,stretch6} = L_{effluent,WWTP\_Sant\_Sadurní} + L_{effluent,WWTP\_Els\_Casots} + L_{downstream,stretch5} + L_{downstream,stretch4}$

Figure 10. Example of mass balance of diclofenac loads in a section of the Anoia river (tributary of the Llobregat). A change in colour mimics the hypothetical degradation of diclofenac in WWTPs and river stretches.

The MFT model estimates the loads and concentrations of diclofenac in the influent and effluent of every WWTP and in every river stretch. We have implemented the model in MATLAB (Mathworks, 2018), and the code is included in Annex 1 (A1.1).

4.1.1.2 Data collection for model calibration

Monitored concentrations of diclofenac in WWTPs and river

Table 3 in Materials and Methods shows the diclofenac concentrations measured in 9 monitoring points along the Llobregat River and in the influents and effluents of the Igualada and Manresa WWTPs. These values will be used for the calibration of the model parameters (section 4.1.1.3 Model calibration). The sampling campaign was conducted in September 2010.

Consumption (sales) and population

We have considered a consumption of diclofenac in 2010 equivalent to 13.5 $DDD \cdot 1000 inh^{-1} \cdot day^{-1}$ (IQVIA, 2018). This value includes the consumption of diclofenac in hospitals and the amount sold in pharmacies (sold with prescription and over-the-counter). The census population connected to each WWTP in 2010 is shown in Table 2. The use of diclofenac for veterinary purposes (i.e., for cattle) was not allowed in Catalonia in 2010; thus, we have ignored this contribution when predicting the diclofenac river concentrations. A limited number of pharmaceutical manufacturing facilities exist in the basin. Unfortunately, it is difficult to obtain the possible discharge load of diclofenac from these facilities due to the confidentiality of such data.

Design and operational data for the WWTPs

The values of the operational variables (i.e., Xss and ϑh) from 34 of the 56 WWTPs for September 2010 are shown in Table 2 and were provided by the Catalan Water Agency. For the remaining 22 WWTPs, it was not possible to collect X_{ss} and ϑ_h (not available from Catalan Water Agency); hence, we assumed an average diclofenac removal efficiency of 29.5% (justification below – uncertainty ranges for model parameters – uncertainty in k_{WWTP}).

Design data for the river

For the river, we considered the same statistical distribution of stretches and geo-hydrological variables (length, water flow rate and mean velocities) as described by Aldekoa et al. (2013). Aldekoa et al. (2013) obtained the flow values for every stretch through a water balance considering measured flow levels, discharged water from WWTPs, extracted water for supplying drinking or irrigation water. Aldekoa et al. (2013) calculated the river velocity relating water flow, slope and drained area with the Manning empirical formula using geomorphological information provided by the Catalan Water Agency. The stretches distributions and length were calculated using a Digital Elevation Model of the Llobregat river catchment and GIS tools. These data are included in Annex 1 - A1.2. Thus, we used a river network composed of 164 stretches and established the connections between them using a customized MATLAB code (Annex 1 - A1.1).

Uncertainty ranges for model parameters

For simplicity, we identified that the three model parameters - F, k_{WWTP} and k_{river} – are the most "uncertain" parameters and the only source of uncertainty in the diclofenac loads. Moreover, based on the results of the sensitivity analysis (justification in section 4.1.2.2 Sensitivity analysis on model parameters), the uncertainty in the diclofenac loads is well explained by the uncertainty in these three model parameters. Hence, we do not assume uncertainty in the rest of the model variables (Sales, Population, Xss, ϑh, River Length and velocity).

- Uncertainty in F

We set F at 16% which represents the excretion factor reported by Ort et al. (2009) and Lienert et al. (2007). In view of observed load variations in WWTP influents (measurements at 4 Spanish WWTPs, data in Annex 1- A1.3) an uncertainty range of 50% was derived and assumed to be uniformly distributed: uniform (-0.5, 0.5). This covers the variable consumption and human excretion. The parameter F includes as well washed off diclofenac when topically applied. We assumed negligible diclofenac removal along sewer pipes from households to WWTPs, as indicated by Jelic et al. (2015). A similar uncertainty range was applied in Ort et al. (2009) based on data from 14 Swiss WWTPs. The existing pharmaceutical manufacturing facilities have their own wastewater treatment plants and discharge to the sewer system after treatment. Any uncertainties generated due to the lack of information on these discharges are included in the model after the Bayesian calibration.

- Uncertainty in k_{WWTP}

We estimated k_{WWTP} variability (using Equation 4) based on 17 diclofenac removal efficiencies measured in 10 Spanish WWTPs over the period from 2005 to 2009 (Gros et al., 2007; Gros et al., 2010; Jelic et al., 2011) and X_{ss} and ϑ_h values provided by the operators of these plants. Thus, based on the shape of the histogram obtained from the estimated k_{WWTP} values, we fitted an exponential distribution to these values (data in Annex 1 - A1.4). The values of k_{WWTP} varied from 0.11 to 2 $L \cdot g_{ss}^{-1} \cdot d^{-1}$, with a mean value of 0.55 $L \cdot g_{ss}^{-1} \cdot d^{-1}$. Overall, 94% of the k_{WWTP} values agreed well with biodegradation rate constants reported in the literature (Pomiès et al., 2013; Suarez et al., 2010), which range from <0.02 to 1.2 $L \cdot g_{ss}^{-1} \cdot d^{-1}$. Additionally, the average diclofenac removal measured in the 10 Spanish WWTPs was 29.5% (as $((L_{inf}-L_{effluent})/L_{inf})*100$), in line with the values found in review studies on pharmaceutical removal in activated sludge (Verlicchi et al., 2012).

- Uncertainty in k_{river}

Nineteen scientific publications were also reviewed in the SCARCE project framework to obtain the variability in k_{river} for diclofenac. These studies were conducted on different water body types (rivers, lakes and wetlands) and using different experiments (in situ and microcosms). Thus, the pseudo-first order decays integrate all the possible removal processes (i.e., biodegradation and photolysis), resulting in great variability among the studies. Based on the shape of the histogram obtained from the k_{river} values, we fitted an exponential distribution to these values (data in Annex 1 - A1.5). The values of k_{river} varied from 6.6E-08 to 9.3E-04 s^{-1}

(minimum and maximum values, respectively), with a mean value of 1.3E-04 s^{-1} (Boithias et al., 2013).

4.1.1.3 Model calibration

Model calibration involved adjusting the MFT model parameters *F*, k_{WWTP} and k_{river} so the simulated diclofenac concentrations fit the experimental data. We used a Bayesian statistical inference to calibrate the three key model parameters using the concentrations of diclofenac measured in the river and in the influents and effluents of the Igualada and Manresa WWTPs (we refer to section 3.3 Model calibration: Bayesian inference approach for further details). For this calibration, we used the MATLAB toolbox and the DiffeRential Evolution Adaptive Metropolis (DREAM) algorithm developed by Vrugt et al. (2008; 2009). Before executing this code, we first defined the input arguments, parameter space and initial sampling as specified in Table 5 .

Table 5. Definition of Input arguments, parameter space and initial sampling needed to run the DiffeRential Evolution Adaptive Metropolis (DREAM) algorithm in MATLAB (Vrugt et al., 2016) and calibrate the model parameters for diclofenac.

Input argument	**Value**	**Justification**
Dimension of the problem	3	Three parameters: F, k_{WWTP} and k_{river}
Number of Markov chains	10	Minimum required was 7 according to Vrugt et al. (2016)
Number of generations	10,000	High enough to allow prior distributions to converge to posterior distributions
Thinning rate	5	Only the 5^{th} sample is stored to reduce computational memory storage
Built-in likelihood function	Gaussian likelihood, measurement error integrated out	We do not consider the measurement error in the observations
Parameter space **Initial sampling**	**Value**	**Justification**
Initial sampling	Based on prior distribution of parameters: F uniform distribution (centred on 0.16 ±50%) k_{WWTP} exponential distribution (mean value of 0.55 $L·g_{ss}^{-1}·d^{-1}$) k_{river} exponential distribution (mean value of 1.3E-04 s^{-1})	See section "data collection for model calibration" and Figure 12
Explicit boundary handling	Fold	Recommended in Vrugt et al. (2016)
Minimum and maximum parameter boundaries	F [0.08 – 0.24] k_{WWTP} [0.11 -2] $L·g_{ss}^{-1}·d^{-1}$ k_{river} [6.6E-08 -9.3E-04] s^{-1}	See section "data collection for model calibration"

The number of function evaluations was established by trial-and-error; we concluded that with 20,000 function evaluations we guaranteed the R- statistic (Gelman et al., 1992) to remain below 1.2 (Figure 11; Vrugt et al., 2016). As such, we took the last 5,000 values of the posterior distributions (calibrated parameter distributions) and fit them to their respective kernel distributions. Finally, the DREAM algorithm provided 5,000 calibrated diclofenac loads at every point along the river network and in the WWTP influent and effluent associated with the 5,000 calibrated parameter values. These concentrations were also estimated by dividing the loads by either the river flow or the influent/effluent discharge.

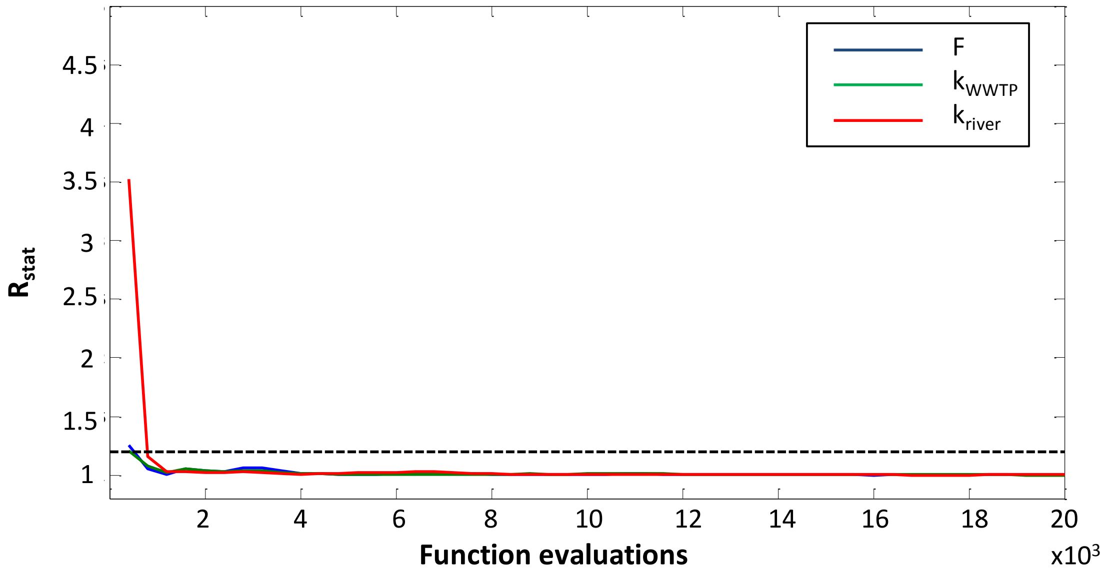


Figure 11. Convergence of sampled chains in Bayesian inference. The R-statistic remains below 1.2 for the three model parameters.

We evaluated the quality of the fit using the goodness-of-fit index (R^2, Equation 7; Nash & Sutcliffe, 1970) defined as

$$R^2 = 1 - \frac{SSE}{SST} = 1 - \frac{\Sigma(y_i - \hat{y}_i)^2}{\Sigma(y_i - \bar{y})^2} \qquad \text{(Eq. 7)}$$

where *SSE* represents the sum of the squared residuals (errors) and *SST* represents the total sum of the squared deviations in the observations (y_i) from the mean ($\bar{y}$). R^2= 1 indicates a perfect match between modelled ($\hat{y}_i$) and observed loads (y_i).

We also conducted a global sensitivity analysis to evaluate the contribution of each parameter to the river load variance using standard regression coefficients (SRC). Thus, we calculated the SRC performing linear regression on the diclofenac loads simulated by the MFT model at each monitoring point as in Flores-Alsina et al. (2012). SRC is a reliable measure of the parameter sensitivity if the sum of squares of SRC (denotes as r^2, coefficient of determination) is greater than 0.7. That would mean that the model can be sufficiently linearised (Helton & Davis, 2003). The higher the absolute values of the SRC, the stronger the influence of the corresponding parameter on determining the river loads. SRC^2 would represent the percent contribution of each parameter to the river load variance (Flores-Alsina et al., 2012).

4.1.2 Results

4.1.2.1 MFT model calibration and performance

We obtained calibrated F values from 0.11 to 0.23 (percentile 2.5th and 97.5th of the posterior distributions respectively), with a median of 0.15; calibrated k_{WWTP} values from 0.12 to 0.70 (percentile 2.5th and 97.5th of the posterior distributions respectively), with a median of 0.25 $L \cdot g_{ss}^{-1} \cdot d^{-1}$; and calibrated k_{river} values from 1.4E-07 to 1.5E-05 (percentile 2.5th and 97.5th of the posterior distributions respectively), with a median of 3.0E-06 s^{-1} (Table 6)

Although the shape of the prior and posterior distributions of F changed, we obtained similar range (difference between percentile 2.5th and 97.5th) and median values of both distributions (Figure 12, top left). This means that the values collected from literature (Gros et al., 2007, Gros et al., 2010, Jelic et al., 2011 – data in Annex 1 - A1.3) to build the prior distribution of F fit well with the concentrations of diclofenac measured at the WWTP influents. Conversely, the posterior distributions of k_{WWTP} and k_{river} adjusted to the lower values of the prior distributions of k_{WWTP} and k_{river} (Figure 12, top right and bottom). This means that most of the values collected from literature (Gros et al., 2007, Gros et al., 2010, Jelic et al., 2011 – data in Annex 1 - A1.4 and A1.5) to build the prior distributions of k_{WWTP} and k_{river} were too high to fit well with the concentrations of diclofeanc measured at the WWTP effluents and rivers and, hence, lower removal in WWTPs and rivers is expected in the Llobregat compared to literature

Table 6. Calibrated model parameters for diclofenac

	Percentile		
	2.5th	50th	97.5th
F	0.11	0.15	0.23
k_{WWTP}	0.12	0.25	0.70
WWTP Removal (%)	23	38	63
k_{river}	1.4E-07	3.0E-06	1.5E-05

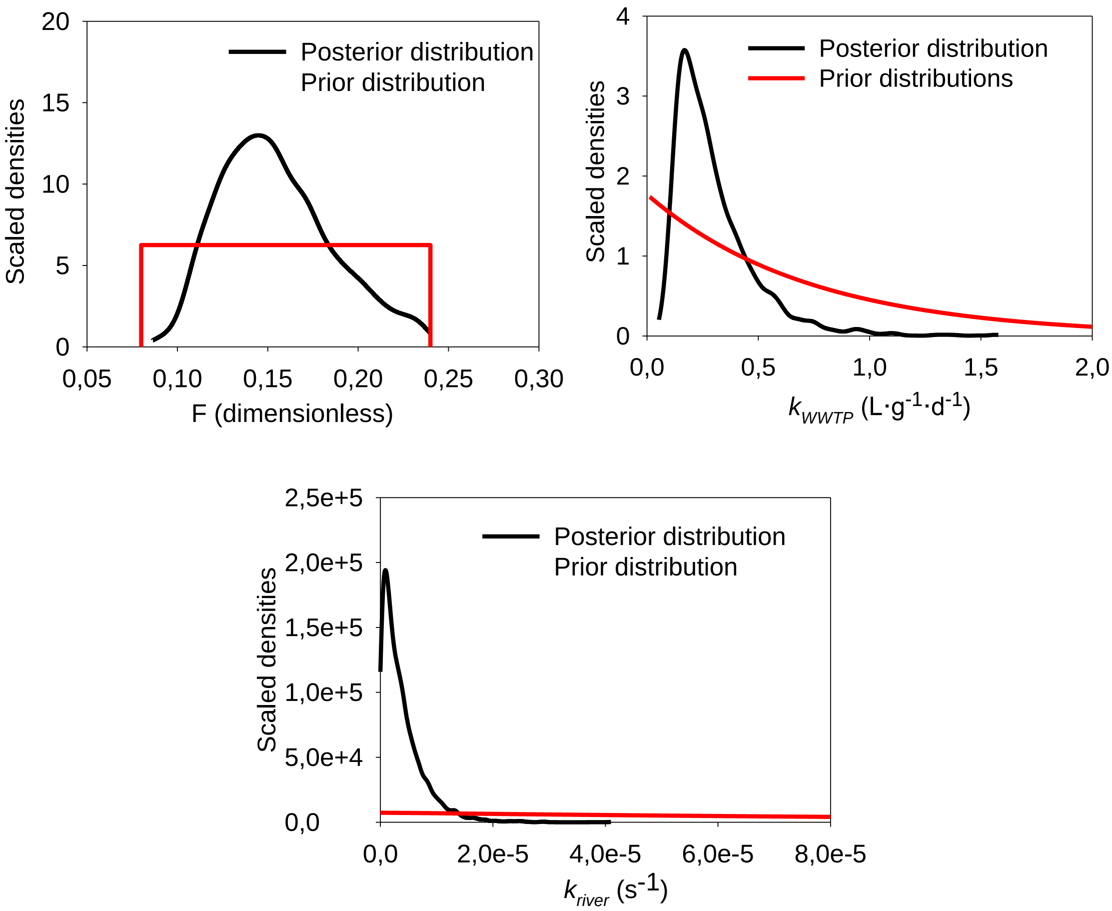


Figure 12. Prior and posterior (calibrated) probability distributions of F (top left), k_{WWTP} (top right) and k_{river} (bottom center) for diclofenac

The calibrated model accurately predicts the diclofenac loads measured at 9 points along the Llobregat River (R^2 = 0.95) and in the influents and effluents of the Igualada and Manresa WWTPs in September 2010 (Figure 13). For each monitoring point in Figure 13, we show the median (circle) and the 2.5 and 97.5 percentiles (vertical bars) of the 5,000 simulated loads; thus, the predictions are presented with uncertainty ranges. The simulated median loads and uncertainty ranges are shown in Table 7. The uncertainty varies from 46% to 106% of the corresponding median and generally decreases downstream for river loads, as in agreement with Ort el al. (2009). These results were obtained by running the MFT model with the calibrated parameter distributions, which are displayed in Figure 12, top left and right and bottom left. Moreover, model predictions satisfactorily lie around the bisector (between twice and half the observation values - dashed lines parallel to the bisector), except for those of ANO1 (overestimated), ANO2 (underestimated) and the WWTP influents and effluents (overestimated) which is justified in the discussion section.

Table 7. Observations and Model Predictions (median and percentiles 2.5th and 97.5th) of diclofenac loads ($g \cdot d^{-1}$) in the river sampling points and in the influents and effluents of the Igualada and Manresa WWTPs after Bayesian calibration

Monitoring point	**Obervations ($g \cdot d^1$)**	**Predictions ($g \cdot d^1$)**		
		Median	**PR2.5**	**PR97.5**
LLO3	6.6	7.3	3.8	12.9
CAR3	1.5	1.8	0.8	3.3
LLO4	16.5	20.5	10.2	36.3
LLO5	23.3	25.0	13.1	43.8
ANO1	0.06	0.2	0.1	0.5
ANO2	15.4	5.9	2.7	10.9
ANO3	20.7	11.0	5.9	19.3
LLO6	26.9	41.7	22.0	73.2
LLO7	115.2	107.9	55.8	189.5
WWTP influent Igualada	5.3	12.4	8.9	19.6
WWTP effluent Igualada	4.2	5.6	2.5	10.4
WWTP Influent Manresa	9.7	17.1	12.3	27.0
WWTP effluent Manresa	5.9	11.3	6.3	19.1

The calibrated model shows that 25 [12-51] $kg \cdot year^{-1}$ of diclofenac were removed at the WWTPs and that 17 [8-42] $kg \cdot year^{-1}$ were removed in the river. The values in brackets represent the 5th and 95th percentile of the respective median removals. There are no statistically significant differences between the total load of diclofenac removed in WWTPs and in rivers (justification in Annex 1- A1.6 Evaluation of statistically significant differences between the amount of diclofenac removed by WWTPs and rivers in the Llobregat). Thus, we cannot exclude the role of rivers in diclofenac degradation in the water cycle (Kehrein et al., 2015). It is worth noting that the model accounts for the differing operating conditions of the numerous WWTPs in the catchment; hence, introducing Xss and ϑh independent values for each WWTP entails different removals of diclofenac.

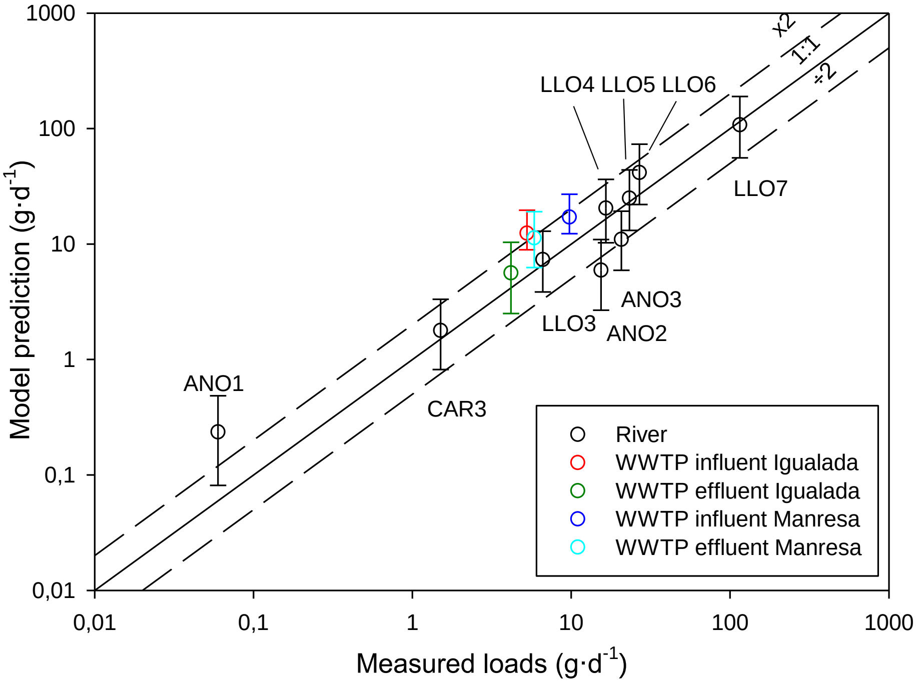


Figure 13. Calibrated Model predictions versus measurements of diclofenac loads ($g \cdot d^{-1}$) in the river sampling points (black symbols) and in the influents and effluents of the Igualada and Manresa WWTPs (coloured symbols).

4.1.2.2 Sensitivity analysis on model parameters

Table 8 shows the standard regression coefficients (SRC) between the simulated concentrations of diclofenac at each monitoring point and the calibrated model parameters. Since the coefficient of determination (r^2) is greater than 0.7 for every case, SRC is a valid measure of sensitivity (Flores-Alsina et al., 2012). The higher the absolute value of the SRC, the more influential the parameter is. We obtain that all 3 parameters contribute to explain the uncertainty in river loads because the SRC values are significant in every case. While F is the most influential parameter in the monitoring points of the Llobregat river (higher SRC values), k_{wwtp} and k_{river} are the second and third most influential parameter in these stations respectively. In the points of the Anoia river, F, k_{wwtp} and k_{river} are the most influential parameters in ANO3, ANO2 and ANO1 respectively.

Table 8. Standard regression coefficients (SRC) calculated from linear regression between simulated concentrations at each monitoring point and the 3 calibrated parameters. The coefficient of determination (r^2) is over 0.7 in every point

	LLO3	**CAR3**	**LLO4**	**LLO5**	**ANO1**	**ANO2**	**ANO3**	**LLO6**	**LLO7**
F	0.71	0.63	0.69	0.71	0.51	0.61	0.72	0.71	0.71
k_{wwtp}	-0.47	-0.6	-0.57	-0.52	-0.54	-0.71	-0.52	-0.51	-0.47
k_{river}	-0.47	-0.38	-0.37	-0.41	-0.56	-0.05	-0.38	-0.42	-0.47
r^2	**0.94**	**0.9**	**0.93**	**0.94**	**0.86**	**0.87**	**0.93**	**0.94**	**0.95**

4.1.3 Discussion

Overall, the MFT model is ready to be used for decision-making. The capacity of the MFT model for predicting diclofenac loads and simulated uncertainty ranges is on the same order of magnitude as the model performances found in the literature (Ort et al., 2009; Kehrein et al., 2015; Alder et al., 2010). Using the Bayesian calibration approach, we have been able to decrease the uncertainty of diclofenac river concentrations by more than half. For instance, the uncertainty concentration range at LLO7 was [-97%, +714%] before calibration (using the prior distribution of parameters, Figure 14 and Table 9) and [-48%, +76%] after calibration. The most striking differences were found for ANO1, where this range was reduced from [-100%, +130,000%] to [-65%, +106%].

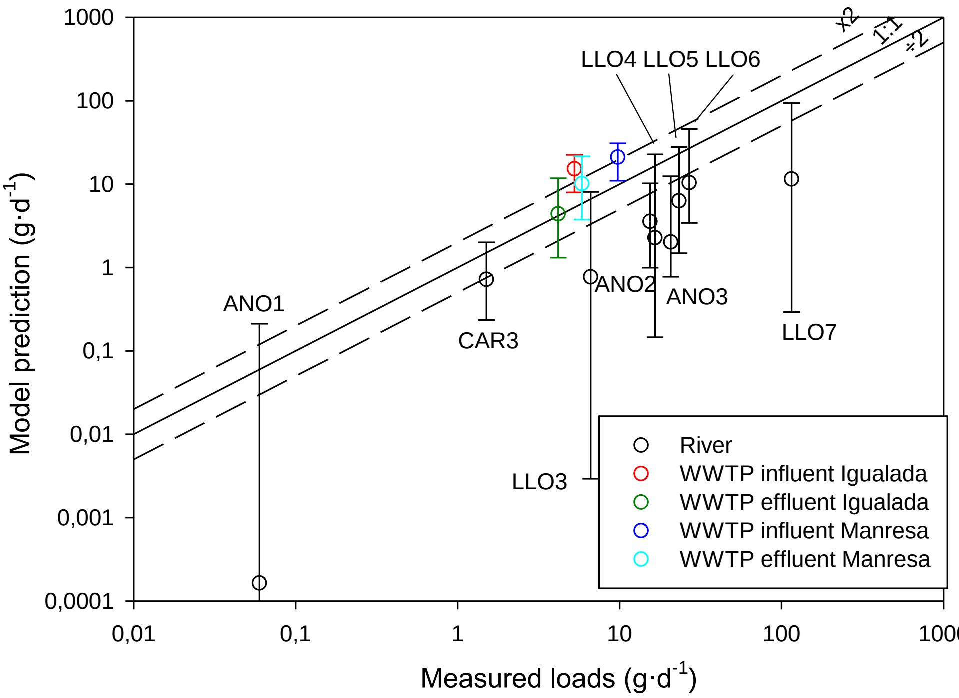


Figure 14. Model predictions versus measurements of diclofenac loads ($g \cdot d^{-1}$) in the river sampling points (black symbols) and in the influents and effluents of the Igualada and Manresa WWTPs (coloured symbols) before calibration.

Table 9. Model Predictions (median and percentiles 2.5th and 97.5th) of diclofenac loads ($g\cdot d^{-1}$) in the river sampling points and in the influents and effluents of the Igualada and Manresa WWTPs before calibration.

Monitoring point	**Obervations ($g\cdot d^{1}$)**	**Predictions ($g\cdot d^{1}$)**		
		Median	**PR2.5**	**PR97.5**
LLO3	6.6	0.8	2.9E-03	8.1
CAR3	1.5	0.7	0.2	2.0
LLO4	16.5	2.3	0.1	22.7
LLO5	23.3	6.3	1.5	27.8
ANO1	0.06	1.6E-04	1.9E-16	0.2
ANO2	15.4	3.6	1.0	10.2
ANO3	20.7	2.0	0.8	12.4
LLO6	26.9	10.4	3.4	45.9
LLO7	115.2	11.5	0.3	93.5
WWTP influent Igualada	5.3	15.3	8.0	22.4
WWTP effluent Igualada	4.2	4.4	1.3	11.8
WWTP Influent Manresa	9.7	21.0	11.0	30.9
WWTP effluent Manresa	5.9	10.2	3.8	21.6

As expected, the largest load was measured at the river mouth (LLO7), and the smallest loads were measured in the most upstream points (ANO1 and CAR3). Obviously, with increasing distance downstream, the number of WWTPs discharging diclofenac into the river increases. Predictions lie close to the bisector (Figure 13), except for ANO2, ANO1 and the WWTP influents and effluents. The overestimated loads associated with the WWTPs (Figure 13) can be explained by the fact that we considered a common census population connected to each WWTP. Instead, a "de facto population" or "chemical loads population" might provide a better estimate of this variable (Lai et al., 2015). In addition, it was observed that the Igualada WWTP effluent discharged 4 $g\cdot d^{-1}$ of diclofenac in September 2010 immediately upstream of ANO2. Consequently, because the MFT model calculates the loads in the river by using a mass balance and because small WWTPs are discharging upstream of ANO2, it inevitably underestimated the observed diclofenac at that point (15 $g\cdot d^{-1}$). This difference could be attributed to possible errors in the sampling campaign design conducted in September 2010. Conversely, the overestimation at ANO1 can be explained by an underestimation of the attenuation capacity of upstream river sections.

4.2 Incorporating model uncertainty into the evaluation of interventions to reduce microcontaminant loads in rivers

High levels of uncertainty compromise the usability of model outcomes for decision-making. Using the probability distribution functions (PDFs) of the calibrated parameters in chapter 4.1, decision makers might only select extreme interventions that drastically reduce microcontaminant loads in rivers, rejecting cheaper and less extreme interventions. The main goal of this chapter is to evaluate how the magnitude of key model parameter uncertainties influence the selection of end-of-pipe interventions (at WWTPs) designed to reduce the microcontaminant loads in rivers.

In this chapter, we evaluate three levels of uncertainty in the key model parameters using the MFT model calibrated in chapter 4.1. The first level of uncertainty corresponds to the reference distributions obtained from the Bayesian calibration. Then, for each parameter, we generate a narrower PDF (decreased uncertainty with respect to the reference) and a wider PDF (increased uncertainty). The narrower PDF would represent the future scenario of having more scientific knowledge on the model parameters and, hence decreased parameter uncertainty. The wider PDF represents the scenario of not having measurements of diclofenac concentrations available for calibration, and hence, increased parameter uncertainty (prior distributions in Figure 12). For each level of uncertainty, we evaluate increasing removal efficiencies of diclofenac at the WWTPs (WWTP interventions).

This chapter concludes that model uncertainty greatly influences the decisions that river basin authorities must make to reduce the microcontaminant loads released by WWTPs into rivers. Indeed, apparent reductions in the diclofenac concentration can only be achieved if diclofenac removal significantly increases (i.e. by installing a tertiary treatment after the secondary treatment) regardless of the level of uncertainty. Interventions to improve the secondary treatment operation resulted in apparent reductions only in the case of reduced uncertainty. Thus, research priorities to help reduce model uncertainty are discussed in the end of this chapter.

Redrafted from:

P. Gimeno, R. Marcé, Ll. Bosch, J. Comas, Ll. Corominas, 2017. Incorporating model uncertainty into the evaluation of interventions to reduce microcontaminant loads in rivers, Water Research, 124, 415-424

4.2.1 Methodology

4.2.1.1 Evaluation of upgrade interventions under uncertainty scenarios

We used the MFT model calibrated in chapter 4.1 to describe the fate and removal of diclofenac along the Llobregat river basin during September 2010. We evaluated 36 scenarios (Figure 15) combining 3 levels of uncertainty in key model parameters and 12 levels of diclofenac removal efficiencies in WWTPs (k_{WWTP}), emulating upgrades in secondary treatment and implementation of tertiary treatment. For evaluation, we used the diclofenac concentrations at the sampling point LLO7, which is at the end of the river catchment (see Figure 5).

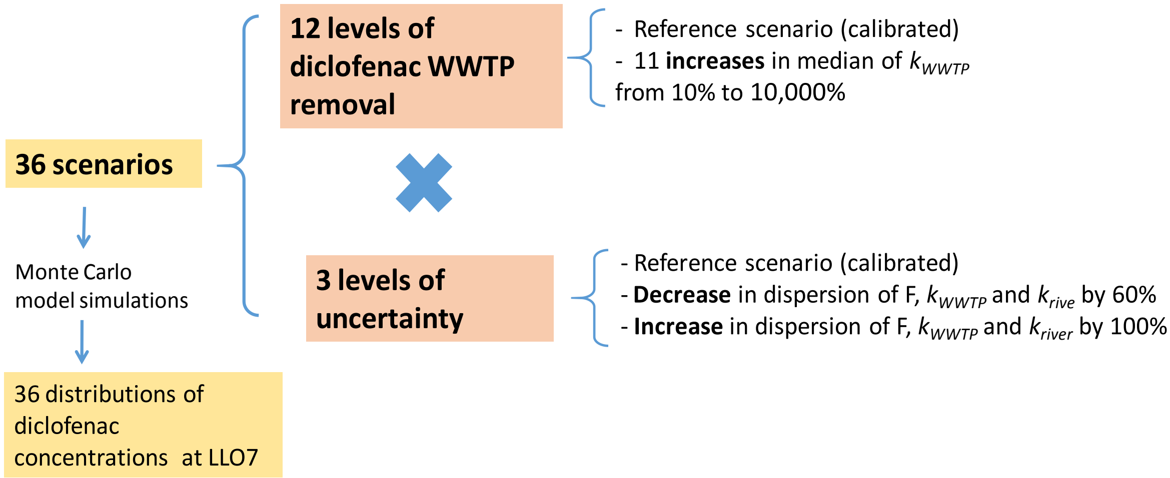


Figure 15. Description of scenarios of uncertainty and diclofenac WWTP removal efficiencies.

4.2.1.2 Generation and simulation of scenarios of uncertainty and WWTP interventions

The levels of uncertainty include the “calibrated” or reference scenario, the “increased uncertainty” scenario and the “decreased uncertainty” scenario. The “calibrated” scenario used the posterior PDFs of the three parameters obtained from the Bayesian calibration. The “increased uncertainty” scenario was obtained by increasing the dispersion of every value in the three PDFs (the difference between a value and the median) by 100% (Figure 15). This scenario mimics the situation of not having diclofenac concentration measurements in the river and WWTPs available for model calibration. The 100% increase matches the uncertainty range before running the Bayesian calibration against observed data. Similarly, the “decreased uncertainty” scenario was obtained by reducing the dispersion of every value in the three PDFs by 60%. This scenario mimics the situation of having more accurate data (e.g. information on the percentage of pharmaceutical that is really consumed and improperly disposed in toilets) for model parameters. This 60% reduction is justified on the basis of k_{WWTP}. The 60% reduction in uncertainty corresponds to lowering the uncertainty bounds of the k_{WWTP} distribution to obtain an approximately 20% uncertainty around the median. The 20% range was obtained from the variability of the measured removal in 14 Swiss WWTPs (Ort et al. 2009). As noted in Ort et al., (2010), large uncertainties (for microcontaminants) are associated with sampling the influents of WWTPs, and the variability observed in the removal rates could arise from inadequate sampling. The measuring campaigns in the 14 Swiss WWTPs were conducted with adequate sampling (the error in these measurements was minimized using volume-proportional 24-h composite samples and high sampling frequency). Hence, for this reduced-uncertainty scenario, we assumed that we can obtain an uncertainty range similar to the ±20% measured from the 14 Swiss WWTPs by using better data sources (eliminating sampling uncertainty). In both scenarios (increased and decreased uncertainty), we kept the medians of the parameter PDFs constant and equal to the calibrated values. Because the three parameters considered (F, k_{WWTP} and k_{river}) contribute greatly to the uncertainty in river concentrations (see 4.1.2.2 Sensitivity analysis on model parameters), we varied the shape of the PDFs for all of them simultaneously. The shapes of these distributions are shown in Figure 16, top left and right and bottom left.

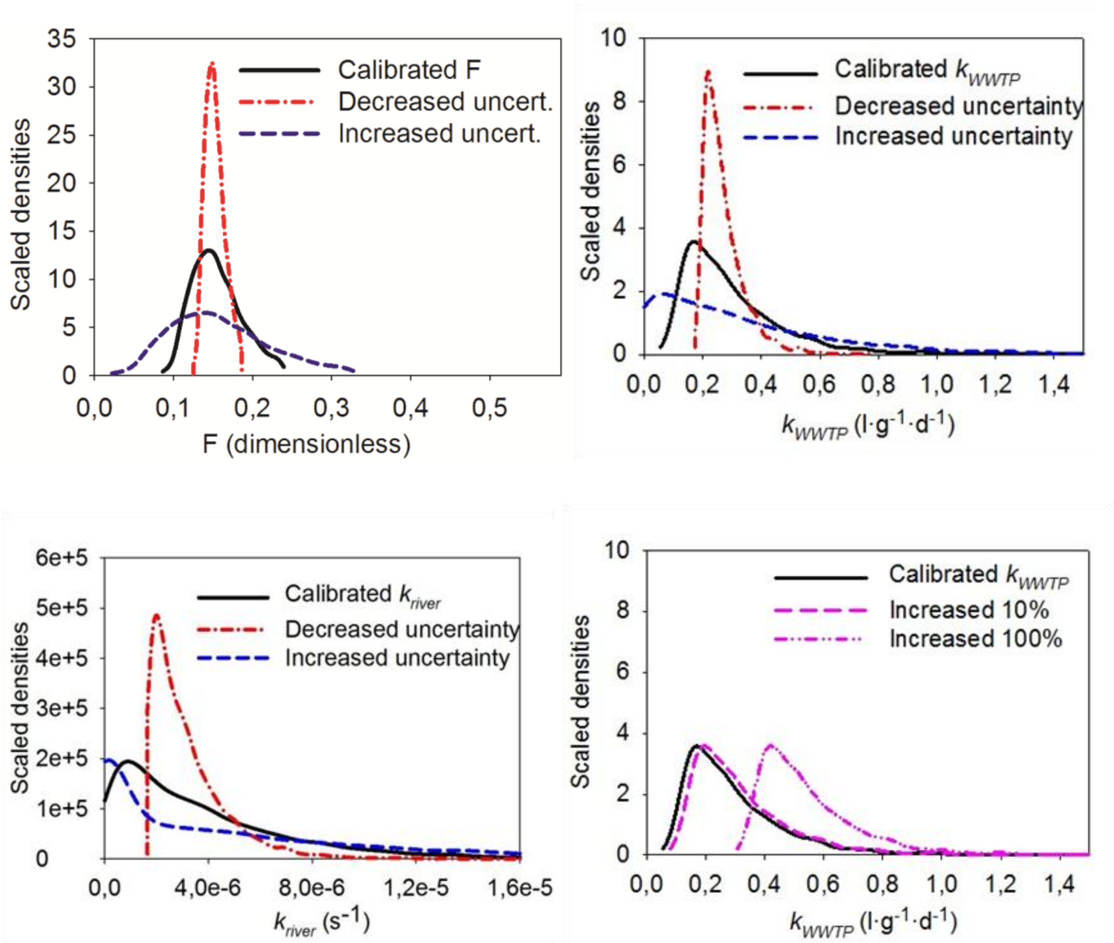


Figure 16. Probability distributions of F (top left), k_{WWTP} (top right) and k_{river} (bottom left) for the calibrated (black line), decreased uncertainty (red dash-dotted line) and increased uncertainty (blue dashed line) scenarios. Bottom right: Calibrated probability distribution of k_{WWTP} (black) increased by 10% (magenta dashes) and 100% (magenta dash-dot-dots).

To simulate WWTP interventions (in the secondary and tertiary treatments), we consider different levels of diclofenac WWTP removal efficiencies. These were obtained by increasing the medians of the "calibrated" k_{WWTP} PDFs by 10%, 20%, 30%, 40%, 50%, 100%, 200%, 500%, 1,000%, 5,000%, and 10,000% while keeping the dispersion constant. In this way, the average

WWTP removal efficiency increases from the “calibrated” scenario (38%) to nearly complete removal (98%) (more details can be found in 4.2.2.1 Evaluation of WWTP upgrades under scenarios of uncertainty). For illustration purposes, Figure 16, bottom right, shows the distributions of calibrated k_{WWTP} when it was increased by 10% and 100%. We repeated this process for the k_{WWTP} PDF associated to the “increased uncertainty” and “decreased uncertainty” scenarios. We scaled the densities of every distribution so that the area below each curve remained equal to 1.

Thus, 36 scenarios were generated by combining 12 levels of increased WWTP removal and 3 levels of uncertainty in the three parameters (Figure 15). Then, we simulated these scenarios running 5,000 Monte Carlo simulations with the MFT model. Therefore, 36 diclofenac concentration distributions were obtained for LLO7.

4.2.1.3 Evaluation of scenarios

We evaluated the probability of each intervention achieving an *apparent reduction* of the diclofenac concentration at LLO7 compared to the reference situation (the calibrated model results). An apparent reduction is achieved when the empirical PDF of the diclofenac concentration at LLO7 (resulting from Monte Carlo simulations of a given scenario) shows minimal overlap with the PDF obtained in the reference situation. The probability of achieving an apparent reduction in a given scenario was computed as the percent of diclofenac concentration from the empirical PDF lying below the 5th percentile of the PDF of the reference situation. For example, if the 5th percentile of the PDF of the reference situation is 40 ng·L^{-1}, an 80% probability of apparent reduction implies that 80% of the diclofenac concentrations from the PDF obtained in the tested scenario are less than 40 ng·L^{-1}. To calculate the probability of achieving an apparent reduction, we generated 10,000 bootstrapping samples (sampled uniformly at random with replacement) for each of the 36 diclofenac concentrations simulated in the scenario analysis and applied equation 8. Because we ran 10,000 samples, we obtained a distribution of 10,000 probabilities for each of the 36 scenarios. We implemented this analysis using the MATLAB code included in Annex 2 –A2.1.

$$\mathrm{Pr}\mathit{obability} = \frac{\mathit{number\ of\ values\ in\ decreased\ concentration} < 5\mathit{th\ percentile\ of\ calibrated\ concentration}}{\mathit{total\ number\ of\ values\ in\ decreased\ concentration}} \qquad \text{(Eq.8)}$$

In addition, we assessed which interventions reduced the diclofenac river concentrations below two limits; first, the environmental standard of 100 ng·L^{-1} as proposed by the European Commission (EC) to amend Directive 2013/39/EU (Johnson et al., 2013). Second, the concentration of 30 ng·L^{-1} which corresponds to the 5th percentile of the Lowest Observed Effect Concentration (LOEC) on aquatic biota (Acuña et al., 2015a)

Finally, we evaluated the influence of hydrological conditions on the selection of WWTP interventions that lead to apparent reductions of diclofenac concentrations at LLO7. We repeated the analysis considering low flows and velocities in the Llobregat river (i.e. 7Q10 (the lowest 7-day average flow that occurs on average once every 10 years) values). For the calculation of 7Q10, we used daily flows measured in the last 10 years at 13 monitoring stations in the Llobregat (Catalan Water Agency, 2017). We conducted a mass-balance in flows to calculate the 7Q10 for ungauged river stretches as it was done in Aldekoa et al. (2013). A power function was fitted to every river flow and velocity pair-values of September 2010 ($v = 0.48*Q^{0.24}$; goodness of fit R^2=0.65). We used this power function to obtain the velocities associated to the 7Q10 river flows in every stretch (the flows and velocities are included in the Annex 2 – A2.2). We simulated the same percentage increases in k_{WWTP} and the same uncertainty levels in the three model parameters as in Figure 15. Thus, we compared the results obtained considering September 2010 hydrological conditions (normal conditions) and 7Q10 conditions (dry weather flow conditions).

4.2.2 Results

4.2.2.1 Evaluation of WWTP upgrades under scenarios of uncertainty

The simulated diclofenac concentrations at LLO7 decrease as the removal in WWTPs increases (i.e., increase in k_{WWTP}) (Figure 17, left). In Figure 17, left, the crosses represent the median of the 5,000 simulated values, and the bars represent the 5th and 95th percentiles. For the reference scenario (calibrated k_{WWTP}), the predicted mean (and the 5th and 95th percentiles in brackets) of WWTPs removal efficiency is 38% (16%-62%). For the other simulated scenarios (with increases in k_{WWTP}), the mean removal efficiency increases from 40% (17%-64%) to 98% (95%-99%) (Figure 17- axis x) as k_{WWTP} increases from 10% to 10,000%. Similarly, the uncertainty (in absolute values) of the diclofenac concentrations decreases in each evaluated scenario as k_{WWTP} increases. Remember that we assumed that the upgrade was only applied to the 34 WWTPs for which we had detailed information. The remaining 22 WWTPs were not upgraded under any scenario evaluated.

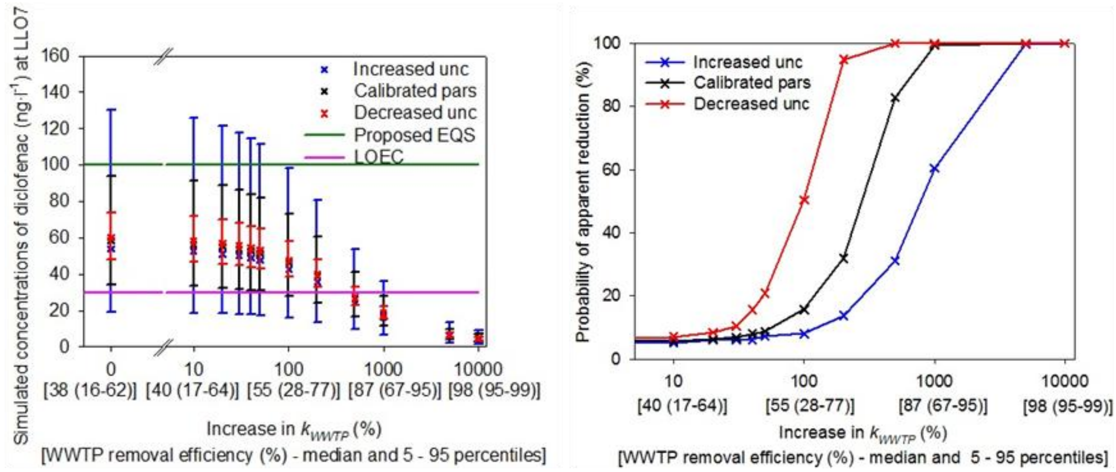
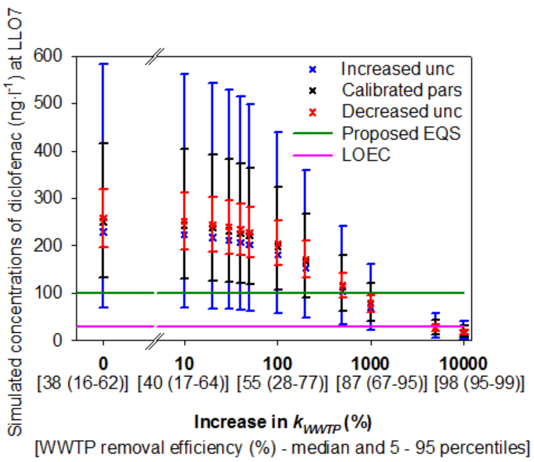


Figure 17. left: Simulated concentrations of diclofenac at LLO7 during September 2010 for the uncertainty scenarios (calibrated: black, increased uncertainty: blue, and decreased uncertainty: red) combined with the 12 scenarios of increases in k_{WWTP}. Right: Probability of achieving apparent reductions (%) in diclofenac concentrations at LLO7 for the increases in k_{WWTP} and for the scenarios of uncertainty.

Figure 17 (right) shows the probability of achieving an apparent reduction in river concentrations at LLO7 for simulated increases in k_{WWTP} under the different parameter uncertainty scenarios. The crosses in Figure 17 (right) symbolize the median of the 10,000 calculated probabilities. A high probability indicates that there is little overlap between the PDFs of the reference situation and the evaluated scenario and, hence indicates an apparent reduction in diclofenac concentrations. Only increases in k_{WWTP} over 1,000% (resulting in WWTP removal efficiencies of over 90%) cause an apparent reduction in the diclofenac concentrations (probability near 100%) compared with the reference scenario, regardless of the level of uncertainty evaluated. If the parameter uncertainty increases, the probability drops rapidly for increases in k_{WWTP} that are less than 1,000%; thus, unapparent reductions would be obtained after implementing such upgrades. However, if the parameter uncertainty decreases, we can obtain apparent reductions (probability > 90%) with increases in k_{WWTP} starting at 200% (over 64% of WWTP removal efficiency). In contrast, increases in k_{WWTP} under 50% do not result in apparent reductions (probability < 20%), regardless of the level of uncertainty. Overall, the parameter uncertainty primarily influences increases in k_{WWTP} between 100% and 1,000% (between 55% and 87% WWTP removal efficiency).

Uncertainty also influences the positive or negative compliance of diclofenac river concentrations with standards. Although the concentrations are always below 100 $ng \cdot L^{-1}$ for the calibrated uncertainty, they do not meet this limit if the parameter uncertainty increases (Figure 17, left). However, we find out that doubling k_{WWTP} (100% increase) is sufficient to comply with the previous boundary under any evaluated scenario of uncertainty. Only increases in k_{WWTP} over 1,000% (increasing WWTP removal efficiency over 90%) decrease the simulated river diclofenac concentrations to below 30 $ng \cdot L^{-1}$, regardless of the level of uncertainty.

These conclusions on the influence of uncertainty remain valid when simulating with low flow conditions in the river (i.e. 7Q10) (Figure 18, right). As expected, we obtained higher concentrations of diclofenac at LLO7 compared to the concentrations simulated with September 2010 data. We find out that increases in k_{WWTP} over 1,000% would be required to comply with the boundary of 100 $ng \cdot L^{-1}$ under any scenario of uncertainty considering low flows. Likewise, only increases in k_{WWTP} over 10,000% decrease the simulated river diclofenac concentrations to below 30 $ng \cdot L^{-1}$ (Figure 18, left).



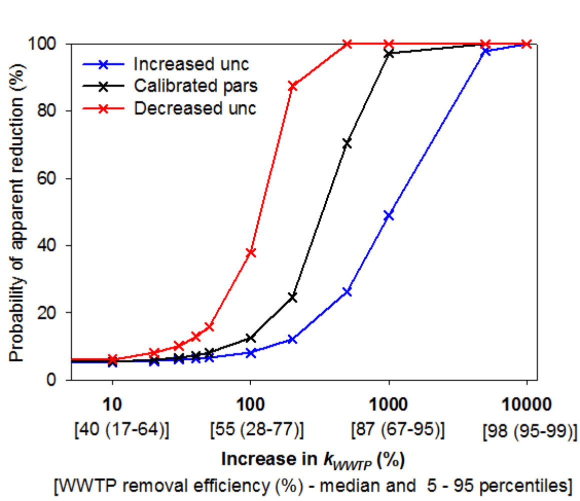


Figure 18. left: Simulated concentrations of diclofenac at LLO7 during 7Q10 flows for the uncertainty scenarios (calibrated: black, increased uncertainty: blue, and decreased uncertainty: red) combined with the 12 scenarios of increases in k_{WWTP}. Right: Probability of achieving apparent reductions (%) in diclofenac concentrations at LLO7 for the increases in k_{WWTP} and for the scenarios of uncertainty.

4.2.3. Discussion

4.2.3.1 Evaluation of WWTP upgrade interventions under the uncertainty scenarios

The results show the influence that model uncertainty has on evaluating scenarios of diclofenac load reduction in rivers. Upgrading WWTPs to tertiary treatment (involving a diclofenac removal rate greater than 90%) result in an *apparent reduction* under all evaluated levels of uncertainty. This level of treatment could be accomplished by installing activated carbon or ozonation technologies (Hollender et al., 2009, Boehler et al., 2012). WWTP upgrades that involve modification of the process configuration (corresponding to a diclofenac removal of approximately 74%, or a k_{WWTP} value of 1.4 $L{\cdot}g_{ss}^{-1}{\cdot}d^{-1}$, as reported in Suarez et al., 2010) result in an *apparent reduction* only under the lowest levels of uncertainty evaluated. Such upgrades include activated sludge followed by an oxic post-treatment, which can increase the performance by up to 70% (Falås et al., 2016), or the enhancement of nitrogen removal through nitrification (Suarez et al., 2010). Therefore, the results confirm our hypothesis that existing knowledge on the model parameter values biases the selection of WWTP upgrade interventions towards the most extreme alternatives that result in very large reductions in loads. Using the calibrated parameter PDFs based on existing knowledge, only extreme interventions that drastically reduce the concentrations of diclofenac (i.e., the installation of tertiary treatments) would be selected by decision makers. Extreme interventions have been previously selected in the water sector. For instance, decision makers are more likely to implement WWTP upgrades (most extreme intervention) to reduce phosphorous loading in a catchment than they are to implement agriculture policy alternatives (Reichert & Borsuk, 2005). Similarly, to reduce damage due to river floods, the construction of a retention basin is more likely to be chosen than dike heightening or reforestation (de Kort & Booij, 2007). Decision makers can use this type of analysis to evaluate whether changes in the model parameter uncertainties (via access to more accurate data for defining the parameter PDFs) would result in the selection of a different intervention. The novelty of this approach is that we demonstrate that interventions in the secondary treatment only become a suitable alternative for the reduction in diclofenac concentrations when parameter uncertainties decrease. Decision makers and researchers can also use this methodology to determine which parameters they should focus on to increase the existing scientific knowledge. In MFT, the three parameters F, k_{WWTP} and k_{river} contribute significantly to the uncertainty in the diclofenac concentrations. Thus, it is important to define them accurately in order to decrease the uncertainty in diclofenac concentrations and to make better decisions.

In this study, for each scenario, we have applied exactly the same upgrade intervention for the 32 WWTPs. Further work will be conducted to evaluate different combinations of interventions in a single scenario using a cost-benefit analysis.

4.2.3.2 Direction of research efforts to decrease uncertainty

In this study, we assumed that some scenarios would include reduced uncertainty in the model parameters compared to the reference (calibrated) model. In reality, further research should be conducted to reduce such uncertainty. The reported values of F vary markedly for individuals, depending on gender, age, nutrition, endocrine function and pre-existing diseases (Park, 2001). Uncertainty could be reduced by increasing model complexity; as an example, different F values could be assigned to different population groups, depending on gender, age, nutrition, endocrine function and pre-existing diseases (Park, 2001). Additionally, the epistemic F uncertainty could be reduced by more precisely estimating the amount of diclofenac consumed per person (i.e., from surveys) or by more precisely estimating the diclofenac loads following routes other than consumption and excretion via toilets. Such alternative routes might include the improper disposal of pills after the expiration date has been exceeded via sinks and toilets or the washing off of diclofenac from the skin during showers or from clothes in washing machines. In addition, further research on the removal of diclofenac in sewers would reduce the uncertainty in k_{WWTP} (Jelic et al., 2015). The uncertainty in k_{WWTP} depends on the accuracy of the estimated removal of pharmaceuticals in WWTPs. Unsuitable sampling modes result in high levels of uncertainty in load estimation for the influents of WWTPs (Ort et al., 2010) and in the estimation of removal efficiencies (Majewsky et al., 2013). In addition, the variability in WWTP removal efficiencies of pharmaceuticals depends on the process configuration, the existing mixture of microcontaminants that can act as competitors and the nature of the wastewater (Luo et al., 2014). Uncertainty in the diclofenac removal in WWTPs could be reduced if different values of k_{WWTP} were assigned to different process configurations. Thus, different k_{WWTP} probability distributions can be proposed for different WWTP groups, and their respective uncertainty can thus be diminished. K_{river} is highly variable among different river segments (the k_{river} values for diclofenac collected from the literature vary by 4 orders of magnitude). Because diclofenac is a very hydrophilic compound (it remains in the aqueous phase), its in-stream attenuation depends on the local environmental conditions (e.g., temperature and dissolved oxygen). To more accurately define the k_{river} uncertainty, direct measurements of processes occurring in the aqueous phase (e.g., biotransformation and photolysis) should be performed (Acuña et al., 2015b; Aymerich et al., 2016). Note that decreasing uncertainty is related to an increase in model complexity and, in turn, an increase in sampling effort. As demonstrated in this study, stimulating research toward obtaining more knowledge on F, k_{WWTP} and k_{river} would help make more appropriate decisions.

4.3 Balancing environmental quality standards and infrastructure upgrade costs for the reduction of pharmaceutical loads in rivers

Investments for upgrading WWTPs with tertiary treatment to reduce pharmaceutical loads in surface waters at catchment scale can be daunting. These investments are highly sensitive to the selection of environmental quality standards (EQSs) for the target pharmaceuticals. Hence, this chapter aims to evaluate the relationship between the potential EQS for pharmaceuticals and the cost of the WWTP upgrades required to avoid EQS exceedance. We used diclofenac as the target compound and ozonation as the upgrading technology. This work is applied to the Llobregat river.

We use the MFT model calibrated in chapter 4.1 coupled to an optimization algorithm to evaluate the relationship between the EQS for pharmaceuticals and the cost of the WWTP upgrades. The algorithm optimizes the number of WWTPs in the Llobregat requiring an upgrade to minimize the total amount of diclofenac that exceeds the EQS in every river section and the total cost. We evaluate 40 scenarios representing a combination of 4 potential EQSs, 5 levels of uncertainty bounds in the predictions of river concentrations and 2 hydrological scenarios.

The results show that there is a nonlinear relationship between the EQS and the required investment and that there is an optimal EQS that balances costs and ecosystem protection. Moreover, the results demonstrate that the selection of the hydrological conditions also plays a key role in the upgrade analysis and that the investment in research would allow the reduction of uncertainties and, hence, a reduction in the WWTP upgrade costs.

Redrafted from:

P. Gimeno, J. Severyns, V, Acuña, J. Comas, Ll. Corominas, 2018. Balancing environmental quality standards and infrastructure upgrade costs for the reduction of pharmaceutical loads in rivers, Water Research, 143, 632-641

4.3.1 Methodology

4.3.1.1 Microcontaminant Fate and Transport model including ozonation.

We used the microcontaminant fate and transport (MFT) model developed in Chapter 4.1 to describe the fate and removal of diclofenac along the entire Llobregat River basin. This model was expanded to include ozonation after secondary wastewater treatments. Ozonation is able to almost completely remove the diclofenac present in secondary effluents (95-99%) at a low ozone dose (Hollender et al., 2009). The estimated cost for ozone appears to be lower than other technologies, such as Ultraviolet and activated carbon (Wahlberg et al., 2016; Mulder et al., 2015). However, harmful by-products are generated during ozonation, so we also considered a filtration step (sand filter) afterwards (Hollender et al., 2009). The percentage of diclofenac removal through ozonation and sand filtration is described by the coefficient α in equation 9. Hence, the diclofenac load from secondary effluent (after conventional activated sludge treatment, L_{eff}) simulated by the MFT model would be additionally removed by (100-α)/100. The load of diclofenac after ozonation and sand filtration is depicted as L_{tert}. We assumed that this technology could only be installed at WWTPs larger than 5,000 PE (18 of 56 WWTPs in the catchment). Installing ozonation in WWTPs smaller than 5,000 PE is not feasible because ozonation requires qualified permanent staff for their operation (Rossi et al., 2013). Moreover, the sum of PE corresponding to the WWTPs smaller than 5,000 PE only represents 6% of the total PE in the Llobregat basin. We have set α to 99 because diclofenac removal is 99% for the ozone dose assumed in this study (0.7 g O3·g DOC^{-1}; see section 4.3.1.2).

$$L_{tert} = L_{eff} * (100 - \alpha)/100 \quad \text{(Eq. 9)}$$

4.3.1.2 Ozonation costs

We collected the yearly costs (capital and operational) of 11 ozonation systems followed by sand filtration from literature (Mulder et al., 2015; Hunziker, 2008; Abegglen et al., 2009; Margot et al., 2013; Biebersdorf, 2014). While the capital costs include investment, realization and project costs, the operational costs account for personnel, maintenance and variable costs. The variable costs include the electrical consumption for ozone generation and sand filtration and the cost of pure oxygen for the ozone production (Table 10). We assumed that ozone is generated from pure oxygen instead of from ambient air. This is justified because almost fivefold higher ozone concentrations can be generated from pure oxygen and only about half the energy is consumed when ozone is generated from oxygen instead of air (Gottschalk et al., 2010). The assumption is that the ozone dosage is 0.7 g O3·g DOC^{-1} and the retention time in the ozonation tank is 25 minutes, which is the lowest ozone dose considered in Mulder et al. (2015) to calculate the ozonation costs. These ozonation operating conditions allow reaching a removal of 99% or higher of diclofenac (Zimmermann et al., 2011, Hollender et al., 2009).

The approach proposed in Mulder et al. (2015) was applied to obtain a full estimate of costs for each of these 11 systems. The capital costs of ozonation for 14,000; 70,000 and 210,000 PE were extracted directly from Mulder et al. (2015). The investment costs of ozonation for 11,000; 45,000, 57,000, 120,000 and 500,000 PE were provided by Hunziker (2008). Abegglen et al. (2009), Margot et al. (2013) and Biebersdorf (2014) provided the investment costs of ozonation for 35,000, 30,000 and 74,000 PE respectively. Thus, we calculated the yearly investment costs assuming a lifetime of 30 years for civil works and 15 years for machinery and electrical equipment and a yearly interest rate of 4% (as well applicable to Spain; Spanish Central Bank, 2010). For the ozonation systems which did not provide yearly capital costs (Hunziker (2008), Abegglen et al. (2009), Margot et al. (2013) and Biebersdorf (2014), we applied an increase of 65% (the ratio between investment and project and realization costs from Mulder et al., 2015) to the investment costs to account for realization and project costs. The yearly maintenance costs are calculated as 3.5% of the total investment costs as in Mulder et al. (2015). These calculations are included in the Annex 3 – A3.1. Personnel and variable costs were adjusted to the reality in Spain (Table 10), hence accounting for Spanish salaries and the price of electricity. We obtained the salary of a qualified operator in WWTPs from the Spanish Ministry of Employment and Social Security (BOE, 2017). We obtained the price of electricity from Eurostat (2017). The price of electricity in Spain in 2017 for non-domestic consumers decreases as the yearly use increases (0.135 €·kWh^{-1} for a use between 20 and 500 MWh·year^{-1}; 0.101 €·kWh^{-1} for a use between 500 and 2,000 MWh·year^{-1} and 0.084 for a use between 2,000 and 20,000 MWh·year^{-1}; Eurostat, 2017). These values include an expected increase of 5.3% in the price of electricity by 2050 (European Commission, 2016b). The cost of pure oxygen also varies depending on the treatment capacity. We used a cost of 0.15 €·kg^{-1} for ozonation systems that treat less than 750 m^3·h^{-1} of wastewater (Prieto-Rodríguez et al., 2013) and 0.08 €·kg^{-1} for ozonation systems that treat more than 750 m^3·h^{-1} (Ried et al., 2009). The calculations to obtain the variable costs are included in the Annex 3 – A3.2. We highlight in green in table 2 those values that were extracted from literature and used directly in our study. We highlight in blue those values that were estimated in this study. The rest of the specifications in Table 10 were extracted from Mulder et al. (2015).

Table 10. Breakdown of the costs per m^3 treated effluent of ozonation followed by sand filtration. We highlight in green those values that were extracted from literature and used directly in our study. We highlight in blue those values that were estimated in this study.

Capacity (PE)	11,000	14,000	30,000	35,000	45,000	57,000	70,000	74,000	120,000	210,000	500,000
Design capacity post treatment (m^3·h^{-1})	130	180	360	430	550	710	900	930	1,400	2,700	6,000
Treated volume (m^3·year^{-1})	759,200	1,024,920	2,102,400	2,511,200	3,212,000	4,146,400	5,124,600	5,431,200	8,176,000	15,373,800	35,040,000
Capital costs (€·year^{-1}) *Investment costs* -Technical life time: civil works (30 years), machinery and electrical equipment (15 years) -Interest: 4% *Realization and project costs: 65% of investment* -Engineering (12%), insurances, permits and other building costs (15%), project management and construction supervision (8%), temporary installations (5%), training personnel (2%), communication (2%), VAT (21%)	170,000	140,000	270,000	150,000	330,000	470,000	590,000	380,000	550,000	1,570,000	1,100,000
Maintenance (€·year^{-1}): 3,5% of investment - Civil works (0.5%), machinery and electrical equipment (3%)	29,000	22,000	43,000	27,000	58,000	79,000	100,000	56,000	93,000	220,000	184,000
Personnel costs (€·year^{-1}) Small WWTP - 1/3 qualified operator salary Medium WWTP - 2/3 qualified operator salary Large WWTP - 1 qualified operator salary	8,300	8,300	8,300	8,300	16,700	16,700	16,700	16,700	25,000	25,000	25,000
Variable costs (€·year^{-1}), including 21% VAT) - Electricity: 0,135 €·kWh^{-1} for 20- 500 MWh·year^{-1}; 0,101 €·kWh^{-1} for 500- 2,000 MWh·year^{-1}; 0,084 €·kWh^{-1} for 2,000-20,000 MWh·year^{-1} - Pure oxygen: 0.15 €·kg^{-1} for design flow < 750 m3·h^{-1} and 0.08 €·kg^{-1} for flow > 750 m3·h^{-1}	32,000	47,000	89,000	106,000	136,000	149,000	137,000	151,000	227,000	440,000	863,000
Total yearly cost (€·year^{-1})	239,300	217,300	410,300	291,300	540,700	714,700	843,700	603,700	895,000	2,255,000	2,172,000
Cost (€·m^{-3})	0.32	0.21	0.20	0.20	0.17	0.17	0.16	0.11	0.11	0.15	0.06

We obtained the cost function using the costs in Table 10 and fitted them to a power function so that we can estimate the cost for any ozonation treatment size (equation 10), where PE accounts for the population equivalent. We included the goodness of fit of the cost values to the potential function (R^2= 0.82) in Figure 19*.* For the WWTPs smaller than 11,000 PE (minimum WWTP size with cost of ozonation in this study), we assumed that the ozonation costs increase following the same power function as in equation 2. This was justified by the use of one single power function that fits real ozonation costs in WWTPs ranging from 5,000 to 1,000,000 PE as in Hillenbrand et al. (2014) and Roccaro et al. (2013).

Cost (€·m^{-3}) $= 6.824 * \mathrm{PE}^{-0.344}$ (Eq. 10)

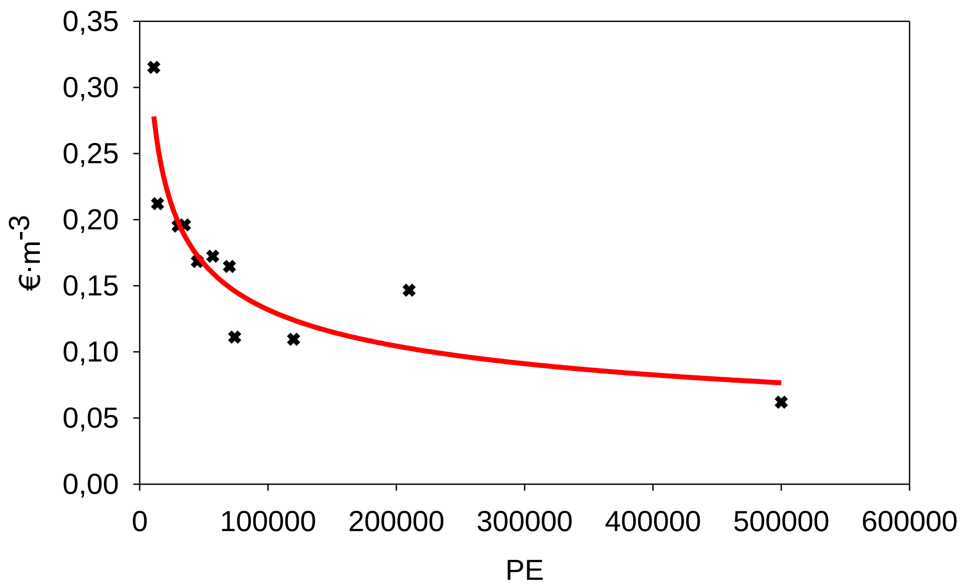


Figure 19. Power cost function fitted to the costs of ozonation for 11 different plants (R^2 = 0.82)

4.3.1.3 Optimization of the number of WWTP to be upgraded.

We used the Non-dominated Sorting Genetic Algorithm II (NSGA-II; Deb et al., 2002) implemented in Matlab (Mathworks, 2018) to find the optimal set of WWTPs that should be upgraded to minimize the cost and EQS exceedance accumulated in all river stretches of the catchment. Hence, we defined two objective functions: (I) minimization of the total yearly cost of the upgrades (Equation 11) and (II) minimization of the total load of diclofenac exceeding EQS (Equation 12).

Min $\sum_{i=1}^{N} Cost$ (Eq. 11)

Min $\sum_{i=1}^{M} ((Conc \times Q_{stretch})\text{-} (EQS \times Q_{stretch})$ (Eq. 12)

where *N* is the number of WWTPs to be upgraded with ozonation and sand filtration, *M* is the number of stretches with EQS exceedance, *Conc* represents the predicted concentration of diclofenac in the river stretch, and $Q_{stretch}$ is the flow simulated in the stretch.

Since there are only 18 WWTPs within the Llobregat River basin with more than 5,000 PE, we selected 18 discrete variables "α" to be optimized either with a value "99" (reflecting that ozonation was installed after that WWTP and 99% of diclofenac was removed before being discharged to rivers) or with a value "0" (reflecting that ozonation was not installed in that WWTP so diclofenac is not further removed). For the rest of the WWTPs in the Llobregat, diclofenac was not further removed (only the removal given by the conventional activated sludge process - average value of 38%; see 4.1.2.1 MFT model calibration and performance). Regarding the NSGA-II parameters, we selected the population size and the number of generations following a "trial and error" approach and ensuring that we evaluate the extreme objective function values (minimum cost and maximum exceedance, and maximum cost and minimum exceedance). Consequently, the population size ranged between 200 and 300, and the number of generations ranged between 100 and 150, depending on the scenario evaluated (see 4.3.1.4 Simulation of scenarios of an EQS under different hydrology and uncertainty levels). The result of the optimization is the "Pareto front" (see example in Figure 20). The "Pareto front" shows the upgrading cost and EQS exceedance of every solution (which includes a particular set of WWTPs) at each generation. The optimal solutions are plotted in the last generation. We selected the optimal solution that minimizes the EQS exceedance the most to compare costs and the number of WWTPs requiring an upgrade between scenarios. We ran the optimization algorithm for each scenario as described hereafter.

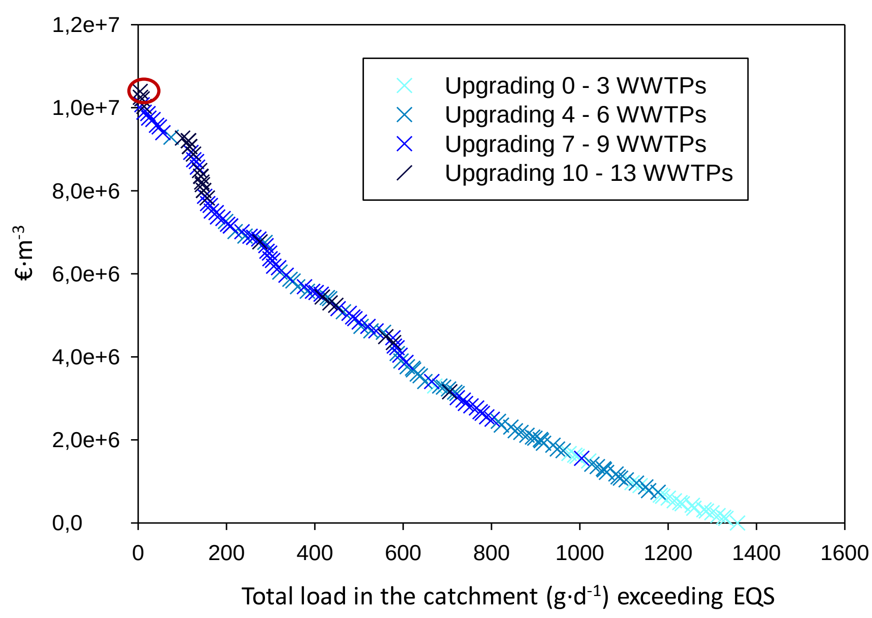


Figure 20. Pareto Front generated in the last generation of the NSGA-II including every optimal solution to avoid 30 ng·L^{-1} exceedance during average flows and considering the highest probable concentrations of diclofenac. We selected (red circle) the optimal solution that minimizes the EQS exceedance the most.

4.3.1.4 Simulation of scenarios of an EQS under different hydrology and uncertainty levels

We evaluated EQS of 10, 30, 50 and 100 ng·L^{-1} in surface waters proposed for diclofenac. We believe that we covered very different levels of environmental protection considering a wide range of EQSs. In 2012, the European Commission (EC) suggested an EQS of 100 ng·L^{-1} for diclofenac (European Commission, 2012). However, noting that this value could be under protective, the EC suggested that this value had to be reviewed later on, taking into account the lowest observed effect concentrations (LOECs) and producing other reliable studies. In 2017, the Swiss Centre for Applied Ecotoxicology suggested an EQS of 50 ng·L^{-1} (Ecotox centre, 2017) based on the NOEC in fish determined by (Birzle, 2015). In addition, Acuña et al. (2015a) suggested a value of 30 ng·L^{-1}, which corresponded to the 5th percentile of the LOEC for aquatic biota. Furthermore, the European Medicines Agency (2006) fixed a threshold safety value of 10 ng·L^{-1} in the environmental risk assessment (ERA) procedures for pharmaceuticals. New ecotoxicity data have to be determined in the future concerning chronic effects and mixtures of chemicals, and the EQS for mixtures may be preferable to derive EQSs for the individual constituent substances (Kienzler et al., 2016). Overall, there is no agreement on the definition of an EQS for diclofenac.

As for the hydrological conditions, we considered *average flows* (those measured in September 2010) and *environmental flows* (minimum flows in the Llobregat River). September 2010 is the period that was used for data collection and model calibration in 4.1.1.2 Data collection for model calibration. The river flows of September 2010 correspond to the average hydrological conditions in the Llobregat. Considering the series of daily flows measured over the last 10 years (flow monitoring stations in Figure 5), the river flows of September 2010 correspond to $Q_{30\%}$ (flow exceeded 30% of the days in 10 years). The *environmental flows* were determined by the Catalan Water Agency (2006) under the principles of progressive implementation and compatibilization of environmental needs and existing uses, with special attention given to safeguarding supply guarantees. This environmental flow regime is defined for all bodies in the district, especially for the flows in the Llobregat river basin which are mainly controlled by a system of upstream reservoirs. The Catalan Water Agency is currently using the environmental flows to assess the compliance of wastewater discharges with environmental standards. Hence, the Catalan Water Agency suggested using the environmental flows as the minimum flows in this study. The Catalan Water Agency is also taking measures to ensure these *environmental flows* in their rivers, even during severe droughts. Considering the series of daily flows measured over the last 10 years (flow monitoring stations in Figure 5), the *environmental flows* correspond to $Q_{99\%}$ (flow exceeded 99% of the days in 10 years).

We evaluated the scenarios of calibrated and reduced model parameters (F, k_{WWTP}, and k_{river}) uncertainty (see 4.2.1.2 Generation and simulation of scenarios). For the scenario of calibrated model parameter uncertainty, we optimized the cost of the WWTP upgrades using the calibrated diclofenac concentrations in the Llobregat in September 2010. For the scenario of reduced model parameter uncertainty, we used the diclofenac concentrations that were simulated with reduced parameter uncertainty with respect to the calibrated uncertainty (simulating the MFT model with reduced parameter uncertainty (i.e., 60% reduction with respect to the calibrated uncertainty) leads to reduced uncertainty in diclofenac concentrations (Figure 17)). For each scenario, we evaluated the highest, median and lowest probable concentrations as in Johnson et al. (2013). The median concentrations are identical in both scenarios of uncertainty. Thus, we evaluated 5 levels of uncertainty in diclofenac concentrations. We simulated the highest probable concentrations using the 95th percentile of F and the 5th percentile of k_{WWTP} and k_{river}, respectively, for each scenario; the median probable concentrations using the 50th percentile of the 3 model parameters and the lowest probable concentrations using the 5th of F and the 95th percentile of k_{WWTP} and k_{river}. We assumed the same calibrated and reduced PDFs of model parameters for both hydrological conditions. However, we expect a higher removal of diclofenac during *environmental flows* because we considered lower velocities in the stretches for these low flows (Kunkel & Radke, 2012).

We combined 4 different EQSs, 2 hydrological conditions and 5 levels of uncertainty (Figure 21). Hence, in total, we optimized the set of WWTPs to be upgraded for 40 scenarios. We ran the optimizer NSGA-II for each scenario, and we selected the optimal solution that minimizes the EQS exceedance the most for each level of uncertainty and hydrological scenario.

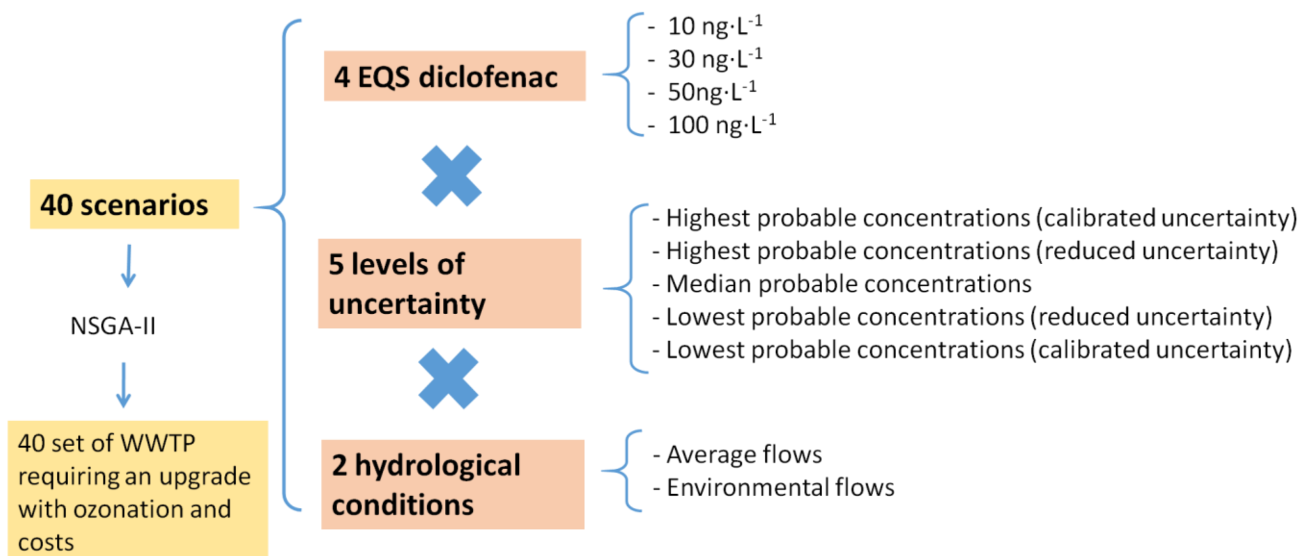


Figure 21. Simulation of scenarios of EQS, uncertainty and hydrological condition for the optimization of WWTP upgrades and costs

4.3.2. Results

4.3.2.1 Influence of different EQSs on the cost of the upgrades

As expected, the total annual cost of the upgrades reduces as the EQS increases, and this is consistent for both hydrological scenarios (Figure 22 and Figure 23). For the scenario *average flows* (Figure 22), we obtained a non-linear relationship between EQS and the cost of the upgrades (negative power relationship, see goodness of fit in Figure 24). The cost to avoid EQS exceedance varied from 10.1 M€·year^{-1} (14 WWTPs requiring upgrade for EQS of 10 ng·L^{-1}) to 4.8 M€·year^{-1} (5

WWTPs requiring upgrade for EQS of 100 ng·L^{-1}), a difference of almost 6 M€·year^{-1} (median values). The highest decrease in costs was found between 10 ng·L^{-1} and 30 ng·L^{-1} (from 10.1 M€·year^{-1} to 6.2 M€·year^{-1}, respectively). For the scenario *environmental flows* (Figure 23) the cost varied linearly from 11.1 M€·year^{-1} to 8.8 M€·year^{-1} (median values for different EQS). The differences in cost among EQS 30 ng·L^{-1} and 50 ng·L^{-1} were lower than 1 M€·year^{-1} for both hydrological scenarios (approximately 0.2 M€·year^{-1} for *average flows* and approximately 1 M€·year^{-1} for *environmental flows*). The sets of WWTPs that are upgraded under each EQS optimization are included in the Annex 3 – A3.3

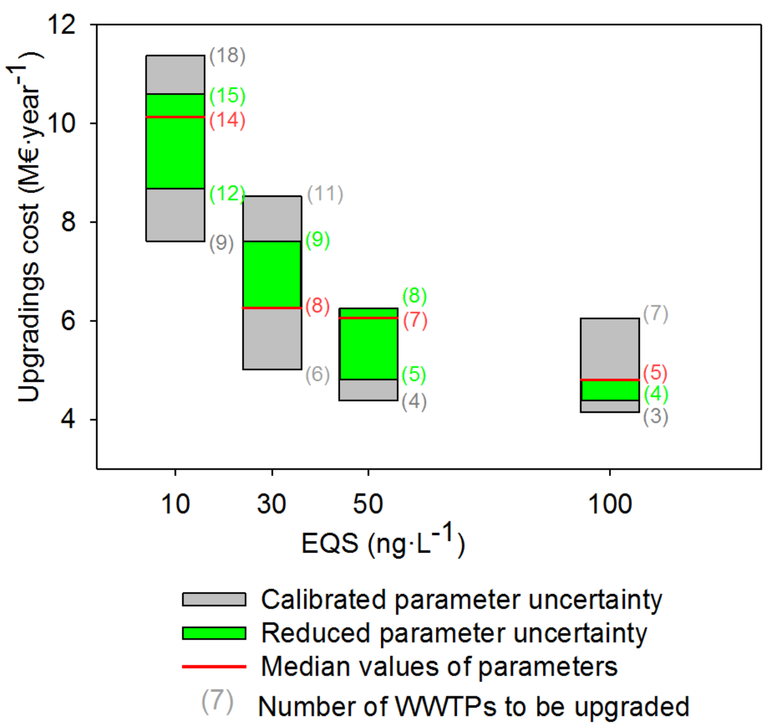


Figure 22. Optimal cost of the required WWTP upgrades with ozonation to reduce diclofenac concentrations in rivers below an EQS of 10, 30, 50 and 100 ng·L^{-1} during average flows and for the calibrated and reduced model parameter uncertainty. The optimal number of WWTPs to be upgraded is shown for the highest, median and lowest probable concentrations of diclofenac.

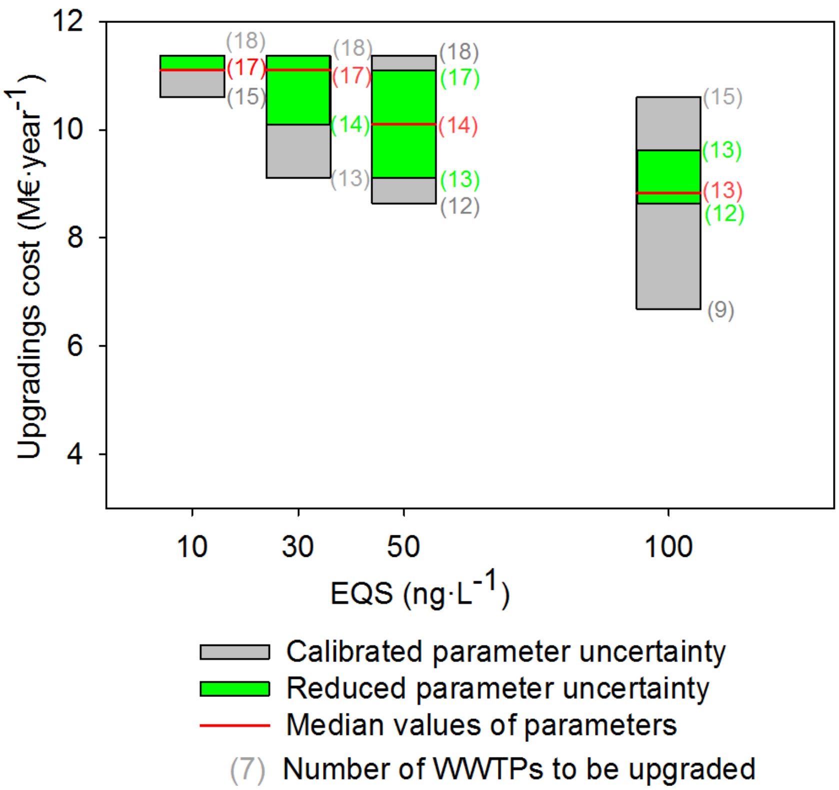


Figure 23. Optimal cost of the required WWTP upgrades with ozonation to reduce diclofenac concentrations in rivers below an EQS of 10, 30, 50 and 100 ng·L^{-1} during environmental flows and for the calibrated and reduced model parameter uncertainty. The optimal number of WWTPs to be upgraded is shown for the highest, median and lowest probable concentrations of diclofenac.

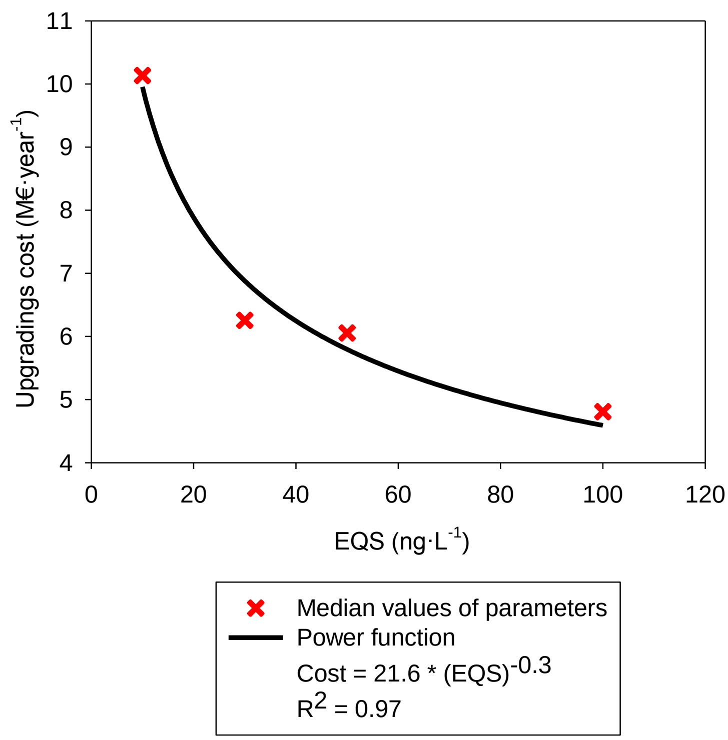


Figure 24. Upgrading costs to avoid exceedance of EQS (10, 30, 50 and 100 ng·L^{-1}) considering the median values of parameters and average flows. A power function was fitted to the data and a high goodness of fit was obtained (R^2= 0.97)

4.3.2.2 Influence of hydrological conditions on the cost of the upgrades

Higher upgrade costs would be required to avoid EQS exceedance under *environmental flows* compared to *average flows* (median values). While the median cost of the upgrades to comply with an EQS of 100, 50 and 30 ng·L^{-1} is lower than 6.5 M€·year^{-1} for *average flows*, the median cost is always higher than 8.5 M€·year^{-1} for *environmental flows*. Indeed, the cost increased by 84% for an EQS of 100 ng·L^{-1}, by 67% for 50 ng·L^{-1} and by 77% for 30 ng·L^{-1} for *environmental flows* compared to *average flows*. The number of upgraded WWTPs under *environmental flows,* being more than twice the number under *average flows,* explains those increases. Nearly the same optimal set of WWTPs to be upgraded is obtained under both hydrological conditions if the EQS was 10 ng·L^{-1}.

4.3.2.3 Influence of uncertainty on the cost of the upgrades

The uncertainty in diclofenac concentrations in the river resulted from simulating the model using the 5th, 50th and 95th percentiles of the parameters (see 4.3.1.4 Simulation of scenarios of an EQS under different hydrology and uncertainty levels). Such uncertainty entails variability in the cost of the upgrades for every EQS and scenario. For the calibrated uncertainty, the variability in the cost ranges from 2% (0.3 M€·year^{-1} for an EQS of 10 ng·L^{-1} and *environmental flows*) to 36% (2.3 M€·year^{-1} for an EQS of 30 ng·L^{-1} and *average flows*). The variability in the cost is larger as the EQS decreases under the *average flows* scenario (from 1.9 M€·year^{-1} for an EQS of 100 ng·L^{-1} to 3.7

M€·year^{-1} for 10 ng·L^{-1}), but the opposite is observed under the *environmental flows* scenario (from 0.8 M€·year^{-1} for 10 ng·L^{-1} to 3.9 M€·year^{-1} for 100 ng·L^{-1}). In the scenario of *average flows*, this is justified by an increase in the number of river stretches exceeding the lower EQS, and therefore, additional WWTPs are likely to be upgraded. Conversely, for *environmental flows*, concentrations of diclofenac are exceeding the lower EQS in almost every river stretch. Thus, nearly every WWTP should be upgraded, hence explaining the lower variability in cost for the lower EQS.

The variability in the cost of the upgrades decreases for every EQS and scenario when the model uncertainty is reduced. The variability in the cost (interquartile range) decreases from 23% (for an EQS of 50 ng·L^{-1} and *average flows*) to 78% (for an EQS of 100 ng·L^{-1} and *average flows*). Most likely, decision-makers would use the highest probable concentrations of diclofenac (highest value observed for each box plot) to make a conservative decision. We observe that the costs of the highest probable concentrations decrease when the model uncertainty is reduced. This means, that reducing uncertainty leads to a solution with decreased costs. As an example, for an EQS of 100 ng·L^{-1} and *average flows*, we obtain a reduction in the cost of the upgrades of 1.3 M€·year^{-1} if the model uncertainty is reduced. Surprisingly, considering the calibrated uncertainty, the lower probable cost of the upgrades to avoid exceedance of a more stringent EQS (e.g., 30 ng·L^{-1} and *average flows*) could be much lower than the median cost required for a less stringent EQS (e.g., 50 ng·L^{-1} and *average flows*). We obtained more accurate solutions and costs considering reduced uncertainty (e.g., the lowest probable cost to avoid 30 ng·L^{-1} exceedance and *average flows* is indeed higher than any probable cost to avoid 50 ng·L^{-1} exceedance). This is explained by the more accurate concentrations of diclofenac simulated using the reduced uncertainty compared to the calibrated uncertainty. These accurate concentrations cause the upgrade of further WWTPs to avoid 30 ng·L^{-1} exceedance compared to 50 ng·L^{-1} exceedance for average flows.

Finally, we observed that there is always a set of 3 WWTPs (Rubí, Terrassa and Sant Feliu) that is included in every optimal solution regardless of the EQS, uncertainty and hydrological scenario (Figure 25. Location of Rubí, Sant Feliu and Terrassa WWTPs.). Thus, an investment of 4.1 M€·year^{-1} is required in any scenario for upgrading these 3 WWTPs.

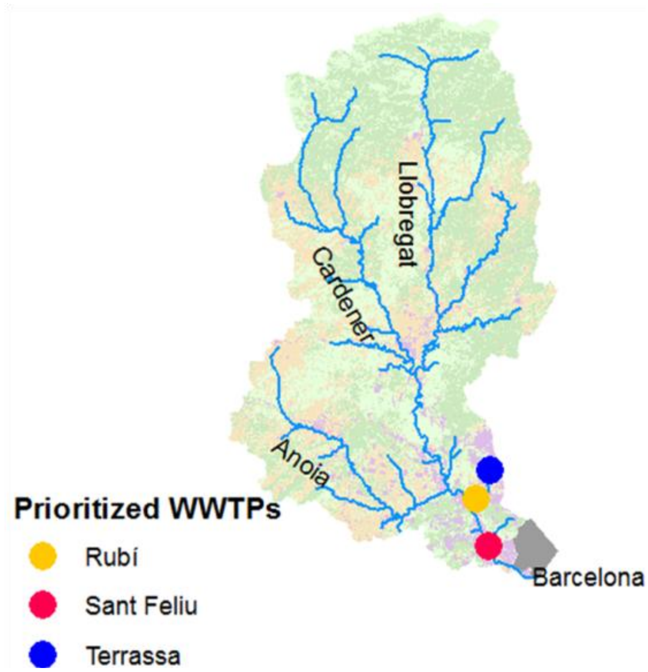


Figure 25. Location of Rubí, Sant Feliu and Terrassa WWTPs.

4.3.3 Discussion

4.3.3.1 Innovation of the study: Relationship between the EQS and the costs of the WWTP upgrades.

The results confirm our hypothesis that the cost of the upgrades is highly sensitive to the potential EQS (from more than 10 M€·year^{-1} for an EQS of 10 ng·L^{-1} to 5 M€·year^{-1} for an EQS of 100 ng·L^{-1} and *average flows*), significantly increasing for the lowest EQS. The relationship between the EQS and costs becomes non-linear (negative power relationship, Figure 24) for *average flows*, and hence, the cost of the upgrades to avoid 10 ng·L^{-1} increases rapidly compared to 30 ng·L^{-1} (from 6 M€·year^{-1} to more than 10 M€·year^{-1}). This is explained by the discrete nature of the optimization variables (WWTPs that are optimized can either be upgraded and removing diclofenac by an extra 99% or not). In this study, a small decrease in the EQS (from 30 to 10 ng·L^{-1}) involves the need for upgrading a significantly higher number of WWTPs (from 8 to 14). The relationship between the EQS and the cost of the upgrades is useful for policy-makers when establishing cost-effective EQSs for microcontaminants and for decision-makers (e.g. the Catalan Water Agency) when proposing interventions to comply with those EQSs. In the derivation of an EQS, given the non-linearities, European policy-makers should consider the daunting cost of the upgrades required to avoid exceedance of the more stringent EQS (i.e., 10 ng·L^{-1}). Ort et al. (2009), Hillenbrand et al. (2014) and Kehrein et al. (2015) evaluated the required interventions at the WWTPs by minimizing diclofenac concentration exceedance for a single EQS of 100 ng·L^{-1}. However, these studies did not evaluate the compliance with other proposed EQSs nor optimize the number of the WWTP upgrades to minimize costs and EQS exceedance. Thus, this is the first study that searches for the trade-off between the cost of the upgrades and compliance with the EQS for microcontaminants.

4.3.3.2 Comparison to existing national strategies for the reduction of microcontaminants in rivers

This section illustrates the advantages of our methodology with respect to other referenced criteria or methods. First, the criteria used to define the optimal number of WWTPs to be upgraded with advanced treatment for the removal of microcontaminants is catchment-dependent, while the use of our model helps river basin authorities (RBA) to find the optimal set of WWTP to be upgraded within any catchment. This is illustrated by implementing the Swiss strategy for the upgrade of WWTPs (BAFU, 2012) on the Llobregat River basin. The Swiss strategy proposed the upgrade of every WWTP serving up to more than 80,000 residents (microcontaminant load reduction), WWTPs serving up to more than 24,000 residents discharging into lakes (drinking water protection) and WWTPs serving up to more than 8,000 residents that contribute to more than 10% of the dry-weather stream flow (low river dilution capacity). This strategy was based on the modeling results from Ort el al. (2009) considering an EQS of 100 ng·L^{-1}. Following this strategy (considering *environmental flows* as the dry-weather stream flow), 8.3 M€·year^{-1} should be invested to upgrade 10 WWTPs in the Llobregat basin. However, by upgrading this set of WWTPs, the median concentrations of diclofenac still exceed the EQS of 100 ng·L^{-1} in 21 river stretches. The solution given by the Swiss strategy seems to be risky compared to any solution that we optimized for the *environmental flows*. For nearly the same cost, we avoid 100 ng·L^{-1} exceedance during *environmental flows* by upgrading 13 WWTPs (median values). Hence, the upgrade of additional WWTPs in the Llobregat and higher costs are required to comply with the more stringent EQS and considering the uncertainty of diclofenac concentrations. On the other hand, lower costs (4.8 M€·year^{-1}) and fewer upgraded WWTPs (only 5) are required to avoid exceedance of 100 ng·L^{-1} considering the median concentrations and *average flows* and compared to the solution given by the Swiss strategy. This means that the set of 10 WWTPs resulting from the Swiss strategy is not the optimal solution for the Llobregat river basin considering the minimization of both the cost of the upgrades and the EQS exceedance. This also suggests that uniform criteria for the selection of WWTPs to be upgraded across Europe would not be suitable for all countries given differences in hydrological conditions, treatment levels, etc.

Our methodology also helps RBAs prioritize which set of WWTPs should be first upgraded to avoid any EQS exceedance. There is always a set of WWTPs (Rubí, Terrassa and Sant Feliu; Figure 25) that is included in every optimal solution regardless of the EQS, uncertainty and hydrological scenario (Annex 3 – A3.3). The effluents of these 3 WWTPs discharge to river stretches with very low river dilution capacity (wastewater contributing to more than 40% of the river flow). This explains the very high diclofenac concentrations simulated just downstream these plants (higher than 400 ng·L^{-1}) that far exceeded any EQS. Therefore, this is the first study on prioritizing investments at WWTPs for the removal of microcontaminants considering both EQS compliance and costs.

4.3.3.3 Framing the optimal solutions into current operational costs and European experiences

The current operational cost of the WWTPs discharging into the Llobregat is 16.8 M€·year^{-1} (Catalan Water Agency, 2016). Considering that the operational cost of the upgrades (personnel, maintenance and variable costs) represents 40% of the total required cost (Table 10), the current operational cost would increase from 10% (considering the upgrade of 3 WWTPs with a total cost of 4.1 M€·year^{-1}) to 27% (upgrade of 18 WWTPs with a cost of 11.4 M€·year^{-1}). The Catalan Water Agency finances the required investment at the WWTPs through a water tax (*cànon de l'aigua*) that is included in each household water bill (Catalan Water Agency, 2016). For an average water use between 108 and 188 m^3·household^{-1}·year^{-1} (second tax block with lower water use) in Catalonia in 2016, the water tax was 102 €·household^{-1}·year^{-1}, and the total water bill (including water supply, wastewater, the water tax and VAT) was 355 €·household^{-1}·year^{-1} (Catalan Water Agency, 2016). Assuming that every household in the Llobregat contributes to the payment of the WWTP upgrades, the cost estimated in this study would represent an increase in the household water bill from 10 to 28 €·household^{-1}·year^{-1}. In percentages, this means an increase from 10% to 28% in the water tax and an increase from 3% to 8% in the total water bill. Assuming that the average household's income in Spain in 2017 is 40,000 €·household^{-1}·year^{-1} (OECD, 2017), the cost of the upgrades ranges from 0.3‰ to 0.7‰ of the household's income. The estimated average willingness to pay per household for upgrading the WWTPs in Switzerland (86 €·household^{-1}·year^{-1}; Logar et al., 2014) involves an increase by 20% in the total water bill in Switzerland (430 €·household^{-1}·year^{-1}; Logar et al., 2014) and just 1.2‰ of the average household's income in 2017 (66,000 €·household^{-1}·year^{-1}; OECD, 2017). Therefore, the cost of the upgrades represents a lower percentage of the household's water bills and income compared to the estimated willingness to pay in Switzerland.

The cost of the upgrades in the Llobregat can be compared with the cost of the upgrades estimated in Switzerland (0.12 billion € annually for the upgrade of 123 WWTPs, as estimated in Logar et al., 2014) and Germany (1.3 billion € annually for the upgrade of 3,013 WWTPs, as in Hillenbrand et al., 2014). Assuming that the cost is covered by every household's water bill in Switzerland and Germany, the required upgrades would mean an increase of 37 and 40 €·household^{-1}·year^{-1}, respectively. These values are larger than the [10-28] €·household^{-1}·year^{-1} estimated for the Llobregat River basin. The costs in Switzerland and Germany might be reduced if a model-based optimization (using real costs) would be applied. Finally, the decrease in parameter uncertainty could lead to savings down to 1.3 M€·year^{-1} in the selection of the optimal set of WWTPs to be upgraded and a reduction in the water tax up to 4 €·household^{-1}·year^{-1}. If a cost-benefit analysis is carried out to support research projects aimed to reduce uncertainties in MFT model parameters, the reduction in the cost of the upgrades can be incorporated in the analysis as a monetary benefit.

4.3.3.4 Use of hydrological conditions for decision-making on the removal of microcontaminants in rivers

In this study, we provide evidence that the cost of optimal interventions varies from 10% to 84% when using *average flows* or *environmental flows*, depending on the EQS. So far, there is no agreement on which river flows should be used for decision-making on the selection of measures to reduce microcontaminant levels at a basin scale. Hillenbrand et al. (2014) evaluated WWTP interventions to decrease concentrations of 12 chemicals, including 4 pharmaceuticals, in the Neckar River basin (Germany) using the annually mean flow from 2008 to 2010. Likewise, Kehrein et al. (2015) considered the mean flow of the period 2012 – 2014 to evaluate measures to reduce diclofenac below EQS in the Ruhr River basin (Germany). Coppens et al. (2015) prioritized the investments at the WWTPs to reduce concentrations of carbamazepine and ibuprofen in Dutch rivers using the average flow of the driest and wettest 3-month period out of ten years (1996 – 2006). Ort et al. (2009) optimized the number of Swiss WWTPs to be upgraded for the removal of diclofenac for the $Q_{95\%}$ river flows (flow exceeded 95% of the time, annually averaged over a ten-year period). Kumar et al. (2014) evaluated the compliance of the estrogen E1 and E2 concentrations with standards in the Yodo River (Japan) for $Q_{50\%}$ and $Q_{75\%}$. In our study, the *environmental flows* scenario is very much conservative, as these conditions occur, on average, less than 1% of days over the year. However, while the use of *average flows* protects the environment against current scenarios of pollution, the use of *environmental flows* would help to protect it against future scenarios of pollution in a climate change context. These results show the importance of selecting the appropriate hydrological conditions when proposing the optimal strategy for the removal of microcontaminants. Hydrological characteristics of European rivers vary greatly, and higher costs are expected for basins with low discharge, such as the Mediterranean basins. In addition, Mediterranean rivers will be particularly affected by climate change, as climate projections predict even lower discharges by the end of the century (Pascual et al., 2014).

4.3.3.5 Recommendations for decision-makers to upgrade WWTPs for the removal of diclofenac

This study provides an overall goal and a realistic budget to decision-makers. The recommendation for them would be to invest in the development of a model with low uncertainty that would then be used for decision-making. The investment in a research project (e.g., 1 M€ as the total cost of the European Industrial Doctorate – TreatRec) would be paid back in less than one year due to the reduction in the cost of the upgrades when simulating the model with reduced parameter uncertainty. The costs of constructing and operating tertiary treatments are in the order of magnitude of 10 M€·year^{-1}, and hence, any investment to enhance the prediction capabilities of the model will result in enormous savings, even in the short term. We believe that adaptive management is an excellent approach to accommodating for future uncertainties and hydrological scenarios. Hence, we would suggest not upgrading all WWTPs at once but starting with the most relevant ones. Our study demonstrated that 3 WWTPs (Rubi, Terrassa and Sant Feliu) can be prioritized in their investment plans since they are included in every solution regardless of the

EQS, uncertainty and hydrological condition. With regards to the trade-off between the EQS and cost, we found that there are no large differences in the number of WWTPs requiring upgrade and the costs between 30 and 50 $ng \cdot L^{-1}$. Hence, a good conservative solution would be to set an EQS of 30 $ng \cdot L^{-1}$, which involves the upgrade of 8 WWTPs and 6.3 M€·year^{-1} for *average flows* and the upgrade of 17 WWTPs and 11.1 M€·year^{-1} for *environmental flows*. Given the power relationship between EQSs and costs, going lower (to 10 $ng \cdot L^{-1}$) would be too precautionary. Going higher (100 $ng \cdot L^{-1}$) might endanger the freshwater ecosystem (Ecotox Centre, 2017).

The model used in this study can be applied to any worldwide catchment as the Matlab code and the specific data of each catchment are well separated. The model uses data that is readily available from Environment and Health Agencies and River Basin Authorities (i.e. river network, flows and velocities, WWTP operational parameters, population connected to the WWTPs, consumption of pharmaceuticals). Moreover, there is no need for user's knowledge on river hydrodynamics to run the model (river flows are imported from other models or from measurements at monitoring stations).

4.3.3.6 Limitations of this study

We acknowledge that the final solution adopted by the Catalan Water Agency must be valid for the removal of a number of representative microcontaminants in the Llobregat, not only for diclofenac. Our model is ready to simulate these microcontaminants, but additional modeling efforts are needed to combine the optimal set of solutions for each microcontaminant (e.g. adjustments in the Matlab code to account for a number of microcontaminants and computational time increase). This study focuses on the influence that the uncertainty in the model parameters - F, k_{WWTP} and k_{river} - has on the estimates of pharmaceutical concentrations in the rivers, and, in turn, on the EQS exceedance, and ultimately, on the cost of the upgrades. Other sources of uncertainty (e.g. 18% of uncertainty in the ozonation costs, Mulder et al., 2015) are not the focus of this study. Finally, source control measures are not considered, and we will address this issue in our next study.

4.4 Can source control avoid the upgrade of WWTPs for the reduction of pharmaceuticals? The case of diclofenac and naproxen

This chapter aims to evaluate the effect that source control measures have on the required end-of-pipe measures for the reduction of pharmaceuticals at catchment scale. Substitutions of the prescriptions and the Over-the-counter (OTC) dispensing by more environmentally-benign pharmaceuticals are assessed as the source control measures and the upgrading of WWTPs with ozone as the end-of-pipe measure. We selected diclofenac as the harmful pharmaceutical and naproxen as the more environmentally-benign equivalent. This work is applied to the Llobregat river catchment.

In this chapter, we calibrate the MFT model parameters for naproxen using Bayesian inference as conducted in chapter 4.1 for diclofenac. Likewise, we use the MFT model coupled to the optimization algorithm developed in chapter 4.3 to estimate the number of WWTPs requiring an upgrade and the associated costs. This is done for diclofenac and naproxen separately. We evaluate different scenarios on the amount of diclofenac (purchased in pharmacies with a prescription or OTC) that is replaced by naproxen. Moreover, we consider different EQS, hydrological conditions and uncertainty in the predicted concentrations in the upgrading analysis.

This chapter shows that apparent reductions in the number of WWTP upgrades are achieved only when 75% of the diclofenac consumed is substituted by naproxen. However, we conclude that any substitution between pharmaceuticals requires a model-based evaluation because significant increases in the concentrations of the new pharmaceutical (naproxen) may lead to unwanted increases in the number of WWTP requiring an upgrade for the lowest EQS.

4.4.1 Methodology

We use the MFT model developed in Chapter 4.1 to describe the fate and removal of diclofenac and naproxen in the Llobregat river basin. The model parameters for diclofenac were calibrated in chapter 4.1 and are summarized in Table 6. The model parameters for naproxen (Table 11) are calibrated following the methodology explained in chapter 1 using a Bayesian inference approach and measurements of naproxen in the river and in WWTPs during September 2010 (Table 4). The calibration for naproxen is described in section 4.4.1.1 Bayesian calibration of model parameters for naproxen. Hence, the MFT model predicts the concentrations of diclofenac and naproxen in every river stretch accounting for the uncertainty in the calibrated model parameters (Table 6 and Table 11). The model predicts three different concentrations of diclofenac and naproxen: worst, median and best probable concentrations. The worst probable concentrations of diclofenac and naproxen –the highest probable concentrations - are simulated using the percentile 97.5th of F and the percentile 2.5th of k_{WWTP} and k_{river} (values in red in Table 11). The best probable concentrations – the lowest probably concentrations - are simulated using the percentile 2.5th of F and the percentile 97.5th of k_{WWTP} and k_{river} (values in green in Table 11). The median concentrations are simulated using the median value of the three parameters (values in blue in Table 11).

	Percentile		
	2.5th	50th	97.5th
F	0.13	0.18	0.25
k_{WWTP}	0.72	1.25	2.61
WWTP Removal (%)	65	76	87
k_{river}	2.2E-06	9.4E-06	2.4E-05

Table 11. Calibrated model parameters for naproxen

4.4.1.1 Bayesian calibration of model parameters for naproxen

We used the MATLAB toolbox and the DiffeRential Evolution Adaptive Metropolis (DREAM) algorithm developed by Vrugt et al. (2008, 2009) to calibrate the model parameters. We defined the prior distribution of F by fitting a uniform distribution to the values of F (Annex 4 – A4.1). These values are calculated using equation 3 and 24 measurements of naproxen at the influent of 5 WWTPs in Catalonia over the period from 2006 to 2009 (Gros et al., 2007; Gros et al., 2010; Jelic et al., 2011) and the consumption of naproxen in Spain during the sampling periods. The consumption is provided by the consultancy IQVIA (2018). We obtained that F varies from 0.07 to 0.68 (percentiles 2.5th and 97.5th respectively) with a median value of 0.24 (Figure 26). These values are higher than the human body excretion factor for naproxen (5-7%, Vree et al. (1993). This indicates that part of the excreted glucuronide compounds are hydrolyzed and deconjugated, increasing the concentration of the naproxen parent compound in sewers (Carballa et al., 2008; Khan & Ongerth, 2004).

We defined the prior distribution of k_{WWTP} by fitting an exponential function to the values of k_{WWTP} (justification in Annex 4 – A4.2). These values are calculated using equation 4 and 24 naproxen removal efficiencies measured in the same 5 Spanish WWTPs over the period from 2006 to 2009

(Gros et al., 2007; Gros et al., 2010; Jelic et al., 2011) and Mixed Liquour Suspendid Solids (X_{ss}) and Hydraulic Retention Time (ϑ_h) values provided by the operators of these plants. We obtained that k_{WWTP} varies from 0.73 (percentile 2.5th) to 24.2 L·g^{-1}·d^{-1} (percentile 97.5th) with a median value of 4.9 L·g^{-1}·d^{-1} (Figure 26). The median value of k_{WWTP} agrees well with the biodegradation constants reported in Suarez et al., (2010). The measured WWTP removal efficiencies used to estimate k_{WWTP} variability range from 42% to 96% with a median of 88% which also agree well with the removal values reported in Verlicchi et al. (2012) and Baalbaki et al. (2016).

We defined the prior distribution of k_{river} by fitting an exponential function to the possible values of k_{river} (justification in Annex 4 – A4.3). Ten scientific publications were reviewed in the SCARCE project framework to obtain the prior distribution of k_{river} for naproxen. These studies were conducted on rivers and using different experiments (in situ and microcosms). Thus, the pseudo-first order decays integrate all possible removal processes (i.e., biodegradation, sorption onto solids and photolysis). The values of k_{river} varied from 1.85E-06 to 6.8E-04 s^{-1} (percentile 2.5th and 97.5th values, respectively), with a median value of 7.9E-05 s^{-1} (Boithias et al., 2013; Figure 26)

We used the same Llobregat river stretches configuration, river flows and velocities and WWTP operational variables (ϑ_h, X_{ss}, Influent and effluent discharge, population connected) as inputs for the MFT model calibration as for diclofenac in chapter 4.1. The values of these variables were averaged for September 2010 which corresponds to the period when the sampling campaign for measuring naproxen in WWTPs and rivers was conducted. Likewise, we used the consumption of naproxen during 2010 which was provided by IQVIA (2018). We also used the same Bayesian input arguments, parameter space and initial sampling as defined for diclofenac in Table 5 adjusting the prior distributions and minimum and maximum parameter boundaries to naproxen (Table 12).

Table 12. Definition of Input arguments, parameter space and initial sampling needed to run the DiffeRential Evolution Adaptive Metropolis (DREAM) algorithm in MATLAB (Vrugt et al., 2016) and calibrate the model parameters for naproxen

Input argument	**Value**	**Justification**
Dimension of the problem	3	There are three parameters: F, k_{WWTP} and k_{river}
Number of Markov chains	10	Minimum required was 7 according to Vrugt et al. (2016)
Number of generations	10,000	High enough to allow prior distributions to converge to posterior distributions
Thinning rate	5	Only the 5th sample is stored to reduce computational memory storage
Built-in likelihood function	Gaussian likelihood, measurement error integrated out	We do not consider the measurement error in the observations
Parameter space		
Initial sampling	**Value**	**Justification**
Initial sampling	Based on prior distribution of parameters: F uniform distribution (centred on 0.38±80%) k_{WWTP} exponential distribution (mean value of 7.8 $L \cdot g_{ss}^{-1} \cdot d^{-1}$) k_{river} exponential distribution (mean value of 1.49E-04 s^{-1})	See section "data collection for model calibration"
Explicit boundary handling	Fold	Recommended in Vrugt et al. (2016)
Minimum and maximum parameter boundaries	F [0.07 – 0.68] k_{WWTP} [0.7 -24] $L \cdot g_{ss}^{-1} \cdot d^{-1}$ k_{river} [1.8E-06 -8.8E-04] s^{-1}	See section "data collection for model calibration"

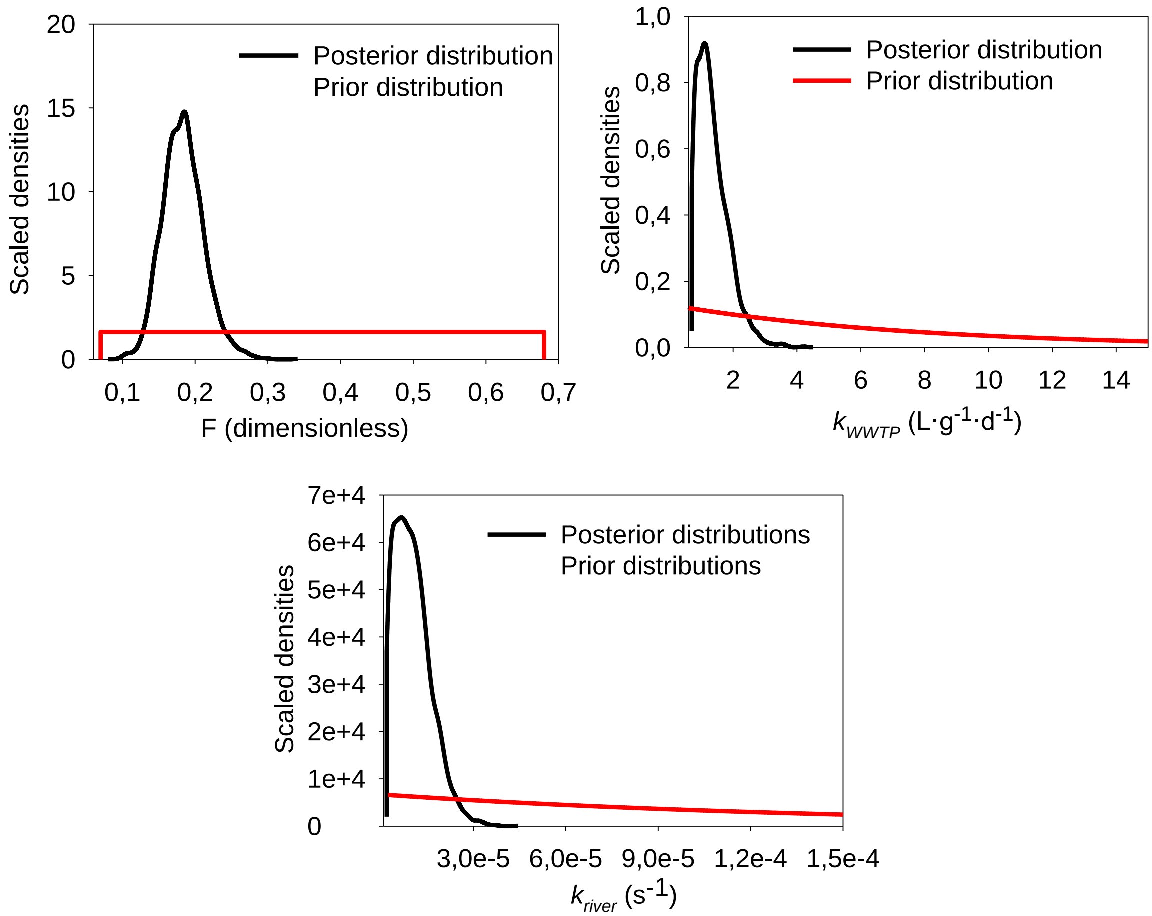


Figure 26. Prior and posterior probability distributions of F (top left), k_{WWTP} (top right) and k_{river} (bottom center) for naproxen

Thus, we obtained the posterior parameter distributions after the Bayesian calibration (Figure 26) and we calculated the median and percentiles 2.5th and 97.5th of these distributions (Table 11). We obtained a very good fit (R^2 = 0.88) between measured and predicted naproxen loads in the rivers (Figure 27). Predictions lie within the dashed lines parallel to the bisector which means that they do not deviate by more than ±50 from the corresponding measured value. The predicted influent loads also match well the measured loads at Igualada and Manresa WWTPs. However, the model overestimates the measured effluent loads. This can be justified by either probable errors in the sampling campaign at the WWTPs, or in the estimation of the inhabitants connected to these WWTPs. Indeed, the measured effluent concentration at Igualada WWTP is lower than any measured effluent concentration at the 5 WWTPs (Gros et al., 2007; Gros et al., 2010; Jelic et al., 2011) which were used to estimate the prior distributions of F and k_{WWTP}.

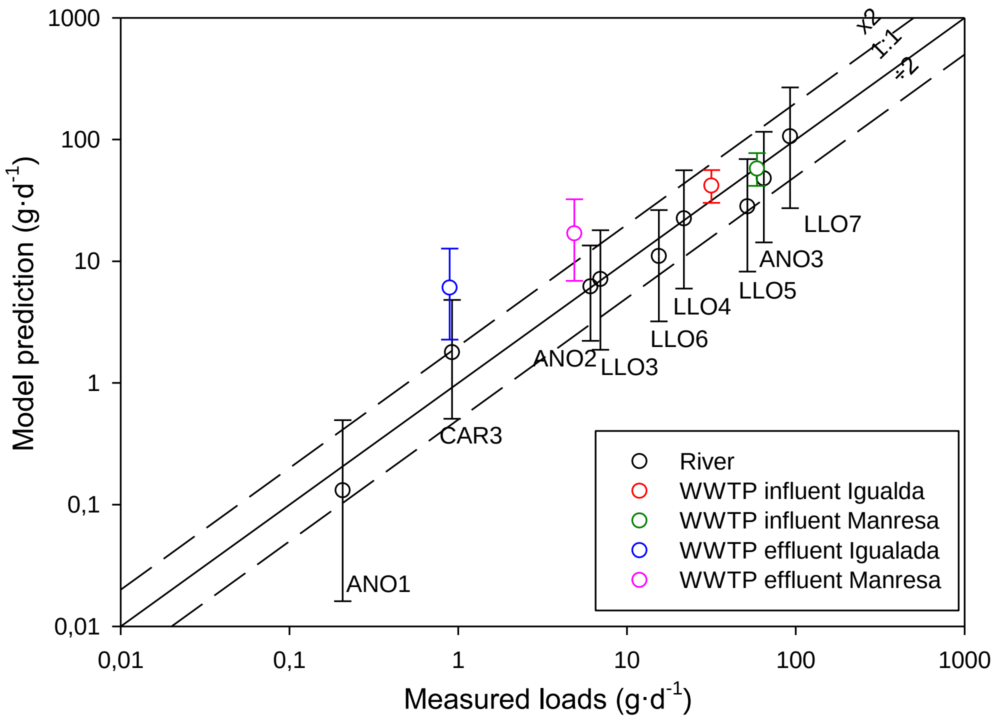


Figure 27. Model predicted versus meaaured loads of naproxen in the river sampling points (black symbols) and in the influents and effluents of the Igualada and Manresa WWTPs (colored symbols). Each prediction consists of 3 simulated values (circle = median loads, bars = worst and best probably loads)

4.4.1.2 Evaluation of source control measures

We evaluated two source control measures: (I) the substitution of diclofenac prescriptions by naproxen prescriptions and (II) the substitution of diclofenac purchased OTC by naproxen purchased OTC. For this evaluation, we use real data on the amounts of diclofenac and naproxen purchased with a prescription and OTC in Spanish farmacies (Table 13) and we assume that all amounts purchased are consumed in the same year by the customers (we use amounts purchased and amounts consumed interchangeably). These amounts cover different substitution rates between diclofenac and naproxen purchased with a prescription and OTC. Thus, we assess the effect of different source control measures on the optimal number of WWTP requiring an upgrade in the Llobregat basin.

Four scenarios in the amounts of diclofenac and naproxen purchased with a prescription and OTC are evaluated (Table 13):

1. The scenario S1 corresponds to the amounts purchased in 2010, just before the EMA recommendation for decreasing the diclofenac prescriptions.

2. The scenario S2 corresponds to the amounts purchased in 2016, four years after the EMA recommendation. Consequently, the amounts of diclofenac and naproxen purchased with a

prescription decreased and increased respectively compared to S1. Although the amounts of both pharmaceuticals purchased OTC increased in S2, the total amount of diclofenac purchased (with a prescription and OTC) in S2 still decreased by 17% compared to S1.

3. The scenario S3 applies an additional decrease in the diclofenac prescriptions only and an equivalent increase in naproxen prescriptions compared to S2. We reduced the diclofenac prescriptions by 40% (1.3 DDD·1000inh^{-1}·day^{-1} - from 3.2 to 1.9 DDD·1000inh^{-1}·day^{-1}). This reduction percentage was based on a Dutch study (Grinten et al., 2016) that quantified the number of diclofenac prescriptions that could be replaced by naproxen. We consider that the amount of naproxen purchased with prescriptions in S3 also increased by 1.3 DDD·1000inh^{-1}·day^{-1} so that the amount of diclofenac that was not prescribed is completely replaced by naproxen. The amounts of diclofenac and naproxen purchased OTC remains the same as in S2. Thus, the total amount of diclofenac purchased in the scenario S3 decreased by 27% compared to S1.

4. The scenario S4 considers a reduction in the amount of diclofenac purchased OTC (from 8 to 1.7 DDD·1000inh^{-1}·day^{-1}) and an equivalent increase in the amount of naproxen OTC (from 3.9 to 10.2 DDD·1000inh^{-1}·day^{-1}). We assume that the amounts of diclofenac and naproxen purchased with prescriptions remains the same as in scenario S3. The reduction in the amount of diclofenac purchased OTC is justified based on the lowest total amount of diclofenac purchased with prescription and OTC in a European country (3.6 DDD·1000inh^{-1}·day^{-1} in the UK; IQVIA, 2018). Hence, the sum of the amount of diclofenac purchased OTC (1.7 DDD·1000inh^{-1}·day^{-1}) and with prescriptions (1.9 DDD·1000inh^{-1}·day^{-1}) in S4 equals the total amount purchased in the UK. The total amount of diclofenac purchased in the scenario S4 decreased by 73% compared to S1.

Table 13. Scenarios in the consumptions of diclofenac and naproxen.

		Diclofenac			Naproxen		
Scenario	Description	Prescribed	OTC	Total	Prescribed	OTC	Total
S1	Consumption in 2010 Reference scenario	6.9	6.6	13.5	5.5	1.5	7
S2	Consumption in 2016 Substitution in S1 prescriptions Increase S1 OTC	3.2	8	11.2	9.9	3.9	13.8
S3	Substitution in S2 prescriptions S2 OTC remains the same.	1.9	8	9.9	11.2	3.9	15.1
S4	Substitution in S2 OTC and prescriptions (same as S3)	1.9	1.7	3.6	11.2	10.2	21.4
	Units:DDD·1000inh^{-1}day^{-1}; DDD for Diclofenac = 0.1 g; DDD for Naproxen = 0.5 g						

4.4.1.3 Optimization of the number of WWTP requiring an upgrade

We used the optimizer Non-Sorting Genetic Algorithm NSGA-II (Deb et al., 2002) coupled to the MFT model as described in chapter 4.3 to obtain the optimal set of WWTPs that should be upgraded in the Llobregat basin to decrease diclofenac and naproxen concentrations in the rivers. Two objective functions were defined: minimization of the total EQS exceedance in the entire Llobregat basin and minimization of the total cost of the upgrades (annual investment and operational cost). Ozonation was again selected as the upgrade technology as it removes diclofenac and naproxen almost completely (near 99%) at low ozone doses (Huber et al., 2005). The function that calculates the ozonation costs based on the treated flow and population equivalents is extracted from chapter 4.3 (Equation 10).

We optimized the number of WWTP upgrades for the proposed EQS for diclofenac (10 and 100 ng·L^{-1}) and for naproxen (640 and 1,700 ng·L^{-1}) using the total consumptions of each scenario (table 3). The total consumptions correspond to the variables *Sales* in the MFT model (chapter 4.1, equation 3). We also ran the optimizations for the average river flows (flows of September 2010) and the minimum river flows (environmental flows) as defined in chapter 4.3. Finally, we also optimized the number of WWTP upgrades using the worst, median and best diclofenac and naproxen concentrations in rivers. Thus, we obtain a range of the optimal number of WWTP upgrades and costs considering the uncertainty in the diclofenac concentrations. Figure 28 and Figure 29 show a sketch of every optimization that was conducted for diclofenac and naproxen.

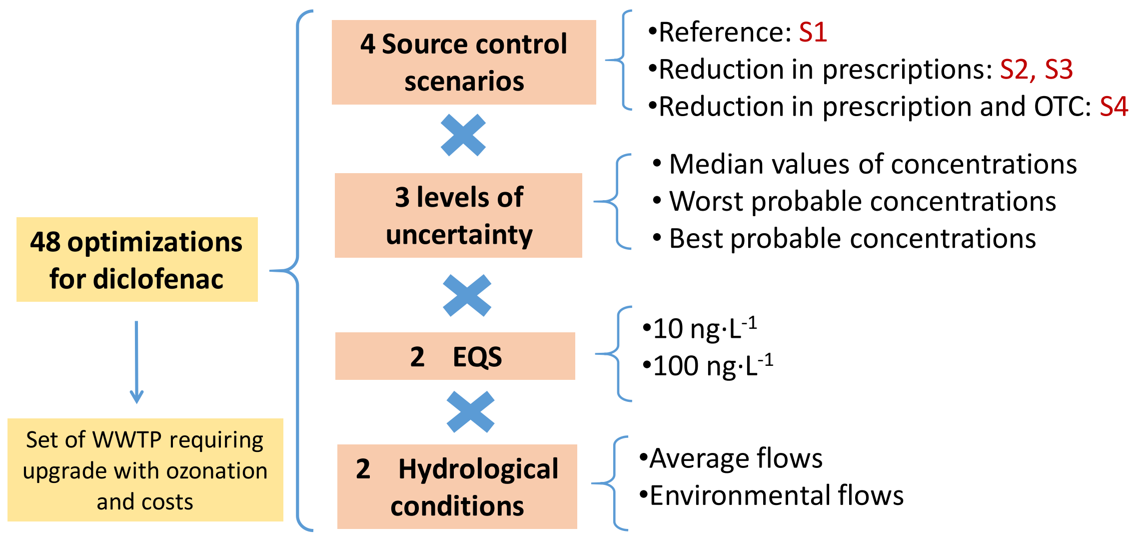


Figure 28. Optimizations of the number of WWTP upgrades for diclofenac

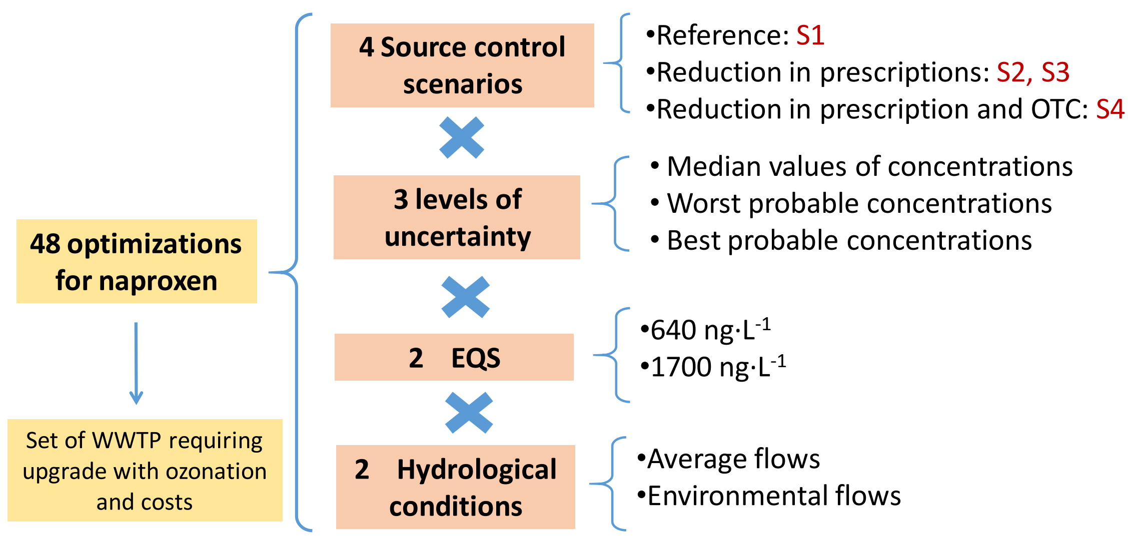


Figure 29. Optimizations of the number of WWTP upgrades for naproxen

Firstly, we assess the reduction in the number of WWTP upgrades and costs due to a reduction in the amount of diclofenac purchased with a prescription and OTC. This is assessed by calculating the probability of achieving apparent reductions in the upgrading costs of each scenario with regard to the scenario S1. We considered that an apparent reduction in the upgrading costs is achieved when the probability of achieving apparent reductions is near 100%. This means that the cost of the upgrades in a particular scenario for the worst concentrations of diclofenac is lower than the cost in the reference scenario (S1) for the best concentrations. Secondly, we assess the increase in the required WWTP upgrades and costs due to an increase in the amount of naproxen purchased. Finally, we compare the number of WWTP upgrades and the costs required to minimize the EQS exceedance for diclofenac and naproxen. Thus, we evaluate whether additional

WWTPs require an upgrade as naproxen consumption increases from scenario S1 to S4 while diclofenac consumption decreases.

4.4.2 Results

4.4.2.1 Effect of a decrease in the diclofenac consumption on the WWTP upgrades

Overall, the costs of the WWTP upgrades decrease as the total diclofenac consumption decreases (Figure 30 and Figure 31). However, apparent reductions in the number of WWTP upgrades and costs are only achieved when the consumption of diclofenac purchased with a prescription and OTC is drastically reduced by 73% (scenario S4) as compared to baseline (scenario S1). This is consistent for both EQS and average flows (Figure 30). For average flows (Figure 30), this translates into a reduction in the number of WWTP upgrades from 14 (scenario S1) down to 8 (scenario S4) for EQS of 10 ng·L^{-1}and from 5 (scenario S1) down to 2 (scenario S4) for EQS of 100 ng·L^{-1}. For minimum flows (Figure 31), apparent reductions in the number of WWTP upgrades are only achieved for EQS of 100 ng·L^{-1}. For the EQS of 10 ng·L^{-1}, every WWTP requires an upgrade for the worst concentrations of diclofenac (even for the scenario S4) so there is not an apparent reduction in the WWTP upgrades nor the costs. Reducing the consumption of diclofenac by only reducing the prescriptions (scenario S2 and S3) does not lead to apparent reductions in the WWTP upgrades and costs compared to the baseline (scenario S1) for both flow conditions. Large savings are obtained when reducing both diclofenac prescriptions and OTC consumption (scenario S4): 4.2 M€·year^{-1} for EQS of 10 ng·L^{-1}, average flows and median values and 4.3 M€·year^{-1} for an EQS of 100 ng·L^{-1}, minimum flows and median values Therefore, source control becomes more relevant for stricter EQS during average flows and for higher EQS during minimum flows.

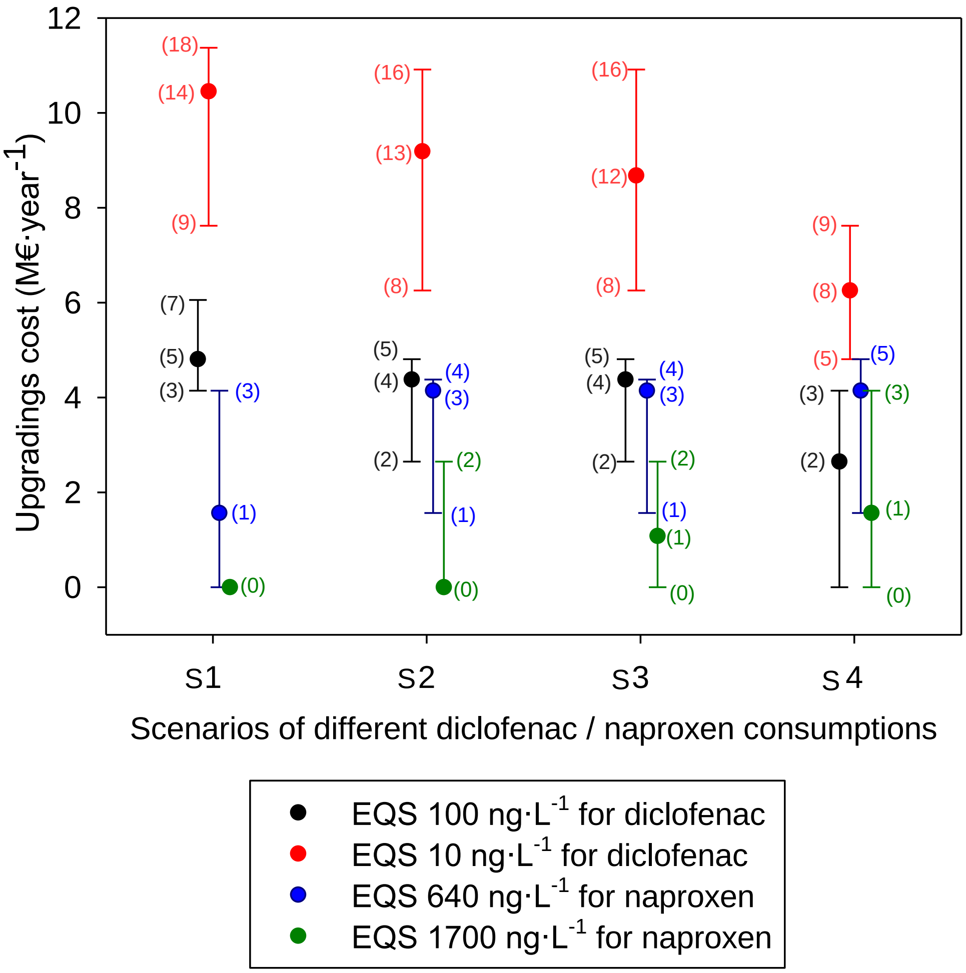


Figure 30. Number of WWTP upgrades (shown in brackets) and upgrading costs optimized to avoid EQS exceedance of 10 and 100 ng·L^{-1} for diclofenac and 640 and 1,700 ng·L^{-1} for naproxen for the average flows. These are calculated for the scenarios S1, S2, S3 and S4 in the consumption of diclofenac and naproxen defined in table 13. The number of WWTP upgrades and the costs are optimized for the median, worst and best concentrations of diclofenac and naproxen.

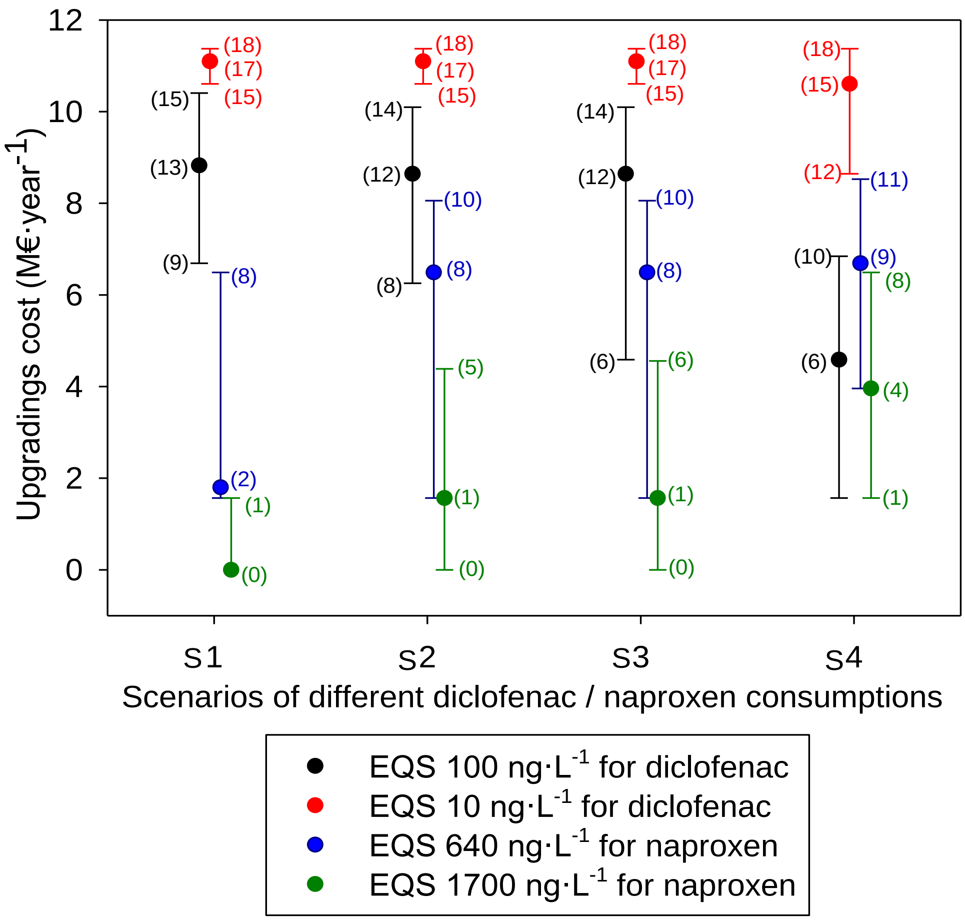


Figure 31. Number of WWTP upgrades (shown in brackets) and upgrading costs optimized to avoid EQS exceedance of 10 and 100 ng·L^{-1} for diclofenac and 640 and 1,700 ng·L^{-1} for naproxen for the minimum flows. These are calculated for the scenarios S1, S2, S3 and S4 in the consumption of diclofenac and naproxen defined in table 13. The number of WWTP upgrades and the costs are optimized for the median, worst and best concentrations of diclofenac and naproxen

4.4.2.2 Effect of an increase in the naproxen consumption on the WWTP upgrades.

Figure 30 and Figure 31 show that the limiting compound for upgrading WWTPs is diclofenac in scenarios S1, S2 and S3 regardless of the EQS, the river flow condition and the uncertainty in the concentrations of diclofenac and naproxen. In these scenarios, adding naproxen into the decision-making process does not imply upgrading further WWTPs. If the decision is based only on naproxen and for the median concentrations, just 1 WWTP at most in scenario S3 would require an upgrade for the EQS of 1,700 ng·L^{-1} and between 3 (average flows) and 8 WWTPs (minimum flows) for the EQS of 640 ng·L^{-1}

However, naproxen concentrations demand for the upgrade of a larger number of WWTP as compared to diclofenac in one particular case (EQS of 100 ng·L^{-1} for diclofenac and EQS of 640 ng·L^{-1} for naproxen in Figure 30 and Figure 31) in scenario S4 regardless of the uncertainty in the concentrations and the river flow condition. In this case, 1 additional WWTPs for the median concentrations and average flows and 3 additional WWTPs for minimum flows would require an upgrade on top of the number required by diclofenac (2 and 6 WWTPs respectively). This means that high substitution percentages between diclofenac and naproxen as in scenario S4 (reduction of 73% in diclofenac and increase of 206% in naproxen total consumptions compared to S1; Table 13) does not always lead to a reduction in the number of WWTP upgrades. Nevertheless, diclofenac is still the limiting compound for upgrading WWTPs in scenario S4 when setting EQS of 10 $ng \cdot L^{-1}$ for diclofenac or when comparing EQS of 100 $ng \cdot L^{-1}$ for diclofenac and EQS of 1,700 $ng \cdot L^{-1}$ for naproxen for both flow conditions.

4.4.3 Discussion

4.4.3.1 Innovation of this study

For the first time, we have evaluated model-based a range of possible source control measures along with optimal end-of-pipe interventions required to decrease pharmaceutical concentrations below EQS. Our modeling approach determines which level of reduction in the consumption is needed to observe apparent reductions in the number of WWTP upgrades and the costs. Our approach is useful for River Basin Authorities when deciding on the optimal set of WWTP upgrades for the removal of pharmaceuticals and supports future national policies on the control of pharmaceuticals from an environmental point of view.

4.4.3.2 Generalization of the results

A decrease in the diclofenac consumption of 73% (Scenario S4 compared to S1) is required to observe apparent reductions in the number of WWTP upgrades and costs in the Llobregat river basin. We optimized the WWTP upgrades using other diclofenac consumptions in between S3 and S4 to assess which is the minimum level of consumption leading to apparent reductions in the WWTP upgrades. Thus, we estimated that the required decrease in the consumption could be lower (i.e. 60% versus 73% of S4) for average flows and EQS of 100 $ng \cdot L^{-1}$ but even higher (i.e. 90% versus 73% of S4) for environmental flows and EQS of 10 $ng \cdot L^{-1}$. Despite the considerable decrease in the consumption, WWTP upgrades are still required in any case.

The Llobregat River is a typical Mediterranean watercourse with an average flow in the mouth of 20 $m^3 \cdot s^{-1}$. The magnitude of wastewater effluents in the whole basin is aproximately 3 $m^3 \cdot s^{-1}$. The overall low dilution during average flows in the Llobregat explains the high concentrations of pharmaceuticals which are significantly exceeding the EQS in particularly dry stretches. This justifies why a considerable decrease in the diclofenac consumption is needed to avoid the upgrade of WWTPs and, hence, achieve apparent reductions in the number of WWTP upgrades. Hillenbrand et al. (2014) also observed that a 20% reduction in the diclofenac consumption on top of the upgrade of every WWTP with more than 50,000 PE did not lead to a significant improvement in the EQS exceedance in the Neckar river basin (Germany). Although the average diclofenac consumption in the Neckar in 2016 was more than twice the consumption in the Llobregat (25 $DDD \cdot 1000inh^{-1} \cdot day^{-1}$ and 11 $DDD \cdot 1000inh^{-1} \cdot day^{-1}$ respectively; IQVIA, 2018), the average flow in the mouth (145 $m^3 \cdot s^{-1}$; Gisen et al., 2017) is approximately 10 times higher than in the Llobregat. Hence, assuming a similar magnitude of wastewater effluents (similar population is actually connected to the WWTPs in both basins), considerable reductions in the consumption of diclofenac are needed to significantly avoid the WWTP upgrades in both catchments with high and low flows. In any case, this still requires a model-based evaluation because the optimal number of WWTPs that requires an upgrade is a catchment-specific problem (see section 4.3.3.2 Comparison to existing national strategies for the reduction of microcontaminants in rivers).

4.4.3.3 Feasibility of the source control measures

Particularly in Spain, the reduction of 73% (corresponding to the levels of diclofenac consumption in the UK; scenario S4) can only be accomplished by reducing both the amount of diclofenac purchased with a prescription and OTC. There are already some initiatives that aim to include environmental aspects on the physician decision when prescribing two equivalent pharmaceuticals (e.g. at national level in Sweden, LIF, 2005; model-based tools; Oldenkamp et al., 2013). A decrease in the number of diclofenac prescriptions would have a larger effect on the required WWTP upgrades in countries where the amount of diclofenac prescribed is more significant (e.g. 75%) compared to the OTC. For instance, the amount of diclofenac prescribed in Germany in 2011 was 14.5 DDD·1000inh^{-1}·day^{-1} (AKDAE, 2013) which accounted for half of the total diclofenac consumption (IQVIA, 2018) in Germany. Moreover, the amount of diclofenac purchased with a prescription in 2011 was four times higher than in Spain. Thus, apparent reductions in the WWTP upgrades in German catchments (e.g. Neckar river) would be potentially achieved by reducing the number of diclofenac prescriptions only.

A more responsible use of OTC drugs would result in a reduction in the pharmaceutical OTC consumption. This can be achieved by e.g. ensuring that pharmaceutical expertise is provided to patients when purchasing OTC diclofenac (Netherlands strategy; Interreg IV B - Nopills project, 2015) or limiting the diclofenac availability as prescribed only (UK strategy; Medicines and Healthcare products Regulatory Agency, 2015). Definitely, the Netherlands and the UK show the lowest consumptions of diclofenac across Europe (7.9 and 3.6 DDD·1000inh^{-1}·day^{-1} respectively; IQVIA, 2018). Commercial advertising of naproxen might also have encouraged the increase in the naproxen OTC consumption in the UK which accounts for the highest consumption of this pharmaceutical in Europe (17.7 DDD·1000inh^{-1}·day^{-1}; IQVIA, 2018). A reduction in the OTC consumption of diclofenac would be especially effective in countries showing high OTC consumption rates, e.g. in Spain and Sweden. For instance, diclofenac purchased OTC represented 75% of the total consumption in Spain in 2016 (IQVIA, 2018; AEMPS, 2017), 70% in Sweden in 2015 (IQVIA, 2018; Eriksen et al., 2017)

4.4.3.4 Substitution of pharmaceuticals and green pharmacy

The substitution of diclofenac by naproxen generally has positive implications for the environment because the concentrations of diclofenac decrease as the consumption decreases. Therefore, the EQS exceedance of diclofenac concentrations reduces in the entire river basin so fewer WWTP upgrades are required. However, the substitution is not beneficial for the environment when the substitution rate between diclofenac and naproxen becomes important and the lowest EQS for naproxen (640 ng·L^{-1}) is compared to the highest EQS for diclofenac (100 ng·L^{-1}). We estimate (i.e. by optimizing the number of WWTP upgrades with other diclofenac and naproxen consumptions) that this occurs starting at reduction rates of 60% in the diclofenac consumption and at an increase rate of 180% for naproxen approximately. At this rate, the number of WWTP upgrades required by diclofenac equals the number required by naproxen for the median concentrations and for both river flow conditions. Although naproxen is less harmful to the environment (any proposed EQS for naproxen is higher than for diclofenac), its DDD is 5 times higher than diclofenac and a larger fraction of unchanged naproxen may be discharged to sewers after human body excretion. This leads to higher concentrations of naproxen in rivers exceeding the lowest EQS and requiring further WWTP upgrades as the substitution rate between diclofenac and naproxen increases. Thus, our modeling approach also helps policy-makers evaluate the consequences of drugs substitutions to the environment considering different scenarios of EQS, hydrology and uncertainty.

The design of a more environmentally-benign drug equivalent to diclofenac (Green pharmacy) would be an alternative to compensate for the reduction in the diclofenac prescribed and purchased OTC (Kümmerer, 2009). The design of a new drug may focus on a reduction of either the DDD or the drug excretion (eco-directed sustainable prescribing; Daughton, 2014). For instance, we assume a new drug with a DDD of 0.1 g (like diclofenac) instead of 0.5 g (naproxen DDD) that is purchased with a prescription and OTC compensating for the reduction in the diclofenac use in each scenario. Considering that the new drug has the same excretion factor and WWTP and river removal efficiency as naproxen, only 2 WWTPs would require an upgrade for the worst concentrations, the average river flows and the EQS of 640 ng·L^{-1} in scenario 4 (scenario that requires higher number of WWTP upgrades) as compared to the 5 WWTPs obtained in Figure 30. Moreover, 5 WWTPs would require an upgrade for the environmental flows as compared to the 11 WWTP obtained in Figure 30. Conversely, we assume a second new drug with the same DDD, WWTP and river removal efficiency as naproxen but an excretion factor of 7% (no glucuronide compounds would be excreted). For the worst concentrations, the average flows and the EQS of 640 ng·L^{-1} in scenario S4, again only 2 WWTPs would require an upgrade as compared to the 5 WWTPs obtained in Figure 30. For the environmental flows, 7 WWTP upgrades would be required. The significant reductions in the WWTP upgrades justify the benefits of investing more research efforts towards the design of more environmentally-benign pharmaceuticals. Finally, our modeling approach can also be useful to identify which DDD and excretion factor of the new drug would be the most beneficial for the environment.

4.4.3.5 Recommendations for decision-makers

- We propose to evaluate source control measures for pharmaceuticals at catchment/national level following a multi-compound approach. This approach involves the evaluation of the EQS exceedance and the required WWTP upgrades for every NSAID marketed and prescribed for the same treatment (e.g. diclofenac / naproxen / ibuprofen for the case of Spain). Thus, decision-makers will have a better understanding on the effect that source control measures have on the WWTP upgrades when the consumption of several pharmaceuticals varies.

- Replacing diclofenac prescriptions by naproxen in the Llobregat catchment has always a positive effect on the WWTP upgrades, although no apparent reductions in the WWTP upgrades are achieved. However, the substitution of diclofenac purchased OTC by naproxen may lead to an increase in the number of WWTP upgrades due to an increase in the naproxen consumption. The set of WWTPs requiring an upgrade for each EQS, uncertainty in the concentrations and river flow condition are included in the Annex 4. Interestingly, for the median and the best concentrations, the sets of WWTP upgrades required to reduce diclofenac concentrations always contain the WWTP upgrades to reduce naproxen concentrations and vice versa. For the worst concentration, this holds true except for the scenario S4 and the minimum flows, in which naproxen and diclofenac concentrations require the upgrade of different WWTPs (11 and 10 WWTPs respectively). Thus, a combination of both solutions resulting in the upgrade of 12 WWTPs would be needed to reduce EQS exceedance of diclofenac and naproxen concentrations together.

5. General discussion

5.1 Innovation of this dissertation

With this dissertation, we provide decision-makers with a set of novel approaches for the evaluation of strategies (end-of-pipe or WWTP upgrades and source control) to reduce pharmaceuticals loads in rivers.

First, we have developed a new customized Microcontaminant Fate and Transport (MFT) model for the estimation of pharmaceutical concentrations in rivers including uncertainty (chapter 4.1). We identified in chapter 4.1 that there is high uncertainty around the processes driving the discharge of pharmaceuticals to sewers (i.e. human body excretion factors) and the removal in WWTP and rivers. Thus, providing estimates of the pharmaceutical concentrations with uncertainty assessment is crucial when using MFT models for decision-making.

We have incorporated uncertainty in the whole decision-making process for the evaluation of strategies to reduce pharmaceutical loads in rivers from the very beginning (e.g. from the definition of the prior parameter distributions as in chapter 4.1). To the author's knowledge, to take into account the uncertainty during the calibration process, this is the first time a MFT model has been automatically calibrated using Bayesian Inference techniques and observations of pharmaceuticals in WWTPS and rivers. The uncertainty has also played a key role in the selection of WWTP interventions as evaluated in chapter 4.2. So far, decision-makers evaluated strategies for a certain level of uncertainty in the predicted concentrations (usually the 95th percentile as in Ort et al., 2009 and Kehrein et al., 2015). However we have provided a model-based approach that takes into account the whole uncertainty range on the selection of WWTP interventions.

Our MFT model only requires a set of flows (i.e. minimum or average flows) in every river section that can be imported from separate hydrological models. This feature makes the MFT model more flexible and easily applied to other catchments. This also allows decision-makers have a fast estimate of the pharmaceutical concentrations in rivers.

The optimization of the number of WWTP requiring an upgrade for the removal of pharmaceuticals based on EQS and costs and including uncertainty is the most innovative part of the dissertation (chapter 4.3). So far, previous studies (Ort et al. 2009, Hillenbrand et al., 2014) optimized the number of WWTP upgrades based on water quality criteria only (no cost optimization was performed). For the first time, we used multiple criteria (minimization of costs and minimization of the EQS exceedance in the whole catchment) in the optimization of the WWTP upgrades at catchment level. We have identified that enormous savings in the cost of the WWTP upgrades at catchment and national level can be achieved if decision-makers make use of our optimization approach. On the other hand, providing an estimation of the cost of the WWTP upgrades for different EQS is also critical for policy-makers when setting the EQS for pharmaceuticals.

Finally, we have addressed for the first time, the effect that source control of pharmaceuticals has on the river water quality and, hence, on the required WWTP upgrades using models (chapter 4.4). Our approach is useful for decision-makers to select the source control measure that significantly reduce the concentrations of environmentally-harmful pharmaceutical and the WWTP upgrades as well as to identify unwanted increases in the concentrations of equivalent pharmaceuticals and WWTP upgrades. The selection of the appropriate source control measure depends greatly on the human consumption patterns of pharmaceuticals in each country so the application of our approach would be ideal at national level.

5.2 Factors affecting the selection of measures for the reduction of pharmaceutical loads

5.2.1 Uncertainty in the estimates of pharmaceutical concentrations

We have demonstrated in chapter 4.1 that the three key model parameters used to describe the fate and removal of pharmaceuticals in catchments exhibit high uncertainty. This uncertainty is propagated to the model outcomes (estimates of pharmaceutical river concentrations) which are utilized in decision-making. Hence, decision-makers can use the best, median or worst probable concentrations when evaluating the efficacy of measures for the reduction of pharmaceutical concentrations. We have also proved in chapter 4.1 and 4.2 that the uncertainty would increase if the model is not calibrated but could also decrease if more scientific knowledge on the model parameters becomes available in the future.

Overall, uncertainty plays a key role in the selection of WWTP upgrades and source control measures. Indeed, the selection of strategies for the reduction of pharmaceuticals significantly changed depending on the level of uncertainty in the predicted concentrations (worst, median or best concentrations) and the scenario of uncertainty considered (calibrated, increase or decreased uncertainty). This justifies the importance of making decisions considering the uncertainty. For instance, upgrading the secondary treatments leads to apparent reductions in the pharmaceutical concentrations in rivers only if uncertainty of concentrations reduces as demonstrated in chapter 4.2. On the other hand, the total cost of the WWTPs requiring an upgrade can increase up to 400% (e.g. from 2 to 10 M€·year^{-1}, for naproxen, EQS 640 ng·L^{-1}, environmental flows and scenario S2 of substitution) when optimizing the number of WWTPs for the best and worst pharmaceuticals concentrations respectively (chapter 4.4). In addition, the variability in the cost of the upgrades (difference between the highest and lowest cost) can decrease up to 80% (e.g. from 2 to 0.4 M€·year^{-1}, for diclofenac, EQS 100 ng·L^{-1}, average flows) if uncertainty in concentrations decreases as demonstrated in chapter 4.3.

5.2.2 Eco-toxicity of pharmaceuticals in rivers (EQS setting)

EQS for pharmaceuticals are established following a scientific and political process (chapter 4.3). Regarding the scientific process, EQS are established based on eco-toxicity studies. The data on chronic exposure to individual pharmaceuticals and mixtures of pharmaceuticals are still scarce so we expect changes in the proposed EQS.

EQS setting for pharmaceuticals also influences the decision-making for the removal of pharmaceuticals. On the one hand, the number of WWTPs requiring an upgrade for the lowest EQS for pharmaceuticals (i.e. for diclofenac and naproxen) can be up to three times higher than the number required for the highest EQS as demonstrated in chapter 4.3 (e.g. while 5 WWTPs require an upgrade to decrease diclofenac river concentrations below 100 $ng \cdot L^{-1}$ and average flows, 14 WWTPs require an upgrade for 10 $ng \cdot L^{-1}$ and average flows). Moreover, the EQS setting can lead to the disregard of source control measures, such as substitution of pharmaceuticals. Indeed, the river concentrations of the substituting pharmaceutical can significantly increase exceeding the lowest EQS and, hence, increasing the number of WWTP requiring an upgrade. However, the substitution of pharmaceuticals is still a positive measure for the environment if the highest EQS is set for the substituting pharmaceutical (chapter 4.4).

5.2.3 Hydrological condition considered in decision-making

We have discussed in chapter 4.3 that the selection of river flows (i.e. average flows or dry weather flows) for decision-making significantly varies among studies. There is no consensus on which river flow should be used. Even among the selection of dry-weather flows, we found differences in literature (e.g. Q_{90}, Q_{95}, environmental flows). EQS are usually established as an annual average threshold (European Commission, 2013). This would justify the use of average flows for selecting measures that reduce concentrations below EQS. However, the river flows in Mediterranean river basins are expected to decrease due to climate change (Pascual et al., 2014) so it seems more appropriate to use dry-weather flows (environmental flows in this dissertation).

We have demonstrated that the number of WWTP upgrades and costs required to decreasing pharmaceutical concentrations below EQS during environmental flows double as compared to average flows (chapter 4.3 for diclofenac and chapter 4.4 for naproxen; scenario S1 and S2). The difference in the number of WWTPs upgrades and costs between both hydrological conditions is even higher (almost three fold) when considering the lowest EQS for pharmaceuticals.

5.2.4 Consumption of pharmaceuticals

The consumption of pharmaceuticals significantly changes over the years as demonstrated in chapter 4.4. The changes in the consumption are motivated by medical reasons (substitution of diclofenac by naproxen from 2010 to 2016; scenario S2 in chapter 4.4) or environmental reasons (scenario S3 and S4). These changes impact the selection of measures for the reduction of pharmaceuticals: the required upgrading costs decreased by 40% on average as consumption of diclofenac reduced to the minimum levels (Scenario S4, chapter 4.4). On the other hand, the upgrading costs tremendously increased (i.e. by 400% on average) as consumption of naproxen increased to the maximum levels (scenario S4, chapter 4.4)

Overall, consumption of pharmaceuticals is expected to increase due to ageing population (Aa et al., 2011). As a consequence, consumption of diclofenac could increase again to the levels of 2010 while naproxen keeps increasing (not evaluated in this dissertation). Thus, no reduction in the upgradings costs would be observed.

5.3 Recommendations for decision-makers

First, we recommend decision-makers to use models that predict the concentrations of pharmaceuticals at catchment scale to test the efficacy of measures. Literature data on the fate and transport of pharmaceuticals is still scarce for most of the pharmaceuticals so uncertainties in the parameters and model outcomes should be well reported.

We have concluded in this dissertation that the selection of measures for the reduction of pharmaceuticals at catchment level is influenced by changing conditions of the uncertainty in the estimated concentrations, climate change, eco-toxicity and consumption of pharmaceuticals.

Hence, we recommend decision-makers to follow adaptive management (Holling, 1978; Lee, 1999) of pharmaceuticals at catchment level in response to these changing conditions. Adaptive management is essential for effective environmental management when uncertainty is high (Dutra et al., 2014). Adaptive management would involve adjusting the strategies (WWTP upgrades and source control measures) in response to the feedback on the progress towards the management objectives (i.e. minimization of pharmaceutical concentrations, minimization costs) as well as responding to changing conditions of uncertainty, EQS, hydrology and consumption.

Thus, as initial step of the adaptive management, decision-makers can use our modeling approach to obtain those strategies that are included in every optimal solution regardless of the uncertainty, EQS, flow condition and consumption. For instance, in the first iteration of the adaptive management, one strategy would be upgrading 2 WWTPs (Terrassa and Rubí). These 2 WWTPs are even included in the set with fewer WWTPs requiring an upgrade using the current consumption of diclofenac (best concentrations of diclofenac, average flows, EQS 100 $ng \cdot L^{-1}$ and scenario S2; figure 3, chapter 4.4). After upgrading these 2 WWTPs, following the adaptive management approach, decision-makers would need to evaluate again the status of the management objectives under changing conditions. In the second iteration of the adaptive management, promoting the prescriptions and OTC use of naproxen could be an option as the second strategy. We disregard upgrading further WWTPs because this would not be required for the scenario with the lowest consumption of diclofenac. Indeed, only the 2 WWTPs (Terrassa and Rubí) upgraded in the first iteration require an upgrade for the median concentrations, average flows, EQS of 100 $ng \cdot L^{-1}$ for diclofenac and EQS of 1,700 $ng \cdot L^{-1}$ for naproxen and scenario S4 (figure 3, chapter 4.4). In the second iteration, the combined strategy (upgrade 2 WWTPs + substitution diclofenac by naproxen) would protect the environment from the median concentrations, which represents a higher protection compared to the first iteration (best concentrations).

In this dissertation, we did not evaluate possible constraints in the budget that would be reserved for the implementation of measures. For instance, we did not assess the Llobregat citizen's willingness to pay for the cost of the WWTP upgrades. However, decision-makers can still use our approach because we considered cost minimization as one of the objective functions. Thus, the optimizer would provide the optimal solutions that minimize the EQS exceedance at the specified willingness to pay (see Pareto front, Figure 20). Adaptive management is also an appropriate approach to adjust the solutions to changing budgetary conditions.

5.4 Potential improvements in the optimization of the WWTP upgrades

- The MFT model used to simulate concentrations of diclofenac has been applied to the Llobregat river catchment. Further work should be conducted to validate the model under different conditions than the ones used for calibration, e.g. different temperature, river flows, etc. Such validation would enhance the confidence of decision-makers on the model outcomes

- We have focused the assessment on diclofenac (chapter 4.1, 4.2, 4.3 and 4.4) and naproxen (chapter 4.4) only. The strategies for the reduction of pharmaceutical concentrations at catchment level should not be defined for just 2 pharmaceuticals but for a number of representative microcontaminants. For instance, 15 microcontaminants, including 11 pharmaceuticals (atenolol, azithromycin, bezafibrate, carbamazepine, clarithromycin, diclofenac, ibuprofen, metoprolol, naproxen, sulfamethoxazole and trimethoprim) are identified as representative of a larger group in Switzerland (Logar et al., 2014). 12 water-relevant microcontaminants, including 5 pharmaceuticals (diclofenac, ibuprofen, metoprolol, sulfamethoxazole, iomeprol) are identified in Germany (Hillenbrand et al., 2014). The upgrading optimization analysis for multiple pharmaceuticals could be done separately (one by one and then combining the optimal set of different WWTPs) or by adjusting the objective function to include every EQS exceedance. Nevertheless, the simulating time for running one optimization is currently rather long (the optimization of the WWTP upgrades (18 variables) takes 4 hours in a computer Intel Core i5-5200U CPU with 2.2 GHz and RAM of 8 GB, considering 100 generations and 200 different solutions in a population). The slow performance should be improved (i.e. by improving the Matlab code) before running the optimization for multiple pharmaceuticals.

- We have only considered ozonation as the upgrading technology because it removes diclofenac and naproxen almost completely and it is less expensive than other technologies (Mulder et al., 2015). However, ozonation generates toxic by-products and the installation of ozonation may not be feasible in certain urban subcatchments (e.g. bromide-containing wastewater; Soltermann et al., 2016), which was not evaluated in this dissertation. Powdered and granular activated carbon, besides the higher cost (Mulder et al., 2015; Margot et al., 2013), do not generate toxic by-products. The optimization of both the number of WWTP upgrades and the type of technology implemented at each WWTP would significantly increase the complexity of the optimization. However, a more realistic solution could be obtained. For instance, Switzerland considers ozonation, GAC and PAC as the possible upgrading technologies.

- We have only considered 2 objective functions (chapter 4.3): minimization of the total costs and minimization of the EQS exceedances. It would be interesting to add additional objective functions, such as minimization of the energy consumed by the upgrading technology at the catchment level. This would be especially useful when several upgrading technologies have to be optimized at every WWTP.

- Concerning the volume treated by the ozonation plant, we have considered the average wastewater flow treated at each WWTP (wastewater flow that corresponded to September 2010). Reducing the volume treated by the ozonation plant while still decreasing the pharmaceutical concentrations below EQS would potentially lead to a reduction in costs. However, this would involve the introduction of new variables (e.g. volume treated by each ozonation plant) to be optimized and, hence, increasing the complexity of the optimization.

- We have optimized the number of WWTPs requiring an upgrade for three different levels of uncertainty (best, median and worst concentration). Optimizing the number of WWTP upgrades using the parameter distributions would provide a more realistic distribution of the WWTP upgrade costs.

5.5 Future research perspectives

- We have discussed in chapter 4.2 and 4.3 that reducing model uncertainty would lead to enormous savings in the cost of the measures selected for the reduction of pharmaceuticals at catchment level. Thus, further research projects aiming to reduce the uncertainties (e.g. in the sales of pharmaceuticals at urban scale, in the human body excretion factors, in the possible removal of pharmaceutical in sewers, in the removal of pharmaceuticals in WWTPs and in rivers) are essential. We include some research directions in the discussion in section 4.2.5

- We have discussed in 5.1 that our approach is easily implemented in other catchments and that is one of the main benefits. Therefore, we believe that there is potential to apply it at larger scale (European level). Hence, we would identify which European regions require higher investment to decrease pharmaceutical river concentrations and which factors explain the distributions of the investments across Europe.

- In chapter 4.4, we have assumed that diclofenac (prescribed and purchased OTC) is replaced by naproxen only. Further research is needed to expand our approach and include the upgrading analysis for every pharmaceutical of the same therapeutic group (e.g. diclofenac, naproxen and ibuprofen). Further pilot studies for the evaluation of the efficacy of source control measures are needed to collect data on changes in the OTC consumption or on the number of medical treatments that could be substituted. In any case, as stated in the introduction, source control of pharmaceuticals is always controversial due to the outstanding benefits of pharmaceuticals for human health. Therefore, the policy changes should be well defined and justified among physicians, pharmacists, eco-toxicologists, river basin authorities and policy-makers all together

- Our model simulates the fate, transport and removal of human pharmaceuticals from households and hospitals that enter into the rivers through WWTP effluents. Further research is required to include other possible sources and routes of pharmaceuticals in rivers, such as, the fate of veterinary pharmaceuticals, the entry of pharmaceuticals into rivers through combined sewer overflows and the reuse of wastewater effluents containing pharmaceuticals for irrigation and drinking water at catchment level or between two different catchments (relevant in Mediterranean river basins). Assessing the relative contribution of industrial point source pollution (i.e. pharmaceutical companies) to the total pharmaceutical load in sewers would also be useful to accurately estimate the load at the WWTP influents

- There is still a research gap around how the cost of the WWTP upgrades would be fairly distributed among polluters: according to the polluter pays principle (United Nations, 1992), the pharmaceutical companies should bear the cost of the upgrades because they produce the pollution to the environment. On the other hand, the water utilities may also be responsible for bearing the cost of the upgrades because the current WWTPs are not removing pharmaceuticals completely. In third place, the citizens, especially due to overmedication, are seen as the polluters as they are the final consumers of pharmaceuticals and responsible for the increase in the river concentrations. In addition, not every WWTP needs an upgrade and, hence policy-makers would have to evaluate whether every national citizen would bear the cost or only the citizens connected to the upgraded WWTP. For example, in Switzerland, 75% of the investment costs are covered by the national budget and the remaining 25% by the municipalities with a WWTP requiring upgrade.

- The complexity of selecting measures for the decrease of pharmaceutical loads makes necessary the use of Environmental Decision Support Systems (EDSSs). Further research is needed to include our approach into a DSS. For instance, our approach lacks a system that allows decision-makers rank the different optimal solutions or give them scores based on objectives. In addition, the decision is normally not taken by one individual but by a group of stakeholders. Thus, a participatory modeling tool would be useful to select the appropriate measures for pharmaceuticals. Moreover, our approach lacks a cost-benefit analysis of the measures because we did not quantify the total benefits (including the non-monetary benefits) of reducing pharmaceuticals.

6. Conclusions

The objectives of this thesis have been achieved, being the main contributions: 1) a new microcontaminant fate and transport model for the estimation of pharmaceutical concentrations in WWTP and in river including uncertainty, 2) a new approach that evaluates the influence of the key model parameter uncertainties on the selection of WWTP interventions for the removal of pharmaceuticals, 3) a new assessment on the optimal number of WWTPs requiring an upgrade and the costs for the removal of pharmaceuticals, demonstrating that there is a balance between costs and EQS at catchment level, 4) a new approach that evaluates the effect of source control measures for the reduction of the pharmaceutical consumption on the optimal WWTP upgrades and costs at catchment level.

For the first contribution, the following conclusions can be drawn

- We have developed a microcontaminant fate and transport model that is capable of accurately estimating (R^2= 0.95) the diclofenac concentrations in rivers and in the influents and effluents of WWTPs. These estimations are provided with uncertainty.

- Bayesian inference allowed reducing the uncertainties of predicted concentrations of pharmaceuticals by more than half

For the second contribution, the following conclusions can be drawn

- Model uncertainty influences the selection of WWTP upgrade interventions to reduce diclofenac loads in rivers.

- Decision makers can use our microcontaminant fate and transport model to simulate alternative end-of-pipe interventions and scenarios of decreased, increased and calibrated uncertainty to evaluate the achievement of apparent reductions and the compliance with environmental standards.

- We conclude that the installation of tertiary treatments (WWTP removal efficiencies of pharmaceuticals > 90%) results in apparent reductions of diclofenac concentrations, regardless of the simulated uncertainty scenario.

- However, upgrades in secondary treatment (WWTP removal efficiencies of pharmaceuticals < 75%) results in apparent reductions in diclofenac concentrations that depend on the simulated level of uncertainty and the increase in WWTP removal efficiency achieved after the upgrade.

- Further research is needed to reduce the uncertainties in human consumption and excretion of pharmaceuticals, in the removal of pharmaceuticals in sewers and in the WWTP and river degradation constants.

For the third contribution, the following conclusions can be drawn

- The cost of the WWTP upgrades decreases non-linearly (from 10.1 to 4.8 M€·year^{-1} for average flows and from 11.1 to 8.8 M€·year^{-1} for environmental flows) as the EQS increases from 10 to 100 ng·L^{-1}. Setting 30 ng·L^{-1} as the EQS for diclofenac would balance costs and ecosystems protection. Our methodology helps river basin authorities find the optimal set of WWTPs that should be upgraded for different EQSs.

- Searching for the optimal set of WWTPs that should be upgraded to comply with EQSs of microcontaminants is a catchment-specific problem. Establishing a uniform strategy in Europe for the upgrade of WWTPs seems to be challenging and suboptimal.

- Investing in research projects aimed at decreasing model parameter uncertainty leads to enormous savings in the cost of the WWTP upgrades (down to 1.3 M€·year^{-1} for 1.1 M inhabitants), which would have a positive effect on our annual water bill (reductions of up to 4 €·household^{-1}·year^{-1}).

For the fourth contribution, the following conclusions can be drawn

- Our approach helps River Basin Authorities to evaluate source control measures combined with end-of-pipe measures accounting for the uncertainties in the pharmaceutical concentrations

- The promotion of a responsible use of OTC pharmaceuticals is an effective source control measure that leads to apparent reductions in the number of WWTP upgrades and the costs, especially in countries where the consumption of pharmaceuticals purchased OTC is very significant (i.e. 75% of the total)

- The prescription of more environmentally-benign pharmaceuticals does not lead to an apparent reduction in the required WWTP upgrades and the costs, especially in catchments where the amount of pharmaceuticals purchased with a prescription is much lower than the amount purchased OTC.

- The effect that the substitution of pharmaceuticals has on the environment needs to always be evaluated because the number of the required WWTP upgrades may increase due to a substantial increase in the consumption of the replacing pharmaceutical. To deal with this drawback, the design of new environmentally-benign pharmaceuticals is crucial.

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Annex 1

A1.1 Microcontaminant fate and transport model – Matlab code

```
clear all; clc; close all;

%This implementation is provided for free in a true academic spirit. However, we do ask you to:
•Send us feed back to lcorominas@icra.cat in case you find errors or possible improvements to the implementations
•Send copies of any publication you write to lcorominas@icra.cat, which are to some extent based on the use of any of these implementations;
•Please acknowledge the work that has been carried out by us at ICRA in any papers you publish, where the use of our model implementations have had an impact.
% This script calculates loads and concentrations of diclofenac in WWTPs and in rivers (influent of WWTPs, effluent of WWTPs and river stretches)
% The user should prepare beforehand an excel file with the possible values of each parameter on each column, an excel file with the operational data in WWTPs and an excel file with river connectivity and geo-hydrological variables
%For our study, parameters values were calibrated using DREAM algorithm (Vrugt et al, 2016)

Pars = xlsread('Parameters_calibrated.xlsx');

PhC(:,1)= Pars(:,1); %F
PhC(:,2)= Pars(:,2); %kWWTP
PhC(:,3)= Pars(:,3); %kriver

[rows columns]=size(PhC);

% DESIGN ALGORITHM LOOP: simulates MFT model with one set of parameter values at a time.

for q=1:rows

diclofenac = [PhC(q,1), PhC(q,2), PhC(q,3), 0.295];  %29.5 is WWTP average removal for diclofenac

WWTPdata   = xlsread('WWTP_data.xlsx'); %WWTPs data
Riverdata  = xlsread('River_data.xlsx'); %river data

%execute MFT model.m file which uses diclofenac, WWTPdata, Riverdata
%we obtain data of influent and effluent loads and concentrations and loads and concentrations at defined river points

MFT model;

%Put together results of every q simulation in matrix format
%river
prediction_loads(q,:) = prediction; %predicted diclofenac load (g/s) at every upstream part of river stretches
prediction_conc(q,:) = concentration; %predicted diclofenac concentration (g/m3)

%wwtp
Influent_loads(q,:) = Linf; %influent load of every WWTP (g/d)
Effluent_loads(q,:) = Leff*86400; %effluent load of every WWTP (g/d)

end
```

MFT model

```
[a,b] = size(WWTPdata);
Pop = zeros(a,1); %census population connected to each WWTP
Lin = zeros(a,1); %influent loads g/d
Leff = zeros(a,1); %effluent loads g/d
Cin = zeros(a,1); %influent concentrations mg/l
Ceff = zeros(a,1); %effluent concentrations mg/l
Sales = 534 mg/y/person;

  for i = 1:a
   F(i) = diclofenac(1); %dimensionless
   Pop(i) = WWTPdata(i,6); %census population connected to each WWTP
   Lin(i) = (F(i)*Pop(i)*Sales)/(365*1000); %units = g/d
   Cin(i) =  Lin(i)/ WWTPdata(i,4); %units = mg/l

   %load and concentration in the effluent:
   k_WWTP(i) = diclofenac(2)/1000; %units l/mg/d
   A = isnan(WWTPdata(:,2));
   if A(i)==1;      %WWTP without data of HRT and MLSS, take average diclofenac WWTP removal
     Removal=1-diclofenac(4);
     Ceff(i) = Cin(i)*Removal; %mg/l
     Leff(i) = Ceff(i)* WWTPdata /(24*60*60); %g/s (eflfuent loads in g/s are required as input for river mass
balance code)
   else         %WWTP with data of HRT and MLSS - we can use formula
     HRT(i) = WWTPdata(i,2); %days
     MLSS(i) = WWTPdata(i,3); %mg/l
     %model Joss et al., 2006
     Ceff(i) = Cin(i)*(1/(1+k_WWTP(i)*HRT(i)*MLSS(i))); %mg/l
     Leff(i) = Cout2010(i)*data(i,5)/(24*60*60); %g/s
   end
end
%Effluent loads are stored under Leff

%recall river mass balance model:
WWTPs =[ids_WWTP(), Leff];
flag=0; %flag=zero means "calculate F from k"
np=size(Riverdata,1);
for i= 1:np
  k_river(i,1) = diclofenac(3); %units 1/s
end

 River_Results = catchment(Riverdata, WWTPs, flag, k_river);

%Extract information from River_results

a = length(River_Results);
prediction = zeros(a,1);
removal_river = zeros(a,1);
concentration = zeros(a,1);
downstream_load = zeros(a,1);
```

```
for i = 1:a
  prediction(i) = River_Results(i).E; %diclofenac load (g/s) at every upstream part of a stretch
  concentration(i) = River_Results(i).Concentration; %diclofenac concentration (g/m3) calculated as the upstream load(sum of mass balance)/flow
  end
```

FUNCTIONS CALLED WITHIN MFT model

```
function [p] = catchment(Riverdata, WWTPs, flag, kriver);

% Format matrix " Riverdata ": each row generates a new object "point"
   % column 01: id of point
   % column 02: id entrance 1
   % column 03: id entrance 2
   % column 04: id exit 1
   % column 05: id exit 2
   % column 06: position x of point
   % column 07: position y of point
   % column 08: flow (m3/s)
   % column 09: type (1 river, 2 lake)
   % column 10: length stretch (m)
   % column 11: average velocity in stretch (m/s)
   % column 12: first order decay rate (1/s)
   % column 13: mass transfer coeficient (m/s)
   % column 14: depth (m)
   % column 15: Area (m^2)
   % column 16: Extraction of water flow from stretch (if applicable) (m3/s)

% Initial check
if(size(dades,2)~=16)
   error ' The matrix "Riverdata" should have 16 columns';
end
% End initial check

% Number of points and WWTPs in the network
np=size(Riverdata,1);
nd=size(WWTPs,1);

% Create a new array "p" of np new points
p = CreatePoints(np);

% We define the properties of np objects "point" from the matrix "Riverdata"
for i=1:np
   % Information on connectivity
   % Take the from the first column
   id          = Riverdata(i,01);
   p(id).id     = id;
   p(id).id_up1   = Riverdata(i,02);
   p(id).id_up2   = Riverdata(i,03);
   p(id).id_down1 = Riverdata(i,04);
   p(id).id_down2 = Riverdata(i,05);

   % At first, we asume every point is not calculable
   p(id).is_calculable = 0;

   % River decay information
   p(id).Q      = Riverdata(i,08); % flow
   p(id).type       = Riverdata(i,09); % river(1) o lake(2)
   p(id).L      = Riverdata(i,10); % length
   p(id).v      = Riverdata(i,11); % velocity
   p(id).k      = kriver(i,1); % decay rate
   p(id).vf      = Riverdata(i,13); % mass transfer coefficient
   p(id).h      = Riverdata(i,14); % depth
   p(id).A      = Riverdata(i,15); % area
   p(id).Qext      = Riverdata(i,16); % extracted flow
end

%%%%%%%%%%%%%%%%%%%%%%%%%%%
% CALCULATE HRT, f & HL for each point %
%%%%%%%%%%%%%%%%%%%%%%%%%%%
   for i=1:np
      % HRT
      p(i).calculateHRT();
      % We calculate HRT according to flag (it is a parameter that we used to call the function)
      if(flag==0)
         % Calculates f from k
         p(i).calculatef_k();
      else
         % Calculates HL
         p(i).calculateHL();
         % Calculates f from vf
         p(i).calculatef_vf();
      end
   end
   % testing: we write manually the f value
   % for i=1:np p(i).f = 0.5 end
% End f calculation

% Count of the initial points of the network
counting_seeds=[];
% We read every point and determine which ones correspond to the start of the
% network (we save them)
for i=1:length(p)
   % if point does not have entrances:
   %  assign a pre-defined entrance (0)
   %  mark it as calculable
   %   sum 1 to the counting of seeds (stating points)
   %  calculate the exit load
   % if point does have entrances
   %     assign NaN (not a number) to the entrance
   %  mark it as NON calculable
   if(p(i).id_up1==0 & p(i).id_up2==0)
```

```
        p(i).E  = 0;
        p(i).is_calculable = 1;
        counting_seeds = [counting_seeds i];
        p(i).calculateS();
    else
        p(i).E  = NaN;
        p(i).is_calculable = 0;
    end
end

% WWTPs
% We need to sum the WWTP loads to the entrance load of a point
for i=1:nd
    id=WWTPs(i,1);
    % As such, we allow more than 1 WWTP to discharge on the same point
    if(isnan(p(id).E))
        p(id).E = WWTPs(i,2);
    else
        p(id).E = p(id).E + WWTPs(i,2);
    end
end

% Find false points (points without entrances nor exits)
False_point=[];
for i=1:np
    if (p(i).id_up1==0 & p(i).id_up2==0 & p(i).id_down1==0 & p(i).id_down2==0)
        False_point =[False_point, i];
    end
end


%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
%   MASS BALANCE CALCULATION             %
%   stops when every node is calculated  %
%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
while (true)
    calculables=[];
    for i=1:length(p)
        if(p(i).is_calculable)
            calculables=[calculables,i];
        end
    end

    if(length(calculables)>=length(p)) break; end

    %Find points where entrances have calculable points
    %This will mean that those points are also calculable and thus we mark them as calculable and we can calculate them
    for i=1:np
        %we take the ids of entrances up(1) i up(2)
        up=[p(i).id_up1 p(i).id_up2];

        %There are 4 cases: 2 entrances that can be equal or different to 0
        % [0 0], [0 1], [1 0], [1 1]

        % If both entrances are 0, these are WWTPs or cases already calculated (calculables)
        if (isequal(up,[0 0]))
            p(i).calculateS();
% now we can continue by the next iteration
            continue
        end

        if (up(1)==0)
            if (p(up(2)).is_calculable)
                p(i).is_calculable=1;
                if(isnan(p(i).E))
                    p(i).E=p(up(2)).S;
                else
                    p(i).E=p(i).E+p(up(2)).S;
                end
                p(i).calculateS();
            end
            continue
        end
        if (up(2)==0)
            if (p(up(1)).is_calculable)
                p(i).is_calculable=1;
                if(isnan(p(i).E))
                    p(i).E=p(up(1)).S;
                else
                    p(i).E=p(i).E+p(up(1)).S;
                end
                p(i).calculateS();
            end
            continue
        end

        %if loop arrives here means both entrances to the point i are different to 0
        %if both entrances are calculable, so does the point i
        if (p(up(1)).is_calculable & p(up(2)).is_calculable)
            p(i).is_calculable=1;
            if(isnan(p(i).E))
                p(i).E=p(up(1)).S+p(up(2)).S;
            else
                p(i).E=p(i).E+p(up(1)).S+p(up(2)).S;
            end
            p(i).calculateS();
        end
    end
end
```

```
function [p]= CreatePoints (n)
% Create an array "p" of [n] objects of type "point"

  % Initiate the array with a new point
  p=[point];

  % Add n-1 objects to the array [p]
  for i=1:(n-1);
    p=[p point];
  end

end
```

```
classdef point < handle
  % Definition of object "point" for the mass balance
  % "point" represents the a river stretch

  properties
    E             % [g/s] Entrance load
    S             % [g/s] Exit load
    id            % id
    id_up1          % id of point of entrance 1
    id_up2          % id of point of entrance 2
    id_down1        % id of point of exit 1
    id_down2        % id of point of exit 2
    is_calculable    % boolea (1 or 0) indicates if the mass balance is applied

    % simulated flow and extracted flow (if so) The initial flow would be Q+Qext
    Q              % [m3/s]
    Qext            % [m3/s]
    Concentration    % [g/m3]

    % implementation river-decay (1)
    type  % [number]  "river"=1; "lake"=2
    f    % [dimensionless]  decimal between 0 and 1: fraction of E that leaves by S(it is calculated from HRT and k)
    L          % [meters] Length of stretch associated to the exit river stretch (for "lake", this will be the volume V)
    v    % [m/s] Average velocity associated to the exit river stretch (for "lake", this will be the flow Q)
    HRT      % [s] Hydraulic Retention Time (defined by L/v)
    k    % [1/s] First order decay rate (defined)

    % implementation river-decay (2) (alternative way to calculate F)
    vf      % [m/s] Mass transfer coefficient (defined)
    HL      % [m/s] Hydraulic Load (defined by h/HRT (river) or v/A (lake))
    h    % [m] River depth (defined)
    A    % [m^2] Surface area (defined)
  end

  methods
    function calculateS(obj)
    % calculate exit S=f*E
      % calculate concentration [g/m3] dividing the entrance load [g/s] by the sum of flows [m3/s]
      obj.Concentration = obj.E/(obj.Q + obj.Qext);

      % We calculate the entrance after an hypothetical extraction "point"
      newE = obj.E - obj.Qext * obj.Concentration;

      % We calculate the new exit load
      obj.S = obj.f * newE;
    end

    function calculateHRT(obj)
    % calculate HRT from length and velocity
      obj.HRT = obj.L / obj.v ;
    end

%%%%%%%%%%%%%%%%%%%%%%%%%%%%
% 2 ways to calculate f, we call only one (they overwrite f)%
%%%%%%%%%%%%%%%%%%%%%%%%%%%%

 function calculatef_k(obj)
    % we calculate f from k
      obj.f = exp(-obj.HRT * obj.k);
    end

    function calculateF_vf(obj)
    % we calculate f from vf
      if obj.type == 1 % for river
        obj.f = exp(-obj.vf / obj.HL);
      elseif obj.type == 2 % for lake
        obj.f = 1 / (1+(obj.vf / obj.HL));
      end
    end

    % End of f calculation

    function calculateHL(obj)
    % HL is calculated differently depending on rivers or lakes
      if obj.type == 1      % river
        obj.HL = obj.h / obj.HRT;
```

```
      elseif obj.type == 2   % lake
        obj.HL = obj.v / obj.A ;
      end
    end
  end

end
```

```
%This function generates a column with the ids
of points where WWTP effluents discharge to
the river.  It is used to create the table "WWTP"
as input for the catchment model

  WWTP
  ---+--------
  id | load
  ---+--------
     |
     |
     |
%
function ids=ids_WWTP()
  ids=[
    1;
    6;
    10;
    11;
    15;
    16;
    18;
    20;
    24;
    28;
    32;
    35;
    38;
    43;
    44;
    46;
    53;
    58;
    62;
    63;
    70;
    72;
    79;
    82;
    84;
    94;
    97;
    101;
    103;
    106;
    110;
    111;
    113;
    114;
    116;
    117;
    123;
    125;
    128;
    130;
    131;
    133;
    134;
    137;
    137;
    139;
    139;
    140;
    141;
    142;
    144;
    150;
    150;
    151;
    153;
    157;
  ];
end
```

A1.2 River data

Table A 1. Hydrological data of September 2010

id	id up 1	id up 2	id down 1	id down 2	x	y	Q ($m^3 \cdot s^{-1}$)	L (m)	v($m \cdot s^{-1}$)	k (s^{-1})
1	0	0	2	0	2.0167	42.2852	0.52	4,648	0.50	0.000001
2	1	0	4	0	1.9860	42.2631	0.52	3,168	0.47	0.000001
3	0	0	4	0	2.0526	42.2756	0.81	13,044	0.70	0.000001
4	2	3	6	0	1.9766	42.2456	1.33	10,925	0.50	0.000001
5	0	0	6	0	1.7758	42.2774	1.26	13,155	0.65	0.000001
6	4	5	8	0	1.8805	42.2314	2.62	2,087	0.84	0.000001
7	0	0	8	0	1.7265	42.2203	0.60	18,141	0.58	0.000001
8	6	7	10	0	1.8704	42.2160	3.22	4,053	0.90	0.000001
9	0	0	0	0	1.8685	42.1881	0.00	0	0.00	0.000001
10	8	0	11	0	1.8685	42.1881	1.84	2,862	0.65	0.000001
11	10	0	14	0	1.8797	42.1224	1.85	61,180,000	1.85	0.000001
12	0	0	13	0	2.0144	42.1724	0.38	13,870	0.45	0.000001
13	12	0	14	0	1.9198	42.1289	0.38	26,220,000	0.38	0.000001
14	11	13	15	0	1.8797	42.1224	3.00	6,313	0.72	0.000001
15	14	0	16	0	1.8773	42.0821	3.05	8,279	0.60	0.000001
16	15	0	19	0	1.8878	42.0187	3.06	2,321	0.60	0.000001
17	0	0	18	0	1.7854	42.0770	0.47	10,819	0.40	0.000001
18	17	0	19	0	1.8531	42.0186	0.47	4,220	0.45	0.000001
19	16	18	20	0	1.8860	42.0034	3.54	7,978	0.88	0.000001
20	19	0	23	0	1.8860	41.9523	3.55	3,337	0.90	0.000001
21	0	0	22	0	2.0534	42.1968	1.42	27,679	0.60	0.000001
22	21	0	23	0	2.0008	42.0331	2.44	23,950	0.62	0.000001
23	20	22	24	0	1.8831	41.9279	5.99	5,500	0.85	0.000001
24	23	0	27	0	1.8900	41.8929	6.00	4,865	0.90	0.000001
25	0	0	26	0	1.8226	41.9282	0.25	7,456	0.40	0.000001
26	25	0	27	0	1.8536	41.8910	0.25	6,245	0.40	0.000001
27	24	26	28	0	1.8812	41.8608	6.25	2,199	0.93	0.000001
28	27	0	30	0	1.8823	41.8484	6.25	2,221	0.80	0.000001
29	0	0	0	0	1.8820	41.8316	0.00	0	0.00	0.000001
30	28	0	44	0	1.8820	41.8316	4.74	7,211	0.60	0.000001
31	0	0	33	0	2.0816	42.1189	0.29	22,915	0.40	0.000001
32	0	0	33	0	2.1069	42.1011	0.27	20,907	0.35	0.000001
33	31	32	36	0	2.0771	41.9774	0.56	6,224	0.50	0.000001
34	0	0	35	0	2.1010	42.0182	0.13	5,227	0.40	0.000001
35	34	0	36	0	2.0982	41.9812	0.13	6,946	0.40	0.000001
36	33	35	40	0	2.0670	41.9463	0.69	4,047	0.48	0.000001
37	0	0	39	0	2.0143	41.9887	0.06	3,650	0.26	0.000001
38	0	0	39	0	2.0424	41.9876	0.05	2,909	0.22	0.000001
39	37	38	40	0	2.0353	41.9672	0.11	6,598	0.40	0.000001
40	36	39	42	0	2.0479	41.9308	0.80	19,185	0.50	0.000001
41	0	0	42	0	1.9979	41.9690	0.30	16,146	0.40	0.000001
42	40	41	43	0	1.9785	41.8631	1.09	1,940	0.45	0.000001
43	42	0	44	0	1.9714	41.8518	1.10	12,694	0.49	0.000001

44	30	43	51	0	1.9099	41.7836	5.86	3,665	0.72	0.000001
45	0	0	46	0	2.1138	41.8353	0.21	4,921	0.45	0.000001
46	45	0	48	0	2.1046	41.8021	0.23	4,192	0.43	0.000001
47	0	0	48	0	2.1679	41.8046	0.40	13,792	0.40	0.000001
48	46	47	50	0	2.0799	41.7854	0.63	11,128	0.50	0.000001
49	0	0	50	0	2.0369	41.7320	0.45	6,691	0.50	0.000001
50	48	49	51	0	2.0134	41.7639	1.08	22,895	0.60	0.000001
51	44	50	54	0	1.8987	41.7567	6.94	5,280	0.65	0.000001
52	0	0	53	0	1.8450	41.8171	0.29	10,867	0.33	0.000001
53	52	0	54	0	1.8757	41.7435	0.36	1,869	0.27	0.000001
54	51	53	56	0	1.8802	41.7313	7.30	1,881	0.85	0.000001
55	0	0	56	0	1.9849	41.6975	0.58	17,064	0.55	0.000001
56	54	55	57	0	1.8779	41.7241	7.89	3,773	0.83	0.000001
57	56	0	58	0	1.8699	41.7041	7.89	1,246	0.80	0.000001
58	57	0	99	0	1.8733	41.6941	7.89	4,036	0.65	0.000001
59	0	0	60	0	1.6460	42.2241	1.07	21,248	0.65	0.000001
60	59	0	64	0	1.6327	42.1292	1.07	21,585,000	1.07	0.000001
61	0	0	62	0	1.5752	42.1882	0.19	2,189	0.35	0.000001
62	61	0	63	0	1.5912	42.1751	0.27	5,260	0.45	0.000001
63	62	0	64	0	1.6057	42.1350	0.27	7,195,000	0.27	0.000001
64	60	63	65	0	1.6077	42.1262	1.34	43,170,000	1.34	0.000001
65	64	0	66	0	1.5864	42.1023	2.00	5,376	0.75	0.000001
66	65	0	67	0	1.5678	42.0575	2.43	7,545	0.80	0.000001
67	66	0	68	0	1.5759	42.0013	2.43	22,740,000	2.43	0.000001
68	67	0	74	0	1.6058	41.9643	3.00	5,934	0.70	0.000001
69	0	0	70	0	1.5024	42.0232	0.07	5,982	0.34	0.000001
70	69	0	73	0	1.5330	41.9828	0.09	11,811	0.33	0.000001
71	0	0	72	0	1.5534	41.9262	0.03	1,569	0.22	0.000001
72	71	0	73	0	1.5691	41.9310	0.03	1,952	0.20	0.000001
73	70	72	74	0	1.5855	41.9404	0.12	6,083	0.30	0.000001
74	68	73	75	0	1.6358	41.9313	3.12	904	0.62	0.000001
75	74	0	77	0	1.6435	41.9337	3.12	2,837	0.52	0.000001
76	0	0	77	0	1.7539	42.1105	0.47	34,659	0.50	0.000001
77	75	76	79	0	1.6657	41.9285	3.59	6,740	0.70	0.000001
78	0	0	0	0	1.7015	41.9161	0.00	0	0.00	0.000001
79	77	0	81	0	1.7140	41.9104	3.58	2,462	0.70	0.000001
80	0	0	81	0	1.7722	42.0496	0.03	24,289	0.27	0.000001
81	79	80	83	0	1.7183	41.8452	3.60	11,967	0.58	0.000001
82	0	0	83	0	1.5741	41.8762	0.01	19,825	0.18	0.000001
83	81	82	84	0	1.7567	41.8244	3.61	7,729	0.80	0.000001
84	83	0	85	0	1.7617	41.8096	3.63	2,262	0.78	0.000001
85	84	0	86	0	1.7728	41.7969	3.63	1,915	0.53	0.000001
86	85	0	89	0	1.7728	41.7969	3.63	3,292	0.80	0.000001
87	0	0	88	0	1.8109	41.8310	0.13	3,932	0.26	0.000001
88	87	0	89	0	1.8052	41.8011	0.13	5,054	0.32	0.000001
89	86	88	91	0	1.7849	41.7777	3.76	3,853	0.60	0.000001
90	0	0	91	0	1.6407	41.7647	0.65	17,452	0.50	0.000001

91	89	90	93	0	1.8007	41.7533	4.41	7,803	0.70	0.000001
92	0	0	93	0	1.5911	41.7533	1.63	35,623	0.60	0.000001
93	91	92	94	0	1.8385	41.7095	6.04	974	1.00	0.000001
94	93	0	95	0	1.8446	41.7048	6.37	708	0.45	0.000001
95	94	0	98	0	1.8465	41.6990	6.37	2,142	0.70	0.000001
96	0	0	97	0	1.7389	41.6469	0.66	10,383	0.45	0.000001
97	96	0	98	0	1.7934	41.6962	0.67	6,731	0.55	0.000001
98	95	97	99	0	1.8387	41.6832	7.04	1,765	0.90	0.000001
99	58	98	100	0	1.8543	41.6804	14.93	4,007	1.00	0.000001
100	99	0	101	0	1.8599	41.6514	14.93	6,819	0.94	0.000001
101	100	0	102	0	1.8628	41.6242	14.96	2,431	0.85	0.000001
102	101	0	103	0	1.8462	41.6141	14.96	2,122	0.80	0.000001
103	102	0	104	0	1.8528	41.5996	14.98	6,323	1.15	0.000001
104	103	0	108	0	1.8822	41.5638	14.98	7,328	1.00	0.000001
105	0	0	107	0	1.7535	41.5897	0.54	16,647	0.43	0.000001
106	0	0	107	0	1.7928	41.5322	0.48	11,402	0.50	0.000001
107	105	106	108	0	1.8723	41.5255	1.02	4,214	0.54	0.000001
108	104	107	110	0	1.9124	41.5306	16.00	3,406	0.72	0.000001
109	0	0	0	0	1.9124	41.5306	0.00	0	0.00	0.000001
110	108	0	115	0	1.9158	41.5058	13.67	2,267	0.90	0.000001
111	0	0	114	0	1.9238	41.5869	0.42	9,745	0.48	0.000001
112	0	0	113	0	1.9765	41.6081	0.47	9,693	0.40	0.000001
113	112	0	114	0	1.9634	41.5477	0.48	3,950	0.52	0.000001
114	111	113	115	0	1.9397	41.5293	0.91	4,930	0.54	0.000001
115	110	114	144	0	1.9235	41.4967	14.57	2,646	0.75	0.000001
116	0	0	118	0	1.5009	41.6966	0.03	9,749	0.20	0.000001
117	0	0	118	0	1.5268	41.7182	0.04	14,166	0.22	0.000001
118	116	117	120	0	1.5196	41.6347	0.08	2,998	0.30	0.000001
119	0	0	120	0	1.4139	41.5946	0.04	14,209	0.29	0.000001
120	118	119	121	0	1.5293	41.6146	0.12	3,234	0.30	0.000001
121	120	0	124	0	1.5473	41.5981	0.12	4,328	0.28	0.000001
122	0	0	123	0	1.4801	41.5580	1.07	6,764	0.44	0.000001
123	122	0	124	0	1.5340	41.5646	1.07	5,420	0.48	0.000001
124	121	123	125	0	1.6066	41.5820	1.18	9,027	0.58	0.000001
125	124	0	126	0	1.6524	41.5677	1.38	910	0.54	0.000001
126	125	0	129	0	1.6618	41.5649	1.38	3,225	0.65	0.000001
127	0	0	128	0	1.4836	41.4675	1.98	19,870	0.50	0.000001
128	127	0	129	0	1.6321	41.5337	1.98	6,232	0.62	0.000001
129	126	128	130	0	1.6785	41.5515	3.36	4,580	0.66	0.000001
130	129	0	131	0	1.6943	41.5267	3.42	7,623	0.75	0.000001
131	130	0	135	0	1.7237	41.4953	3.44	10,996	0.84	0.000001
132	0	0	133	0	1.5347	41.4773	0.17	11,590	0.30	0.000001
133	132	0	134	0	1.6195	41.4761	0.17	17,601	0.30	0.000001
134	133	0	135	0	1.7513	41.4419	0.19	4,068	0.34	0.000001
135	131	134	139	0	1.7858	41.4446	3.63	5,291	0.65	0.000001
136	0	0	138	0	1.6873	41.4054	0.52	6,928	0.40	0.000001
137	0	0	138	0	1.7711	41.3828	0.55	2,909	0.50	0.000001

138	136	137	139	0	1.7490	41.3967	1.07	10,276	0.50	0.000001
139	135	138	140	0	1.8175	41.4265	4.72	4,802	0.70	0.000001
140	139	0	143	0	1.8552	41.4427	4.73	2,770	0.65	0.000001
141	0	0	142	0	1.8163	41.4872	0.24	2,804	0.30	0.000001
142	141	0	143	0	1.8349	41.4735	0.24	5,442	0.35	0.000001
143	140	142	144	0	1.8658	41.4513	4.98	8,000	0.58	0.000001
144	115	143	145	0	1.9351	41.4797	19.64	4,041	1.10	0.000001
145	144	0	147	0	1.9657	41.4743	19.64	4,121	0.90	0.000001
146	0	0	147	0	1.9358	41.4260	0.25	6,083	0.47	0.000001
147	145	146	152	0	1.9857	41.4450	19.90	1,421	0.60	0.000001
148	0	0	149	0	1.9833	41.6520	0.41	12,152	0.46	0.000001
149	148	0	150	0	2.0347	41.5667	0.41	5,433	0.31	0.000001
150	149	0	151	0	2.0306	41.4844	0.99	10,029	0.40	0.000001
151	150	0	152	0	2.0013	41.4616	1.24	3,233	0.55	0.000001
152	147	151	154	0	1.9962	41.4374	21.14	4,048	0.70	0.000001
153	0	0	154	0	2.0899	41.4298	0.40	12,358	0.45	0.000001
154	152	153	156	0	2.0121	41.4174	21.54	2,345	0.60	0.000001
155	0	0	0	0	2.0140	41.4083	0.00	0	0.00	0.000001
156	154	0	157	0	2.0230	41.3908	20.89	1,830	0.68	0.000001
157	156	0	159	0	2.0230	41.3908	21.47	4,151	0.35	0.000001
158	0	0	0	0	2.0315	41.3778	0.00	0	0.00	0.000001
159	157	0	160	0	2.0482	41.3496	19.26	7,008	0.42	0.000001
160	159	0	0	0	2.1129	41.3272	19.26	3,434	0.25	0.000001

A1.3 Observed variations in diclofenac influent loads

Table A 2. Influent concentrations of diclofenac obtained from Gros et al., 2007, Gros et al., 2010 and Jelic et al., 2011. Number of inhabitants connected to each WWTP provided by Statistical Institute of Catalonia, 2016. Influent flows provided by WWTP operators. Loads of diclofenac calculated based on the influent concentration, inhabitants and influent flows

WWTP	Month	Year	Influent conc.(ng·L^{1})	Inhabitants	Influent flow (m^{3}·d^{-1})	*Load (*mg·year^{-1}·inh^{-1})
LLE	November	2005	947.11	129,693	54,938	146.44
LLE	November	2006	1,106.00	131,039	45,372	139.78
TAR	March	2008	1,113.97	139,074	23,807	69.60
TAR	March	2009	1,121.85	141,654	25,958	75.03
TAR	December	2007	830.00	135,471	25,818	57.74
TAR	June	2008	1,673.90	139,074	27,837	122.30
VIC	June	2008	860.53	48,855	25,685	165.13
VIL	March	2009	964.26	47,515	21,689	160.66
VIL	December	2007	504.76	42,076	19,605	85.84
VIL	November	2008	674.28	45,793	19,621	105.45
VIL	July	2007	565.48	42,076	39,730	194.89
					Median	122.29
					Percentil 5th	63.7
					Percentil 95th	180.01

The uncertainty of diclofenac influent loads around the median value of 122.29 mg·year^{-1}·inh^{-1} resulted in [-52%, +47%].

A1.4 Estimation of the prior probability distribution function of k_{WWTP} of diclofenac

Table A 3. Removal (%) of diclofenac obtained from Gros et al., 2007, Gros et al., 2010 and Jelic et al., 2011. HRT and MLSS were provided by WWTP operators. k_{WWTP} was calculated using equation (4) of the main text.

WWTP	Month	Year	HRT (days)	MLSS ($mg \cdot L^{-1}$)	Removal (%)	k_{WWTP} ($L \cdot g^{1} \cdot d^{1}$)
LLE	November	2005	0.17	1,781	20.36	0.844
LLE	November	2006	0.2	1,747	41.14	2
LOG	July	2008	0.33	1,173	8.78	0.249
MIR	July	2008	1.42	3,591	60.6	0.302
MIR	June	2005	1.42	3,204	51.24	0.231
MIR	June	2006	1.42	4,045	43.67	0.135
PAM	October	2007	0.49	2,735	27.81	0.286
TAR	March	2008	0.38	2,955	29.49	0.377
TAR	March	2009	0.34	1,838	6.64	0.114
TAR	December	2007	0.34	2,746	22.38	0.309
TAR	June	2008	0.32	2,456	47.96	1.172
VIC	June	2008	1.03	5,601	61	0.271
VIL	March	2009	0.29	1,561	22.98	0.661
VIL	December	2007	0.32	1,575	36.6	1.146
VIL	November	2008	0.32	1,375	15.28	0.41
VIL	July	2007	0.24	3,537	39.87	0.776
ZAR	July	2008	0.33	1,800	15.99	0.317

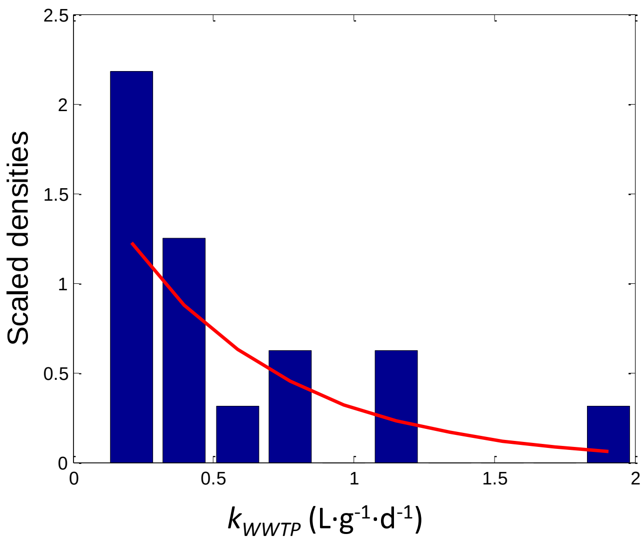

Figure A 1. Histogram plot of k_{WWTP} values of diclofenac (blue bars). We fitted an exponential distribution (red curve) with a mean of 0.55 $L \cdot g^{-1} \cdot d^{-1}$ to the k_{WWTP} values using maximum likelihood (command fitdist of Matlab)

Goodness of fit was assessed comparing the cumulative distribution of the k_{WWTP} values of diclofenac and the cumulative exponential distribution fitted to the k_{WWTP} values (Figure A 2)

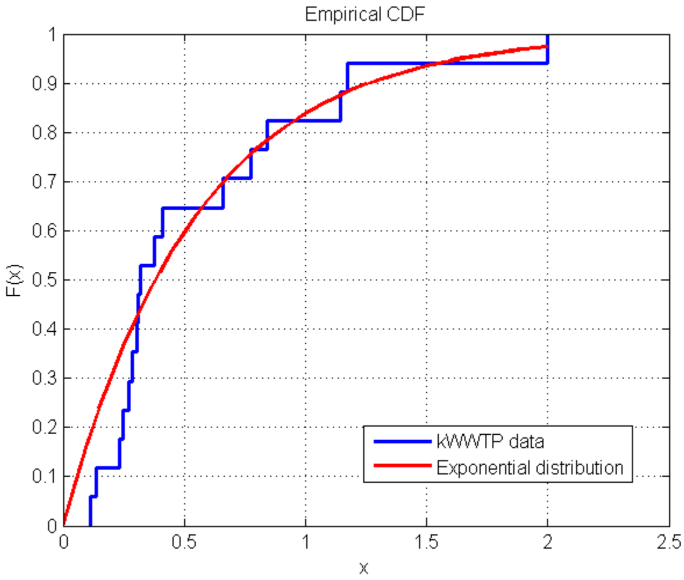

Figure A 2. Cumulative distribution of the k_{WWTP} values of diclofenac (blue curve) and cumulative exponential distribution fitted to the k_{WWTP} values (red curve)

A1.5 Estimation of the prior probability distribution function of k_{river} of diclofenac

Table A 4. k_{river} values of diclofenac reviewed from 19 publications in the framework of the project SCARCE (Boithias et al., 2013).

k_{river} (s^{-1})
0.00019
9.07E-05
0.00012
4.28E-06
4.63E-05
0.00033
0.00031
2.29E-06
1.65E-06
5.96E-07
0.00094
8.06E-06
1.97E-05
7.69E-07
1.02E-06
0.00033
4.72E-05
0.00010
5.09E-08

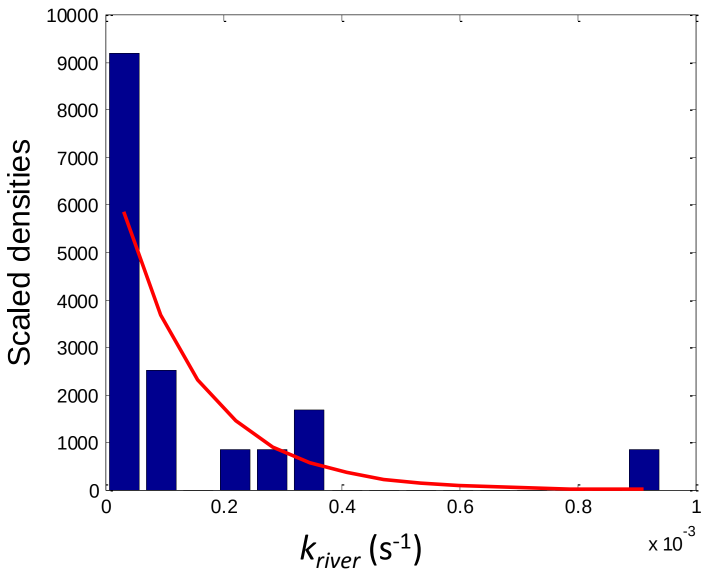

Figure A 3. Histogram plot of k_{river} values of diclofenac (blue bars). We fitted an exponential distribution (red curve) with a mean of 1.3E-04 s^{-1} to the k_{river} values using maximum likelihood (command fitdist of Matlab)

Goodness of fit was assessed comparing the cumulative distribution of the k_{river} values of diclofenac and the cumulative exponential distribution fitted to the k_{river} values (Figure A 4)

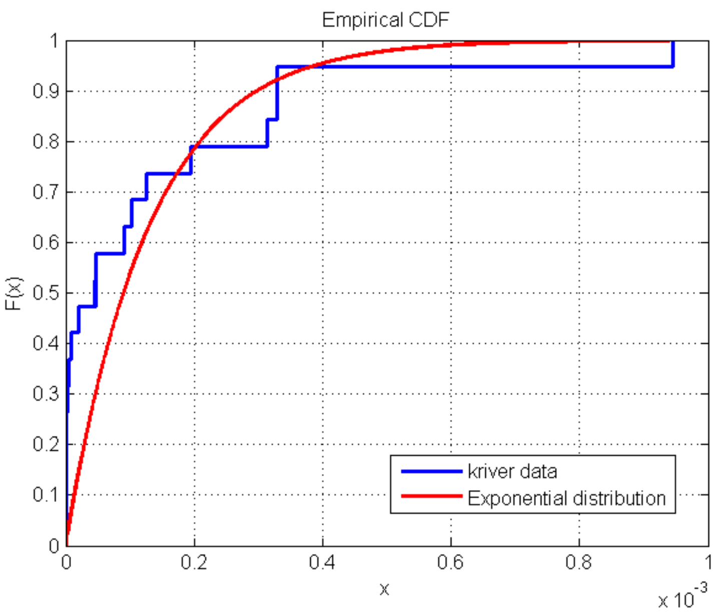

Figure A 4. Cumulative distribution of the k_{river} values of diclofenac (blue curve) and cumulative exponential distribution fitted to the k_{river} values (red curve)

A1.6 Evaluation of statistically significant differences between the amount of diclofenac removed by WWTPs and rivers in the Llobregat

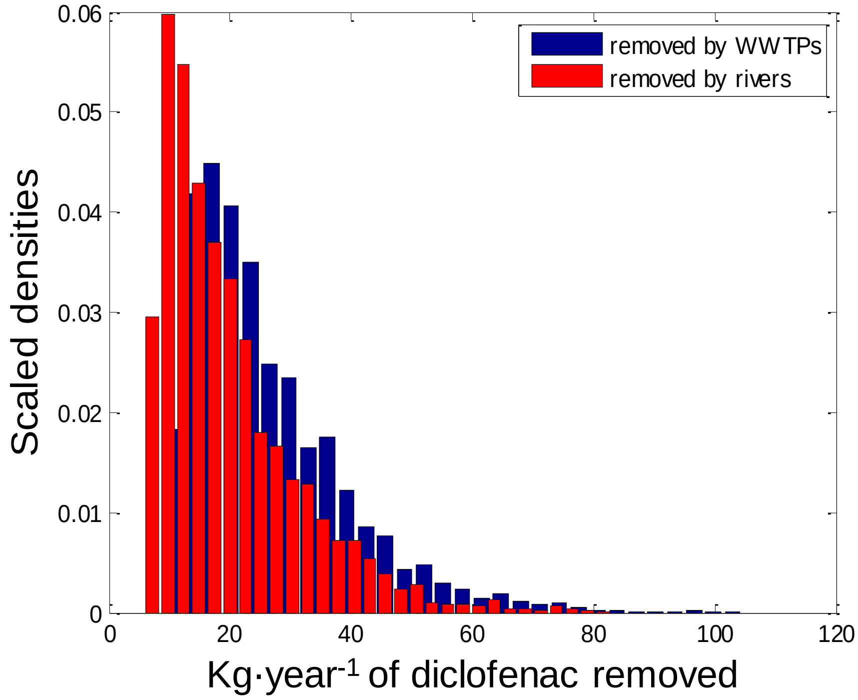

Figure A 5. Histogram plot of kg·year^{-1} of diclofenac removed by WWTPs (blue) and rivers (red)

We evaluated the statistically significant differences between the kg·year^{-1} removed in WWTPs and the kg·year^{-1} removed in rivers by calculating the probability of the amount removed in WWTPs being higher than the amount removed in rivers. If significant differences exist, this probability should be high (close to 100%). To calculate this probability, we generated 10,000 bootstrapping samples (sampled uniformly at random with replacement) for the distribution of kg·year^{-1} removed by WWTPs and rivers. We obtained that there is only a probability of 67% [64%-71%] that the kg·y^{-1} removed in WWTPs are higher than the kg·year^{-1} removed in rivers. In other words, the rivers remove more diclofenac than the WWTPs in 33% [29% - 36%] of the samples. Therefore, we conclude that there are not statistically significant differences between the amount removed in WWTs and rivers.

Annex 2

A2.1 Probability of achieving an apparent reduction in diclofenac concentrations – Matlab code

For a given scenario of uncertainty (calibrated, decreased or increased), we built a matrix in Matlab including the 5,000 diclofenac concentrations simulated at LLO7 with different increases in WWTP removal rate constant (10%, 20%, 30%, 40%, 50%, 100%, 200%, 500%, 1,000%, 5,000% and 10,000%). In the next Matlab code, this matrix is represented as AA.

```
boot = zeros(11,10000); %probability of achieving an apparent reduction of river concentrations for an increase in WWTP rate constant with regard to calibrated concentrations. 11 scenarios of increases in WWTP rate constant are considered and 10,000 bootstrap replications
mean_boot_AA = zeros(1,11); % mean of probabilities
percentile5_AA = zeros(1,11); % percentile 5 of probabilities
percentile95_AA = zeros(1,11); %percentile 95 of probabilities


for j=1:11
for i=1:10000
   sample=datasample(AA(:,j+1),5000); % returns 5000 observations sampled uniformly at random, with replacement, from the concentration simulated with the measure
   boot(j,i)=sum(sample<prctile(AA(:,1),5))/length(sample); % calculation of probability

end
   mean_boot_AA(j) = mean(boot(j,:))*100;
   percentile5_AA(j) = prctile(boot(j,:),5)*100;
   percentile95_AA(j) = prctile(boot(j,:),95)*100;
end
```

Percentiles 5 and 95 of probabilities are not represented in *figure 5, right* of the main text because the resulting bars were very small and overlap with the symbol representing the mean probability.

A2.2 River data 7Q10

Table A 5. Hydrological data of 7Q10 flows

id	id up 1	id up 2	id down 1	id down 2	x	y	Q ($m^3 \cdot s^{-1}$)	L (m)	v($m \cdot s^{-1}$)	k (s^{-1})
1	0	0	2	0	2.0167	42.2852	0.1000	4,648	0.28	0.000023
2	1	0	4	0	1.9860	42.2631	0.1000	3,168	0.28	0.000023
3	0	0	4	0	2.0526	42.2756	0.1894	13,044	0.32	0.000023
4	2	3	6	0	1.9766	42.2456	0.2894	10,925	0.36	0.000023
5	0	0	6	0	1.7758	42.2774	0.2161	13,155	0.33	0.000023
6	4	5	8	0	1.8805	42.2314	0.5300	2,087	0.41	0.000023
7	0	0	8	0	1.7265	42.2203	0.2772	18,141	0.35	0.000023
8	6	7	10	0	1.8704	42.2160	0.8072	4,053	0.46	0.000023
9	0	0	0	0	1.8685	42.1881	0.0000	0	0.43	0.000023
10	8	0	11	0	1.8685	42.1881	0.1575	2,862	0.31	0.000023
11	10	0	14	0	1.8797	42.1224	0.1607	61,180,000	0.31	0.000023
12	0	0	13	0	2.0144	42.1724	0.1925	13,870	0.33	0.000023
13	12	0	14	0	1.9198	42.1289	0.1925	26,220,000	0.19	0.000023
14	11	13	15	0	1.8797	42.1224	1.1000	6,313	0.49	0.000023
15	14	0	16	0	1.8773	42.0821	1.1477	8,279	0.50	0.000023
16	15	0	19	0	1.8878	42.0187	1.1617	2,321	0.50	0.000023
17	0	0	18	0	1.7854	42.0770	0.1289	10,819	0.30	0.000023
18	17	0	19	0	1.8531	42.0186	0.1304	4,220	0.30	0.000023
19	16	18	20	0	1.8860	42.0034	1.2921	7,978	0.51	0.000023
20	19	0	23	0	1.8860	41.9523	1.3043	3,337	0.51	0.000023
21	0	0	22	0	2.0534	42.1968	0.3810	27,679	0.38	0.000023
22	21	0	23	0	2.0008	42.0331	0.6549	23,950	0.43	0.000023
23	20	22	24	0	1.8831	41.9279	1.9593	5,500	0.56	0.000023
24	23	0	27	0	1.8900	41.8929	1.9700	4,865	0.56	0.000023
25	0	0	26	0	1.8226	41.9282	0.0512	7,456	0.24	0.000023
26	25	0	27	0	1.8536	41.8910	0.0514	6,245	0.24	0.000023
27	24	26	28	0	1.8812	41.8608	2.0214	2,199	0.57	0.000023
28	27	0	30	0	1.8823	41.8484	2.0307	2,221	0.57	0.000023
29	0	0	0	0	1.8820	41.8316	0.0000	0	0.06	0.000023
30	28	0	44	0	1.8820	41.8316	2.0305	7,211	0.35	0.000023
31	0	0	33	0	2.0816	42.1189	0.0387	22,915	0.22	0.000023
32	0	0	33	0	2.1069	42.1011	0.0368	20,907	0.22	0.000023
33	31	32	36	0	2.0771	41.9774	0.0755	6,224	0.26	0.000023
34	0	0	35	0	2.1010	42.0182	0.0170	5,227	0.18	0.000023
35	34	0	36	0	2.0982	41.9812	0.0196	6,946	0.19	0.000023
36	33	35	40	0	2.0670	41.9463	0.0950	4,047	0.28	0.000023
37	0	0	39	0	2.0143	41.9887	0.0080	3,650	0.15	0.000023
38	0	0	39	0	2.0424	41.9876	0.0107	2,909	0.16	0.000023
39	37	38	40	0	2.0353	41.9672	0.0187	6,598	0.19	0.000023
40	36	39	42	0	2.0479	41.9308	0.1138	19,185	0.29	0.000023
41	0	0	42	0	1.9979	41.9690	0.0390	16,146	0.22	0.000023
42	40	41	43	0	1.9785	41.8631	0.1528	1,940	0.31	0.000023
43	42	0	44	0	1.9714	41.8518	0.1562	12,694	0.31	0.000023
44	30	43	51	0	1.9099	41.7836	2.2133	3,665	0.58	0.000023

45	0	0	46	0	2.1138	41.8353	0.0162	4,921	0.18	0.000023
46	45	0	48	0	2.1046	41.8021	0.0359	4,192	0.22	0.000023
47	0	0	48	0	2.1679	41.8046	0.0315	13,792	0.21	0.000023
48	46	47	50	0	2.0799	41.7854	0.0675	11,128	0.25	0.000023
49	0	0	50	0	2.0369	41.7320	0.0351	6,691	0.22	0.000023
50	48	49	51	0	2.0134	41.7639	0.1026	22,895	0.28	0.000023
51	44	50	54	0	1.8987	41.7567	2.3159	5,280	0.59	0.000023
52	0	0	53	0	1.8450	41.8171	0.0229	10,867	0.20	0.000023
53	52	0	54	0	1.8757	41.7435	0.0929	1,869	0.27	0.000023
54	51	53	56	0	1.8802	41.7313	2.4088	1,881	0.30	0.000023
55	0	0	56	0	1.9849	41.6975	0.0886	17,064	0.27	0.000023
56	54	55	57	0	1.8779	41.7241	2.4974	3,773	0.35	0.000023
57	56	0	58	0	1.8699	41.7041	2.4974	1,246	0.60	0.000023
58	57	0	99	0	1.8733	41.6941	2.5031	4,036	0.60	0.000023
59	0	0	60	0	1.6460	42.2241	0.0076	21,248	0.15	0.000023
60	59	0	64	0	1.6327	42.1292	0.0076	21,585,000	0.01	0.000023
61	0	0	62	0	1.5752	42.1882	0.0017	2,189	0.11	0.000023
62	61	0	63	0	1.5912	42.1751	0.0032	5,260	0.12	0.000023
63	62	0	64	0	1.6057	42.1350	0.0063	7,195,000	0.01	0.000023
64	60	63	65	0	1.6077	42.1262	0.0138	43,170,000	0.01	0.000023
65	64	0	66	0	1.5864	42.1023	0.5625	5,376	0.25	0.000023
66	65	0	67	0	1.5678	42.0575	0.7356	7,545	0.45	0.000023
67	66	0	68	0	1.5759	42.0013	0.7356	22,740,000	0.45	0.000023
68	67	0	74	0	1.6058	41.9643	0.7850	5,934	0.45	0.000023
69	0	0	70	0	1.5024	42.0232	0.0016	5,982	0.11	0.000023
70	69	0	73	0	1.5330	41.9828	0.0231	11,811	0.20	0.000023
71	0	0	72	0	1.5534	41.9262	0.0039	1,569	0.13	0.000023
72	71	0	73	0	1.5691	41.9310	0.0041	1,952	0.13	0.000023
73	70	72	74	0	1.5855	41.9404	0.0271	6,083	0.20	0.000023
74	68	73	75	0	1.6358	41.9313	0.8121	904	0.46	0.000023
75	74	0	77	0	1.6435	41.9337	0.8121	2,837	0.46	0.000023
76	0	0	77	0	1.7539	42.1105	0.0764	34,659	0.26	0.000023
77	75	76	79	0	1.6657	41.9285	0.8585	6,740	0.46	0.000023
78	0	0	0	0	1.7015	41.9161	0.0000	0	0.20	0.000023
79	77	0	81	0	1.7140	41.9104	0.8423	2,462	0.30	0.000023
80	0	0	81	0	1.7722	42.0496	0.0275	24,289	0.21	0.000023
81	79	80	83	0	1.7183	41.8452	0.8698	11,967	0.47	0.000023
82	0	0	83	0	1.5741	41.8762	0.0090	19,825	0.20	0.000023
83	81	82	84	0	1.7567	41.8244	0.8945	7,729	0.47	0.000023
84	83	0	85	0	1.7617	41.8096	0.9100	2,262	0.47	0.000023
85	84	0	86	0	1.7728	41.7969	0.9100	1,915	0.47	0.000023
86	85	0	89	0	1.7728	41.7969	0.9100	3,292	0.47	0.000023
87	0	0	88	0	1.8109	41.8310	0.0101	3,932	0.16	0.000023
88	87	0	89	0	1.8052	41.8011	0.0111	5,054	0.17	0.000023
89	86	88	91	0	1.7849	41.7777	0.9211	3,853	0.47	0.000023
90	0	0	91	0	1.6407	41.7647	0.0510	17,452	0.24	0.000023
91	89	90	93	0	1.8007	41.7533	0.9721	7,803	0.30	0.000023
92	0	0	93	0	1.5911	41.7533	0.1273	35,623	0.30	0.000023

93	91	92	94	0	1.8385	41.7095	1.0993	974	0.49	0.000023
94	93	0	95	0	1.8446	41.7048	1.4298	708	0.40	0.000023
95	94	0	98	0	1.8465	41.6990	1.4298	2,142	0.35	0.000023
96	0	0	97	0	1.7389	41.6469	0.0516	10,383	0.24	0.000023
97	96	0	98	0	1.7934	41.6962	0.0571	6,731	0.24	0.000023
98	95	97	99	0	1.8387	41.6832	1.4869	1,765	0.53	0.000023
99	58	98	100	0	1.8543	41.6804	3.9900	4,007	0.67	0.000023
100	99	0	101	0	1.8599	41.6514	3.9900	6,819	0.67	0.000023
101	100	0	102	0	1.8628	41.6242	4.0163	2,431	0.67	0.000023
102	101	0	103	0	1.8462	41.6141	4.0163	2,122	0.67	0.000023
103	102	0	104	0	1.8528	41.5996	4.0445	6,323	0.67	0.000023
104	103	0	108	0	1.8822	41.5638	4.0445	7,328	0.67	0.000023
105	0	0	107	0	1.7535	41.5897	0.0077	16,647	0.15	0.000023
106	0	0	107	0	1.7928	41.5322	0.0086	11,402	0.16	0.000023
107	105	106	108	0	1.8723	41.5255	0.0164	4,214	0.16	0.000023
108	104	107	110	0	1.9124	41.5306	4.0608	3,406	0.67	0.000023
109	0	0	0	0	1.9124	41.5306	0.0000	0	0.54	0.000023
110	108	0	115	0	1.9158	41.5058	2.6293	2,267	0.60	0.000023
111	0	0	114	0	1.9238	41.5869	0.0114	9,745	0.17	0.000023
112	0	0	113	0	1.9765	41.6081	0.0067	9,693	0.15	0.000023
113	112	0	114	0	1.9634	41.5477	0.0193	3,950	0.18	0.000023
114	111	113	115	0	1.9397	41.5293	0.0334	4,930	0.21	0.000023
115	110	114	144	0	1.9235	41.4967	2.6626	2,646	0.40	0.000023
116	0	0	118	0	1.5009	41.6966	0.0031	9,749	0.12	0.000023
117	0	0	118	0	1.5268	41.7182	0.0038	14,166	0.13	0.000023
118	116	117	120	0	1.5196	41.6347	0.0069	2,998	0.15	0.000023
119	0	0	120	0	1.4139	41.5946	0.0031	14,209	0.12	0.000023
120	118	119	121	0	1.5293	41.6146	0.0100	3,234	0.16	0.000023
121	120	0	124	0	1.5473	41.5981	0.0100	4,328	0.16	0.000023
122	0	0	123	0	1.4801	41.5580	0.0010	6,764	0.09	0.000023
123	122	0	124	0	1.5340	41.5646	0.0023	5,420	0.11	0.000023
124	121	123	125	0	1.6066	41.5820	0.0123	9,027	0.17	0.000023
125	124	0	126	0	1.6524	41.5677	0.2101	910	0.33	0.000023
126	125	0	129	0	1.6618	41.5649	0.2101	3,225	0.20	0.000023
127	0	0	128	0	1.4836	41.4675	0.0030	19,870	0.12	0.000023
128	127	0	129	0	1.6321	41.5337	0.0065	6,232	0.15	0.000023
129	126	128	130	0	1.6785	41.5515	0.2166	4,580	0.33	0.000023
130	129	0	131	0	1.6943	41.5267	0.2685	7,623	0.35	0.000023
131	130	0	135	0	1.7237	41.4953	0.2923	10,996	0.30	0.000023
132	0	0	133	0	1.5347	41.4773	0.0079	11,590	0.15	0.000023
133	132	0	134	0	1.6195	41.4761	0.0100	17,601	0.16	0.000023
134	133	0	135	0	1.7513	41.4419	0.0257	4,068	0.20	0.000023
135	131	134	139	0	1.7858	41.4446	0.3180	5,291	0.37	0.000023
136	0	0	138	0	1.6873	41.4054	0.0075	6,928	0.15	0.000023
137	0	0	138	0	1.7711	41.3828	0.0098	2,909	0.16	0.000023
138	136	137	139	0	1.7490	41.3967	0.0173	10,276	0.18	0.000023
139	135	138	140	0	1.8175	41.4265	0.3552	4,802	0.30	0.000023
140	139	0	143	0	1.8552	41.4427	0.3673	2,770	0.38	0.000023

141	0	0	142	0	1.8163	41.4872	0.0147	2,804	0.18	0.000023
142	141	0	143	0	1.8349	41.4735	0.0181	5,442	0.19	0.000023
143	140	142	144	0	1.8658	41.4513	0.3854	8,000	0.38	0.000023
144	115	143	145	0	1.9351	41.4797	3.1444	4,041	0.63	0.000023
145	144	0	147	0	1.9657	41.4743	3.1444	4,121	0.50	0.000023
146	0	0	147	0	1.9358	41.4260	0.0071	6,083	0.15	0.000023
147	145	146	152	0	1.9857	41.4450	3.1515	1,421	0.50	0.000023
148	0	0	149	0	1.9833	41.6520	0.0139	12,152	0.17	0.000023
149	148	0	150	0	2.0347	41.5667	0.0139	5,433	0.22	0.000023
150	149	0	151	0	2.0306	41.4844	0.5959	10,029	0.33	0.000023
151	150	0	152	0	2.0013	41.4616	0.8468	3,233	0.32	0.000023
152	147	151	154	0	1.9962	41.4374	3.9983	4,048	0.50	0.000023
153	0	0	154	0	2.0899	41.4298	0.0111	12,358	0.17	0.000023
154	152	153	156	0	2.0121	41.4174	4.0094	2,345	0.35	0.000023
155	0	0	0	0	2.0140	41.4083	0.0000	0	0.43	0.000023
156	154	0	157	0	2.0230	41.3908	3.3601	1,830	0.35	0.000023
157	156	0	159	0	2.0230	41.3908	3.9400	4,151	0.20	0.000023
158	0	0	0	0	2.0315	41.3778	0.0000	0	0.64	0.000023
159	157	0	160	0	2.0482	41.3496	0.6100	7,008	0.20	0.000023
160	159	0	0	0	2.1129	41.3272	0.6100	3,434	0.15	0.000023

Annex 3

A3.1. Capital costs ozonation

Table A 6. Capital costs of ozonation

Mulder 2015	Yearly maintenance (euros)	Yearly investment (4% IR)			
14,000 PE; 180 $m^3 \cdot h^{-1}$	22,000	140,000			
70,000 PE; 900 $m^3 \cdot h^{-1}$	10,000	590,000			
210,000 PE; 2700 $m^3 \cdot h^{-1}$	220,000	1,570,000			
Abegglen 2009 **35,000 PE; 430 $m^3 \cdot h^{-1}$**	Investment cost (CHF)	Investment cost (euros)	Yearly maintenance (euros)	Lifetime (years)	*Yearly investment (4% IR)*
Civil works	250,000	120,000	600	30	*-7,000*
Mechanical Equipment	310,000	200,000	6,000	15	*-19,000*
Electrical equipment	140,000	90,000	2,700	15	*-9,000*
Equipment for ozone generation	950,000	600,000	18,000	15	*-55,000*
Total	1,650,000	1,010,000	27,300		*-90,000*
Yearly capital cost					*-150,000*
Note: the costs in Abegglen do not include sand filter. We have added 0,08 euros/m3 to the costs to account for the sand filter as suggested in Mulder et al. (2015)					
Huzinker 2009					
ARA Untersee **11,000 PE; 130 $m^3 \cdot h^{-1}$**	Investment cost (CHF)	Investment cost (euros)	Yearly maintenance (euros)	Lifetime (years)	*Yearly investment (4% IR)*
Civil works	715,000	350,000	1,800	30	*-21,000*
Mechanical Equipment	975,000	610,000	18,000	15	*-55,000*
Electrical equipment	446,000	280,000	9,000	15	*-26,000*
Total	2,136,000	1,240,000	29,000		*-103,000*
Yearly capital cost					*-170,000*
ARA Aadorf **45,000 PE; 550 $m^3 \cdot h^{-1}$**					
Civil works	1,275,000	610,000	3,000	30	*-36,000*
Mechanical Equipment	1,607,500	1,010,000	31,000	15	*-91,000*
Electrical equipment	1,280,000	800,000	24,000	15	*-72,000*
Total		2,420,000	58,000		*-200,000*
Yearly capital cost					*-330,000*
ARA Furt **57,000 PE; 710 $m^3 \cdot h^{-1}$**					
Civil works	2,215,000	1,060,000	5,300	30	*-62,000*
Mechanical Equipment	2,185,000	1,370,000	41,100	15	*-124,000*
Electrical equipment	1,700,000	1,070,000	32,100	15	*-97,000*
Total		3,500,000	79,000		*-283,000*
Yearly capital cost					*-470,000*
ARA Au **120,000 PE; 1,400 $m^3 \cdot h^{-1}$**					
Civil works	2,446,000	1,170,000	6,000	30	*-68,000*
Mechanical Equipment	2,705,000	1,700,000	51,000	15	*-153,000*
Electrical equipment	1,931,000	1,210,000	36,000	15	*-110,000*

Total		4,080,000	93,000		*-331,000*
Yearly capital cost					*-550,000*
ARA Luzern					
500,000 PE; 6,000 $m^3 \cdot h^{-1}$					
Civil works	5,165,000	2,460,000	12,000	30	*-144,000*
Mechanical Equipment	5,960,000	3,730,000	112,000	15	*-340,000*
Electrical equipment	3,151,000	1,970,000	60,000	15	*-180,000*
Total		8,160,000	184,000		*-665,000*
Yearly capital cost					*-1,100,000*
Biebersdorf 2014					
74,000 PE; 930 $m^3 \cdot h^{-1}$					
Civil works	-	1,470,000	7,350	30	*-85,000*
Mechanical Equipment	-	1,150,000	34,500	15	*-104,000*
Electrical equipment	-	460,000	13,800	15	*-41,000*
Total		3,080,000	56,000		*-230,000*
Yearly capital cost					*-380,000*
Margot 2013					
30,000 PE; 360 $m^3 \cdot h^{-1}$; 4,5% IR	Investment cost (euros/m3)	Yearly investment (4,5% IR)	Yearly volume (m3)	Investment cost (euros/m3)	
total	0.133				
Civil works	0.038	*-47,885*	1,257,984	*-0.038*	
Mechanical Equipment	0.056	*-69,650*	1,257,984	*-0.056*	
Electrical equipment	0.039	*-49,667*	1,257,984	*-0.039*	
30,000 PE; 360 $m^3 \cdot h^{-1}$; 4% IR	Investment cost (euros)	Yearly maintenance (euros)	Lifetime (years)	*Yearly investment (4% IR)*	
Civil works	780,000	3,900	30	*-46,000*	
Mechanical Equipment	906,000	27,180	15	*-82,000*	
Electrical equipment	393,000	11,790	15	*-36,000*	
Total		43,000		*-164,000*	
Yearly capital cost				*-270,000*	

A3.2. Variable costs ozonation

Table A 7. Variable costs of ozonation

		WWTP size (PE)										
		11,000	**14,000**	**30,000**	**35,000**	**45,000**	**57,000**	**70,000**	**74,000**	**120,000**	**210,000**	**500,000**
Design capacity post treatment	$m^3 \cdot h^{-1}$	130	180	360	430	550	710	900	930	1,400	2,700	6,000
electricity	€·kWh^{-1}	0.135	0.135	0.135	0.135	0.135	0.101	0.101	0.101	0.101	0.101	0.084
pure oxygen	€·kg	0.15	0.15	0.15	0.15	0.15	0.15	0.08	0.08	0.08	0.08	0.08
ozone dosage	g O_3·g DOC^{-1}	0.7	0.7	0.7	0.7	0.7	0.7	0.7	0.7	0.7	0.7	0.7
DOC effluent	mg·L^{-1}	11	11	11	11	11	11	11	11	11	11	11
ozone dosage	mg O_3·L^{-1}	7.7	7.7	7.7	7.7	7.7	7.7	7	7.7	7.7	7.7	7.7
Electrical consumption ozone generation	kWh·kg^{-1}	10	10	10	10	10	10	10	10	10	10	10
Electrical consumption other equipment	W·m^{-3}	45	45	45	45	45	45	45	45	45	45	45
calculations												
ozone used per hour	kg O_3·h^{-1}	1.001	1.386	2.772	3.31	4.235	5.467	6.3	7.161	10.78	20.79	46.2
cost oxygen per year	€·year^{-1}	8,768.76	12,141.36	24,282.72	29,004.36	37,098.6	47,890.92	29,433.6	33,456.192	50,364.16	97,130.88	215846.4
cost electricity ozone per year	€·year^{-1}	7,908.99	10,950.92	21,901.83	26,160.52	33,461.13	32,183.43	37,087.18	42,155.76	63,460.29	122,387.70	226,274.61
cost electricity other equipment per year	€·year^{-1}	4,622.14	6,399.89	12,799.77	15,288.62	19,555.21	18,808.50	23,841.76	24,636.49	37,087.18	71,525.28	132,238.41
yearly variable cost (oxygen + electricity)	€·year^{-1}	21,299.89	29,492.16	58,984.32	70,453.50	90,114.94	98,882.85	90,362.54	100,248.44	150,911.63	291,043.86	574,359.42
Dutch yearly total variable cost (Mulder et al., 2015)	€·year^{-1}	373,000	24,000	373,000	373,000	373,000	373,000	126,000	373,000	373,000	373,000	373,000
Dutch yearly other variable cost (Mulder et al., 2015) (e.g. backwash water pumps)	€·year^{-1}	187,000	14,000	187,000	187,000	187,000	187,000	64,000	187,000	187,000	187,000	187,000
yearly other variable cost (e.g. backwash water pumps)	€·year^{-1}	10,678.50	17,203.76	29,571.23	35,321.19	45,178.27	49,573.98	45,898.43	50,258.60	75,658.11	145,912.07	287,949.63
total yearly variable cost	€·year^{-1}	31,978.39	46,695.92	88,555.55	105,774.69	135,293.21	148,456.83	136,260.98	150,507.04	226,569.74	436,955.93	862,309.06

A3.3 Sets of WWTPs requiring upgrade for each scenario

The optimal sets of WWTPs requiring upgrade for each scenario of EQS, uncertainty and hydrological condition are highlighted in yellow in figures below. As described in the manuscript, there is always a set of 3 WWTPs (Rubí, Terrassa and Sant Feliu) that is included in every optimal solution regardless of the EQS, uncertainty and hydrological scenario

Average flows																		
10ng/l																		
highest conc. calibrated unc	Berga	Sallent	Moià	St Fruitos	Solsona	Suria	Manresa	Monistrol	Abrera	Igualada	Capellades	Piera	St Sarduni	Masquefa	Martorell	Terrassa	Rubí	St Feliu
highest conc. reduced unc	Berga	Sallent	Moià	St Fruitos	Solsona	Suria	Manresa	Monistrol	Abrera	Igualada	Capellades	Piera	St Sarduni	Masquefa	Martorell	Terrassa	Rubí	St Feliu
median	Berga	Sallent	Moià	St Fruitos	Solsona	Suria	Manresa	Monistrol	Abrera	Igualada	Capellades	Piera	St Sarduni	Masquefa	Martorell	Terrassa	Rubí	St Feliu
lowest conc. reduced unc	Berga	Sallent	Moià	St Fruitos	Solsona	Suria	Manresa	Monistrol	Abrera	Igualada	Capellades	Piera	St Sarduni	Masquefa	Martorell	Terrassa	Rubí	St Feliu
lowest conc. calibrated unc	Berga	Sallent	Moià	St Fruitos	Solsona	Suria	Manresa	Monistrol	Abrera	Igualada	Capellades	Piera	St Sarduni	Masquefa	Martorell	Terrassa	Rubí	St Feliu
30 ng/l																		
highest conc. calibrated unc	Berga	Sallent	Moià	St Fruitos	Solsona	Suria	Manresa	Monistrol	Abrera	Igualada	Capellades	Piera	St Sarduni	Masquefa	Martorell	Terrassa	Rubí	St Feliu
highest conc. reduced unc	Berga	Sallent	Moià	St Fruitos	Solsona	Suria	Manresa	Monistrol	Abrera	Igualada	Capellades	Piera	St Sarduni	Masquefa	Martorell	Terrassa	Rubí	St Feliu
median	Berga	Sallent	Moià	St Fruitos	Solsona	Suria	Manresa	Monistrol	Abrera	Igualada	Capellades	Piera	St Sarduni	Masquefa	Martorell	Terrassa	Rubí	St Feliu
lowest conc. reduced unc	Berga	Sallent	Moià	St Fruitos	Solsona	Suria	Manresa	Monistrol	Abrera	Igualada	Capellades	Piera	St Sarduni	Masquefa	Martorell	Terrassa	Rubí	St Feliu
lowest conc. calibrated unc	Berga	Sallent	Moià	St Fruitos	Solsona	Suria	Manresa	Monistrol	Abrera	Igualada	Capellades	Piera	St Sarduni	Masquefa	Martorell	Terrassa	Rubí	St Feliu
50ng/l																		
highest conc. calibrated unc	Berga	Sallent	Moià	St Fruitos	Solsona	Suria	Manresa	Monistrol	Abrera	Igualada	Capellades	Piera	St Sarduni	Masquefa	Martorell	Terrassa	Rubí	St Feliu
highest conc. reduced unc	Berga	Sallent	Moià	St Fruitos	Solsona	Suria	Manresa	Monistrol	Abrera	Igualada	Capellades	Piera	St Sarduni	Masquefa	Martorell	Terrassa	Rubí	St Feliu
median	Berga	Sallent	Moià	St Fruitos	Solsona	Suria	Manresa	Monistrol	Abrera	Igualada	Capellades	Piera	St Sarduni	Masquefa	Martorell	Terrassa	Rubí	St Feliu
lowest conc. reduced unc	Berga	Sallent	Moià	St Fruitos	Solsona	Suria	Manresa	Monistrol	Abrera	Igualada	Capellades	Piera	St Sarduni	Masquefa	Martorell	Terrassa	Rubí	St Feliu
lowest conc. calibrated unc	Berga	Sallent	Moià	St Fruitos	Solsona	Suria	Manresa	Monistrol	Abrera	Igualada	Capellades	Piera	St Sarduni	Masquefa	Martorell	Terrassa	Rubí	St Feliu
100ng/l																		
highest conc. calibrated unc	Berga	Sallent	Moià	St Fruitos	Solsona	Suria	Manresa	Monistrol	Abrera	Igualada	Capellades	Piera	St Sarduni	Masquefa	Martorell	Terrassa	Rubí	St Feliu
highest conc. reduced unc	Berga	Sallent	Moià	St Fruitos	Solsona	Suria	Manresa	Monistrol	Abrera	Igualada	Capellades	Piera	St Sarduni	Masquefa	Martorell	Terrassa	Rubí	St Feliu
median	Berga	Sallent	Moià	St Fruitos	Solsona	Suria	Manresa	Monistrol	Abrera	Igualada	Capellades	Piera	St Sarduni	Masquefa	Martorell	Terrassa	Rubí	St Feliu
lowest conc. reduced unc	Berga	Sallent	Moià	St Fruitos	Solsona	Suria	Manresa	Monistrol	Abrera	Igualada	Capellades	Piera	St Sarduni	Masquefa	Martorell	Terrassa	Rubí	St Feliu
lowest conc. calibrated unc	Berga	Sallent	Moià	St Fruitos	Solsona	Suria	Manresa	Monistrol	Abrera	Igualada	Capellades	Piera	St Sarduni	Masquefa	Martorell	Terrassa	Rubí	St Feliu

Figure A 6. Optimal set of WWTPs requiring an upgrade for each scenario of EQS and uncertainty in diclofenac concentrations during average flows.

Environmental flows																		
10ng/l																		
highest conc. calibrated unc	Berga	Sallent	Moià	St Fruitos	Solsona	Suria	Manresa	Monistrol	Abrera	Igualada	Capellades	Piera	St Sarduni	Masquefa	Martorell	Terrassa	Rubí	St Feliu
highest conc. reduced unc	Berga	Sallent	Moià	St Fruitos	Solsona	Suria	Manresa	Monistrol	Abrera	Igualada	Capellades	Piera	St Sarduni	Masquefa	Martorell	Terrassa	Rubí	St Feliu
median	Berga	Sallent	Moià	St Fruitos	Solsona	Suria	Manresa	Monistrol	Abrera	Igualada	Capellades	Piera	St Sarduni	Masquefa	Martorell	Terrassa	Rubí	St Feliu
lowest conc. reduced unc	Berga	Sallent	Moià	St Fruitos	Solsona	Suria	Manresa	Monistrol	Abrera	Igualada	Capellades	Piera	St Sarduni	Masquefa	Martorell	Terrassa	Rubí	St Feliu
lowest conc. calibrated unc	Berga	Sallent	Moià	St Fruitos	Solsona	Suria	Manresa	Monistrol	Abrera	Igualada	Capellades	Piera	St Sarduni	Masquefa	Martorell	Terrassa	Rubí	St Feliu
30 ng/l																		
highest conc. calibrated unc	Berga	Sallent	Moià	St Fruitos	Solsona	Suria	Manresa	Monistrol	Abrera	Igualada	Capellades	Piera	St Sarduni	Masquefa	Martorell	Terrassa	Rubí	St Feliu
highest conc. reduced unc	Berga	Sallent	Moià	St Fruitos	Solsona	Suria	Manresa	Monistrol	Abrera	Igualada	Capellades	Piera	St Sarduni	Masquefa	Martorell	Terrassa	Rubí	St Feliu
median	Berga	Sallent	Moià	St Fruitos	Solsona	Suria	Manresa	Monistrol	Abrera	Igualada	Capellades	Piera	St Sarduni	Masquefa	Martorell	Terrassa	Rubí	St Feliu
lowest conc. reduced unc	Berga	Sallent	Moià	St Fruitos	Solsona	Suria	Manresa	Monistrol	Abrera	Igualada	Capellades	Piera	St Sarduni	Masquefa	Martorell	Terrassa	Rubí	St Feliu
lowest conc. calibrated unc	Berga	Sallent	Moià	St Fruitos	Solsona	Suria	Manresa	Monistrol	Abrera	Igualada	Capellades	Piera	St Sarduni	Masquefa	Martorell	Terrassa	Rubí	St Feliu
50ng/l																		
highest conc. calibrated unc	Berga	Sallent	Moià	St Fruitos	Solsona	Suria	Manresa	Monistrol	Abrera	Igualada	Capellades	Piera	St Sarduni	Masquefa	Martorell	Terrassa	Rubí	St Feliu
highest conc. reduced unc	Berga	Sallent	Moià	St Fruitos	Solsona	Suria	Manresa	Monistrol	Abrera	Igualada	Capellades	Piera	St Sarduni	Masquefa	Martorell	Terrassa	Rubí	St Feliu
median	Berga	Sallent	Moià	St Fruitos	Solsona	Suria	Manresa	Monistrol	Abrera	Igualada	Capellades	Piera	St Sarduni	Masquefa	Martorell	Terrassa	Rubí	St Feliu
lowest conc. reduced unc	Berga	Sallent	Moià	St Fruitos	Solsona	Suria	Manresa	Monistrol	Abrera	Igualada	Capellades	Piera	St Sarduni	Masquefa	Martorell	Terrassa	Rubí	St Feliu
lowest conc. calibrated unc	Berga	Sallent	Moià	St Fruitos	Solsona	Suria	Manresa	Monistrol	Abrera	Igualada	Capellades	Piera	St Sarduni	Masquefa	Martorell	Terrassa	Rubí	St Feliu
100ng/l																		
highest conc. calibrated unc	Berga	Sallent	Moià	St Fruitos	Solsona	Suria	Manresa	Monistrol	Abrera	Igualada	Capellades	Piera	St Sarduni	Masquefa	Martorell	Terrassa	Rubí	St Feliu
highest conc. reduced unc	Berga	Sallent	Moià	St Fruitos	Solsona	Suria	Manresa	Monistrol	Abrera	Igualada	Capellades	Piera	St Sarduni	Masquefa	Martorell	Terrassa	Rubí	St Feliu
median	Berga	Sallent	Moià	St Fruitos	Solsona	Suria	Manresa	Monistrol	Abrera	Igualada	Capellades	Piera	St Sarduni	Masquefa	Martorell	Terrassa	Rubí	St Feliu
lowest conc. reduced unc	Berga	Sallent	Moià	St Fruitos	Solsona	Suria	Manresa	Monistrol	Abrera	Igualada	Capellades	Piera	St Sarduni	Masquefa	Martorell	Terrassa	Rubí	St Feliu
lowest conc. calibrated unc	Berga	Sallent	Moià	St Fruitos	Solsona	Suria	Manresa	Monistrol	Abrera	Igualada	Capellades	Piera	St Sarduni	Masquefa	Martorell	Terrassa	Rubí	St Feliu

Figure A 7. Optimal set of WWTPs requiring an upgrade for each scenario of EQS and uncertainty in diclofenac concentrations during environmental flows.

Annex 4

A4.1 Estimation of the prior probability distribution function of F of naproxen

Table A 8. Variability of F values of naproxen. Influent concentrations of naproxen were obtained from Gros et al., 2007, Gros et al., 2010 and Jelic et al., 2011. The number of inhabitants connected to each WWTP was provided by Statistical Institute of Catalonia, 2016. Influent flows were provided by WWTP operators. Loads of diclofenac were calculated based on the influent concentration, inhabitants and influent flows. Naproxen consumption was obtained from IQVIA (2018)

WWTP	**Month**	**Year**	**Inhab**	**Influent flow ($m^3 \cdot d^{-1}$)**	**Influent concentration ($ng \cdot L^{-1}$)**	**Influent load ($mg \cdot year^{-1} \cdot inh^{-1}$)**	**Naproxen consumption ($mg \cdot year^{-1} inh^{-1}$)**	**F**
LLE	July	2008	137,631	61,604	1,701.46	277.98	1,420.70	0.20
LLE	June	2006	131,039	61,705	1,400.00	240.62	1,326.62	0.18
LLE	November	2006	131,039	45,372	3,900.00	492.88	1,326.62	0.37
LLE	October	2007	132,962	60,163	1,180.28	194.93	1,405.80	0.14
TAR	March	2008	139,074	23,807	4,950.98	309.34	1,420.70	0.22
TAR	March	2009	141,654	25,958	7,503.18	501.85	1,298.89	0.39
TAR	December	2007	135,471	25,818	3,720.00	258.77	1,405.80	0.18
TAR	November	2008	139,074	28,399	4,616.27	344.07	1,420.70	0.24
TAR	July	2007	135,471	21,472	4,580.00	264.96	1,405.80	0.19
TAR	June	2008	139,074	27,837	6,881.86	502.78	1,420.70	0.35
TAR	June	2008	139,074	27,837	4,653.92	340.01	1,420.70	0.24
TAR	June	2008	139,074	27,837	10,149.51	741.50	1,420.70	0.52
TAR	November	2007	135,471	24,825	4,230.00	282.92	1,405.80	0.20
TAR	September	2008	139,074	25,040	6,793.70	446.47	1,420.70	0.31
TOR	June	2006	41,710	6,336	2,310.00	128.08	1,326.62	0.10
TOR	November	2006	41,710	8,104	1,740.00	123.40	1,326.62	0.09
TOR	October	2007	42,521	8,389	892.96	64.30	1,405.80	0.05
VIC	March	2008	48,855	18,015	4,881.67	657.03	1,420.70	0.46
VIC	December	2007	47,998	16,932	1,850.00	238.20	1,405.80	0.17
VIC	July	2007	47,998	16,574	3,440.00	433.57	1,405.80	0.31
VIC	November	2007	47,998	19,352	2,320.00	341.42	1,405.80	0.24
VIL	March	2008	45,793	18,194	8,862.25	1,285.19	1,420.70	0.90
VIL	March	2009	47,515	21,689	3,193.73	532.11	1,298.89	0.41
VIL	December	2007	42,076	19,605	2,870.00	488.10	1,405.80	0.35
							median	**0.24**
							percentil 2.5th	**0.07**
							percentil 97.5th	**0.68**

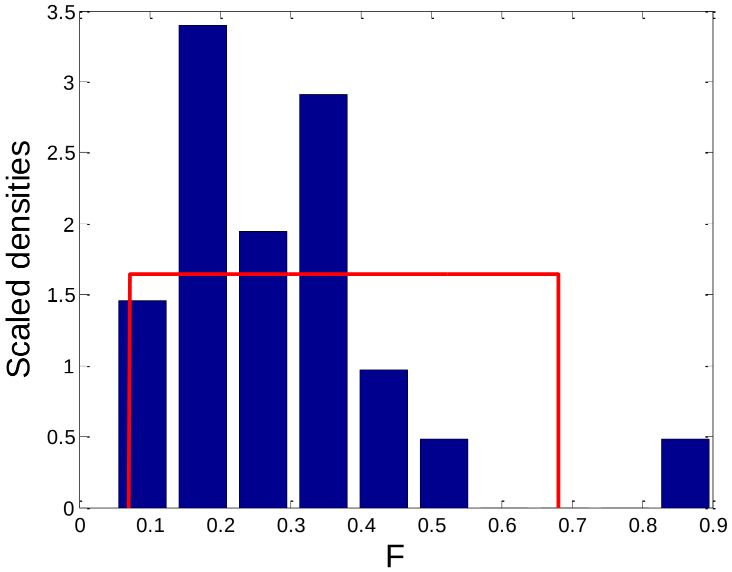

Figure A 8. Histogram plot of F values of naproxen (blue bars). A uniform distribution (red curve) with a mean of 0.38 fitted the F values

Goodness of fit was assessed comparing the cumulative distribution of the F values of naproxen and the cumulative uniform distribution fitted to the F values (Figure A 9)

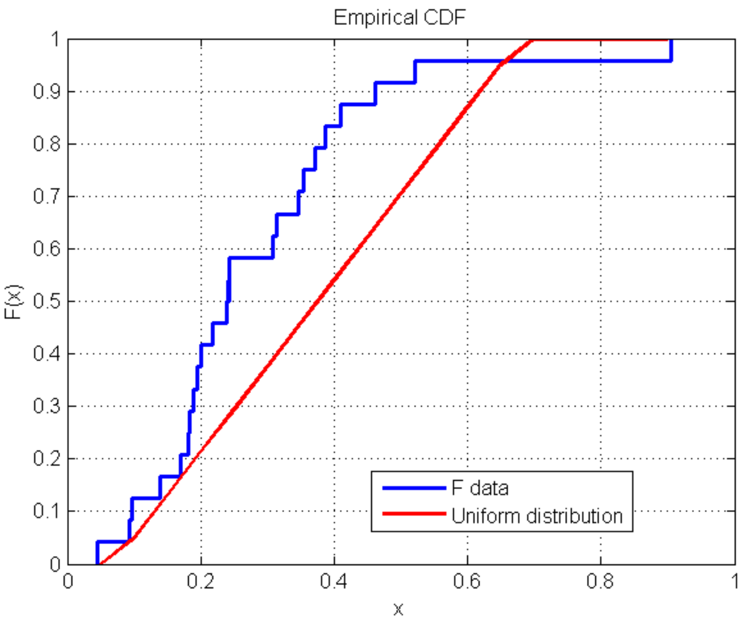

Figure A 9. Cumulative distribution of the F values of naproxen (blue curve) and cumulative uniform distribution fitted to the F values (red curve)

A4.2 Estimation of the prior probability distribution function of k_{WWTP} of naproxen

Table A 9.Naproxen influent and effluent concentrations obtained from Gros et al., 2007, Gros et al., 2010 and Jelic et al., 2011. HRT and MLSS were provided by WWTP operators. k_{WWTP} was calculated using equation (4) of the main text.

WWTP	Month	Year	HRT (d)	MLSS ($mg·L^{-1}$)	Influent concentration ($ng·L^{-1}$)	Effluent concentration ($ng·L^{-1}$)	k_{wwtp} ($L·g^{-1}·d^{-1}$)
LLE	July	2008	0.15	1,516	1,701.46	388.81	14.85
LLE	June	2006	0.15	1,776	1,400.00	640.00	4.46
LLE	November	2006	0.20	1,747	3,900.00	545.00	17.62
LLE	October	2007	0.16	2,079	1,180.28	513.76	3.90
TAR	March	2008	0.38	2,955	4,950.98	2,624.02	0.80
TAR	March	2009	0.34	1,838	7,503.18	813.05	13.17
TAR	December	2007	0.34	2,746	3,720.00	2,390.00	0.60
TAR	November	2008	0.31	2,609	4,616.27	876.64	5.21
TAR	July	2007	0.41	2,582	4,580.00	610.00	6.15
TAR	June	2008	0.32	2,456	6,881.86	675.81	11.68
TAR	June	2008	0.32	2,456	4,653.92	1,044.66	4.40
TAR	June	2008	0.32	2,456	10,149.51	1,141.20	10.04
TAR	November	2007	0.35	2,419	4,230.00	1,110.00	3.32
TAR	September	2008	0.36	2,564	6,793.70	1,470.59	3.97
TOR	June	2006	1.58	2,733	2,310.00	82.50	6.25
TOR	November	2006	1.23	3,266	1,740.00	73.00	5.68
TOR	October	2007	0.59	2,970	892.96	99.54	4.55
VIC	March	2008	1.49	4,059	4,881.67	306.96	2.46
VIC	December	2007	1.53	4,323	1,850.00	106.88	2.47
VIC	July	2007	1.58	4,920	3,440.00	92.66	4.65
VIC	November	2007	1.36	4,909	2,320.00	95.41	3.49
VIL	March	2008	0.34	2,335	8,862.25	1,445.69	6.46
VIL	March	2009	0.29	1,561	3,193.73	218.93	30.12
VIL	December	2007	0.32	1,575	2,870.00	261.01	19.84
						median	**4.93**
						percentil 2.5th	**0.71**
						percentil 97.5th	**24.21**

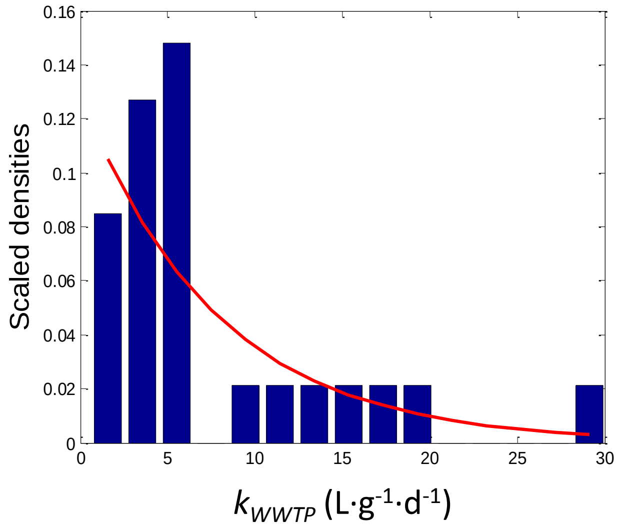

Figure A 10. Histogram plot of k_{WWTP} values of naproxen (blue bars). We fitted an exponential distribution (red curve) with a mean of 7.76 L·g^{-1}·d^{-1} to the k_{WWTP} values using maximum likelihood (command fitdist of Matlab)

Goodness of fit was assessed comparing the cumulative distribution of the k_{WWTP} values of naproxen and the cumulative exponential distribution fitted to the k_{WWTP} values (Figure A 11)

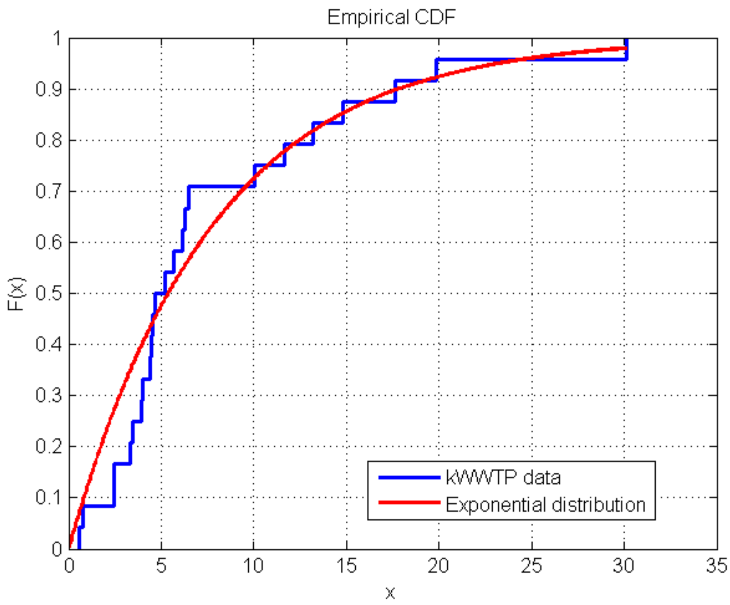

Figure A 11. Cumulative distribution of the k_{WWTP} values of naproxen (blue curve) and cumulative exponential distribution fitted to the k_{WWTP} values (red curve)

A4.3 Estimation of the prior probability distribution function of k_{river} of naproxen

Table A 10. k_{river} values of naproxen reviewed from 10 publications in the framework of the project SCARCE (Boithias et al., 2013).

k_{river}	
7.91E-05	
7.02E-06	
2.57E-04	
7.76E-05	
1.85E-06	
8.02E-05	
1.85E-06	
8.80E-04	
3.13E-06	
1.36E-04	
2.73E-04	
1.71E-04	
1.17E-04	
2.18E-06	
7.96E-05	**median**
1.85E-06	**percentil 2.5th**
6.83E-04	**percentil 97.5th**

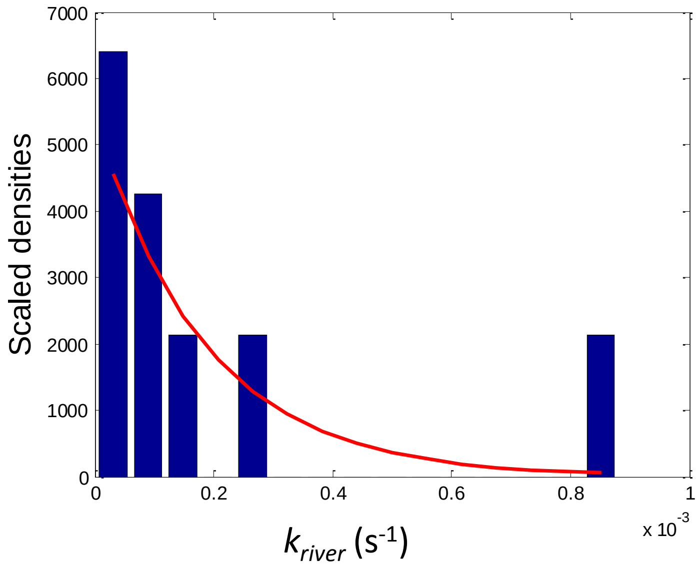

Figure A 12. Histogram plot of k_{river} values of naproxen (blue bars). We fitted an exponential distribution (red curve) with a mean of 1.9E-04 s^{-1} to the k_{river} values using maximum likelihood (command fitdist of Matlab)

Goodness of fit was assessed comparing the cumulative distribution of the k_{river} values of naproxen and the cumulative exponential distribution fitted to the k_{river} values (Figure A 13)

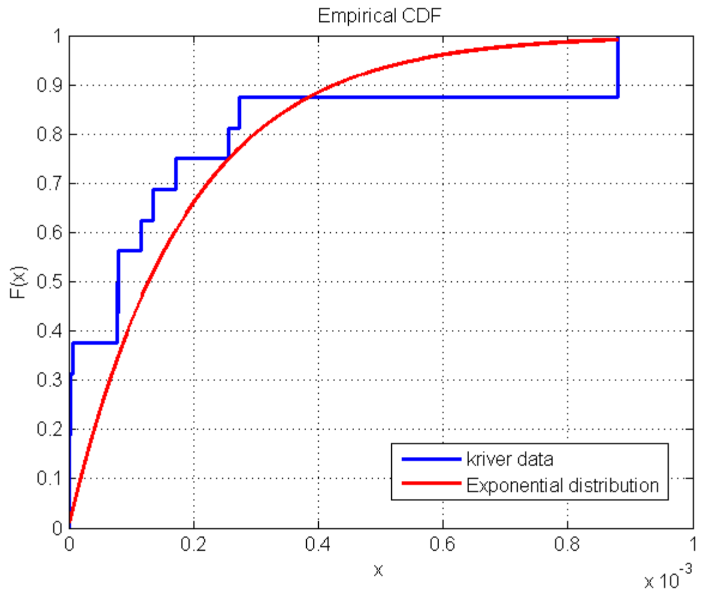

Figure A 13. Cumulative distribution of the k_{river} values of naproxen (blue curve) and cumulative exponential distribution fitted to the k_{river} values (red curve)

A4.4 Sets of WWTPs requiring upgrade for each scenario

The optimal sets of WWTPs requiring upgrade for each scenario of EQS, uncertainty and hydrological condition are highlighted in yellow in figures below

Average flows																		
EQS 100																		
Scenario S1																		
highest conc	Berga	Sallent	Moià	St Fruitos	Solsona	Súria	Manresa	Monistrol	Abrera	Igualada	Capellades	Piera	St Sarduní	Masquefa	Martorell	Terrassa	Rubí	St Feliu
median conc	Berga	Sallent	Moià	St Fruitos	Solsona	Súria	Manresa	Monistrol	Abrera	Igualada	Capellades	Piera	St Sarduní	Masquefa	Martorell	Terrassa	Rubí	St Feliu
lowest conc	Berga	Sallent	Moià	St Fruitos	Solsona	Súria	Manresa	Monistrol	Abrera	Igualada	Capellades	Piera	St Sarduní	Masquefa	Martorell	Terrassa	Rubí	St Feliu
Scenario S2																		
highest conc	Berga	Sallent	Moià	St Fruitos	Solsona	Súria	Manresa	Monistrol	Abrera	Igualada	Capellades	Piera	St Sarduní	Masquefa	Martorell	Terrassa	Rubí	St Feliu
median conc	Berga	Sallent	Moià	St Fruitos	Solsona	Súria	Manresa	Monistrol	Abrera	Igualada	Capellades	Piera	St Sarduní	Masquefa	Martorell	Terrassa	Rubí	St Feliu
lowest conc	Berga	Sallent	Moià	St Fruitos	Solsona	Súria	Manresa	Monistrol	Abrera	Igualada	Capellades	Piera	St Sarduní	Masquefa	Martorell	Terrassa	Rubí	St Feliu
Scenario S3																		
highest conc	Berga	Sallent	Moià	St Fruitos	Solsona	Súria	Manresa	Monistrol	Abrera	Igualada	Capellades	Piera	St Sarduní	Masquefa	Martorell	Terrassa	Rubí	St Feliu
median conc	Berga	Sallent	Moià	St Fruitos	Solsona	Súria	Manresa	Monistrol	Abrera	Igualada	Capellades	Piera	St Sarduní	Masquefa	Martorell	Terrassa	Rubí	St Feliu
lowest conc	Berga	Sallent	Moià	St Fruitos	Solsona	Súria	Manresa	Monistrol	Abrera	Igualada	Capellades	Piera	St Sarduní	Masquefa	Martorell	Terrassa	Rubí	St Feliu
Scenario S4																		
highest conc	Berga	Sallent	Moià	St Fruitos	Solsona	Súria	Manresa	Monistrol	Abrera	Igualada	Capellades	Piera	St Sarduní	Masquefa	Martorell	Terrassa	Rubí	St Feliu
median conc	Berga	Sallent	Moià	St Fruitos	Solsona	Súria	Manresa	Monistrol	Abrera	Igualada	Capellades	Piera	St Sarduní	Masquefa	Martorell	Terrassa	Rubí	St Feliu
lowest conc	Berga	Sallent	Moià	St Fruitos	Solsona	Súria	Manresa	Monistrol	Abrera	Igualada	Capellades	Piera	St Sarduní	Masquefa	Martorell	Terrassa	Rubí	St Feliu
EQS 10																		
Scenario S1																		
highest conc	Berga	Sallent	Moià	St Fruitos	Solsona	Súria	Manresa	Monistrol	Abrera	Igualada	Capellades	Piera	St Sarduní	Masquefa	Martorell	Terrassa	Rubí	St Feliu
median conc	Berga	Sallent	Moià	St Fruitos	Solsona	Súria	Manresa	Monistrol	Abrera	Igualada	Capellades	Piera	St Sarduní	Masquefa	Martorell	Terrassa	Rubí	St Feliu
lowest conc	Berga	Sallent	Moià	St Fruitos	Solsona	Súria	Manresa	Monistrol	Abrera	Igualada	Capellades	Piera	St Sarduní	Masquefa	Martorell	Terrassa	Rubí	St Feliu
Scenario S2																		
highest conc	Berga	Sallent	Moià	St Fruitos	Solsona	Súria	Manresa	Monistrol	Abrera	Igualada	Capellades	Piera	St Sarduní	Masquefa	Martorell	Terrassa	Rubí	St Feliu
median conc	Berga	Sallent	Moià	St Fruitos	Solsona	Súria	Manresa	Monistrol	Abrera	Igualada	Capellades	Piera	St Sarduní	Masquefa	Martorell	Terrassa	Rubí	St Feliu
lowest conc	Berga	Sallent	Moià	St Fruitos	Solsona	Súria	Manresa	Monistrol	Abrera	Igualada	Capellades	Piera	St Sarduní	Masquefa	Martorell	Terrassa	Rubí	St Feliu
Scenario S3																		
highest conc	Berga	Sallent	Moià	St Fruitos	Solsona	Súria	Manresa	Monistrol	Abrera	Igualada	Capellades	Piera	St Sarduní	Masquefa	Martorell	Terrassa	Rubí	St Feliu
median conc	Berga	Sallent	Moià	St Fruitos	Solsona	Súria	Manresa	Monistrol	Abrera	Igualada	Capellades	Piera	St Sarduní	Masquefa	Martorell	Terrassa	Rubí	St Feliu
lowest conc	Berga	Sallent	Moià	St Fruitos	Solsona	Súria	Manresa	Monistrol	Abrera	Igualada	Capellades	Piera	St Sarduní	Masquefa	Martorell	Terrassa	Rubí	St Feliu
Scenario S4																		
highest conc	Berga	Sallent	Moià	St Fruitos	Solsona	Súria	Manresa	Monistrol	Abrera	Igualada	Capellades	Piera	St Sarduní	Masquefa	Martorell	Terrassa	Rubí	St Feliu
median conc	Berga	Sallent	Moià	St Fruitos	Solsona	Súria	Manresa	Monistrol	Abrera	Igualada	Capellades	Piera	St Sarduní	Masquefa	Martorell	Terrassa	Rubí	St Feliu
lowest conc	Berga	Sallent	Moià	St Fruitos	Solsona	Súria	Manresa	Monistrol	Abrera	Igualada	Capellades	Piera	St Sarduní	Masquefa	Martorell	Terrassa	Rubí	St Feliu

Figure A 14. Optimal set of WWTP upgrades for each scenario of diclofenac consumption, 3 uncertainty levels, average flows and EQS 10 and 100

Average flows																		
EQS 640																		
Scenario S1																		
highest conc	Berga	Sallent	Moià	St Fruitos	Solsona	Súria	Manresa	Monistrol	Abrera	Igualada	Capellades	Piera	St Sarduní	Masquefa	Martorell	Terrassa	Rubí	St Feliu
median conc	Berga	Sallent	Moià	St Fruitos	Solsona	Súria	Manresa	Monistrol	Abrera	Igualada	Capellades	Piera	St Sarduní	Masquefa	Martorell	Terrassa	Rubí	St Feliu
lowest conc	Berga	Sallent	Moià	St Fruitos	Solsona	Súria	Manresa	Monistrol	Abrera	Igualada	Capellades	Piera	St Sarduní	Masquefa	Martorell	Terrassa	Rubí	St Feliu
Scenario S2																		
highest conc	Berga	Sallent	Moià	St Fruitos	Solsona	Súria	Manresa	Monistrol	Abrera	Igualada	Capellades	Piera	St Sarduní	Masquefa	Martorell	Terrassa	Rubí	St Feliu
median conc	Berga	Sallent	Moià	St Fruitos	Solsona	Súria	Manresa	Monistrol	Abrera	Igualada	Capellades	Piera	St Sarduní	Masquefa	Martorell	Terrassa	Rubí	St Feliu
lowest conc	Berga	Sallent	Moià	St Fruitos	Solsona	Súria	Manresa	Monistrol	Abrera	Igualada	Capellades	Piera	St Sarduní	Masquefa	Martorell	Terrassa	Rubí	St Feliu
Scenario S3																		
highest conc	Berga	Sallent	Moià	St Fruitos	Solsona	Súria	Manresa	Monistrol	Abrera	Igualada	Capellades	Piera	St Sarduní	Masquefa	Martorell	Terrassa	Rubí	St Feliu
median conc	Berga	Sallent	Moià	St Fruitos	Solsona	Súria	Manresa	Monistrol	Abrera	Igualada	Capellades	Piera	St Sarduní	Masquefa	Martorell	Terrassa	Rubí	St Feliu
lowest conc	Berga	Sallent	Moià	St Fruitos	Solsona	Súria	Manresa	Monistrol	Abrera	Igualada	Capellades	Piera	St Sarduní	Masquefa	Martorell	Terrassa	Rubí	St Feliu
Scenario S4																		
highest conc	Berga	Sallent	Moià	St Fruitos	Solsona	Súria	Manresa	Monistrol	Abrera	Igualada	Capellades	Piera	St Sarduní	Masquefa	Martorell	Terrassa	Rubí	St Feliu
median conc	Berga	Sallent	Moià	St Fruitos	Solsona	Súria	Manresa	Monistrol	Abrera	Igualada	Capellades	Piera	St Sarduní	Masquefa	Martorell	Terrassa	Rubí	St Feliu
lowest conc	Berga	Sallent	Moià	St Fruitos	Solsona	Súria	Manresa	Monistrol	Abrera	Igualada	Capellades	Piera	St Sarduní	Masquefa	Martorell	Terrassa	Rubí	St Feliu
EQS1700																		
Scenario S1																		
highest conc	Berga	Sallent	Moià	St Fruitos	Solsona	Súria	Manresa	Monistrol	Abrera	Igualada	Capellades	Piera	St Sarduní	Masquefa	Martorell	Terrassa	Rubí	St Feliu
median conc	Berga	Sallent	Moià	St Fruitos	Solsona	Súria	Manresa	Monistrol	Abrera	Igualada	Capellades	Piera	St Sarduní	Masquefa	Martorell	Terrassa	Rubí	St Feliu
lowest conc	Berga	Sallent	Moià	St Fruitos	Solsona	Súria	Manresa	Monistrol	Abrera	Igualada	Capellades	Piera	St Sarduní	Masquefa	Martorell	Terrassa	Rubí	St Feliu
Scenario S2																		
highest conc	Berga	Sallent	Moià	St Fruitos	Solsona	Súria	Manresa	Monistrol	Abrera	Igualada	Capellades	Piera	St Sarduní	Masquefa	Martorell	Terrassa	Rubí	St Feliu
median conc	Berga	Sallent	Moià	St Fruitos	Solsona	Súria	Manresa	Monistrol	Abrera	Igualada	Capellades	Piera	St Sarduní	Masquefa	Martorell	Terrassa	Rubí	St Feliu
lowest conc	Berga	Sallent	Moià	St Fruitos	Solsona	Súria	Manresa	Monistrol	Abrera	Igualada	Capellades	Piera	St Sarduní	Masquefa	Martorell	Terrassa	Rubí	St Feliu
Scenario S3																		
highest conc	Berga	Sallent	Moià	St Fruitos	Solsona	Súria	Manresa	Monistrol	Abrera	Igualada	Capellades	Piera	St Sarduní	Masquefa	Martorell	Terrassa	Rubí	St Feliu
median conc	Berga	Sallent	Moià	St Fruitos	Solsona	Súria	Manresa	Monistrol	Abrera	Igualada	Capellades	Piera	St Sarduní	Masquefa	Martorell	Terrassa	Rubí	St Feliu
lowest conc	Berga	Sallent	Moià	St Fruitos	Solsona	Súria	Manresa	Monistrol	Abrera	Igualada	Capellades	Piera	St Sarduní	Masquefa	Martorell	Terrassa	Rubí	St Feliu
Scenario S4																		
highest conc	Berga	Sallent	Moià	St Fruitos	Solsona	Súria	Manresa	Monistrol	Abrera	Igualada	Capellades	Piera	St Sarduní	Masquefa	Martorell	Terrassa	Rubí	St Feliu
median conc	Berga	Sallent	Moià	St Fruitos	Solsona	Súria	Manresa	Monistrol	Abrera	Igualada	Capellades	Piera	St Sarduní	Masquefa	Martorell	Terrassa	Rubí	St Feliu
lowest conc	Berga	Sallent	Moià	St Fruitos	Solsona	Súria	Manresa	Monistrol	Abrera	Igualada	Capellades	Piera	St Sarduní	Masquefa	Martorell	Terrassa	Rubí	St Feliu

Figure A 15. Optimal set of WWTP upgrades for each scenario of naproxen consumption, 3 uncertainty levels, average flows and EQS 640 and 1,700

Environmental flows																		
EQS 100																		
Scenario S1																		
highest conc	Berga	Sallent	Moià	St Fruitos	Solsona	Súria	Manresa	Monistrol	Abrera	Igualada	Capellades	Piera	St Sarduní	Masquefa	Martorell	Terrassa	Rubí	St Feliu
median conc	Berga	Sallent	Moià	St Fruitos	Solsona	Súria	Manresa	Monistrol	Abrera	Igualada	Capellades	Piera	St Sarduní	Masquefa	Martorell	Terrassa	Rubí	St Feliu
lowest conc	Berga	Sallent	Moià	St Fruitos	Solsona	Súria	Manresa	Monistrol	Abrera	Igualada	Capellades	Piera	St Sarduní	Masquefa	Martorell	Terrassa	Rubí	St Feliu
Scenario S2																		
highest conc	Berga	Sallent	Moià	St Fruitos	Solsona	Súria	Manresa	Monistrol	Abrera	Igualada	Capellades	Piera	St Sarduní	Masquefa	Martorell	Terrassa	Rubí	St Feliu
median conc	Berga	Sallent	Moià	St Fruitos	Solsona	Súria	Manresa	Monistrol	Abrera	Igualada	Capellades	Piera	St Sarduní	Masquefa	Martorell	Terrassa	Rubí	St Feliu
lowest conc	Berga	Sallent	Moià	St Fruitos	Solsona	Súria	Manresa	Monistrol	Abrera	Igualada	Capellades	Piera	St Sarduní	Masquefa	Martorell	Terrassa	Rubí	St Feliu
Scenario S3																		
highest conc	Berga	Sallent	Moià	St Fruitos	Solsona	Súria	Manresa	Monistrol	Abrera	Igualada	Capellades	Piera	St Sarduní	Masquefa	Martorell	Terrassa	Rubí	St Feliu
median conc	Berga	Sallent	Moià	St Fruitos	Solsona	Súria	Manresa	Monistrol	Abrera	Igualada	Capellades	Piera	St Sarduní	Masquefa	Martorell	Terrassa	Rubí	St Feliu
lowest conc	Berga	Sallent	Moià	St Fruitos	Solsona	Súria	Manresa	Monistrol	Abrera	Igualada	Capellades	Piera	St Sarduní	Masquefa	Martorell	Terrassa	Rubí	St Feliu
Scenario S4																		
highest conc	Berga	Sallent	Moià	St Fruitos	Solsona	Súria	Manresa	Monistrol	Abrera	Igualada	Capellades	Piera	St Sarduní	Masquefa	Martorell	Terrassa	Rubí	St Feliu
median conc	Berga	Sallent	Moià	St Fruitos	Solsona	Súria	Manresa	Monistrol	Abrera	Igualada	Capellades	Piera	St Sarduní	Masquefa	Martorell	Terrassa	Rubí	St Feliu
lowest conc	Berga	Sallent	Moià	St Fruitos	Solsona	Súria	Manresa	Monistrol	Abrera	Igualada	Capellades	Piera	St Sarduní	Masquefa	Martorell	Terrassa	Rubí	St Feliu
EQS 10																		
Scenario S1																		
highest conc	Berga	Sallent	Moià	St Fruitos	Solsona	Súria	Manresa	Monistrol	Abrera	Igualada	Capellades	Piera	St Sarduní	Masquefa	Martorell	Terrassa	Rubí	St Feliu
median conc	Berga	Sallent	Moià	St Fruitos	Solsona	Súria	Manresa	Monistrol	Abrera	Igualada	Capellades	Piera	St Sarduní	Masquefa	Martorell	Terrassa	Rubí	St Feliu
lowest conc	Berga	Sallent	Moià	St Fruitos	Solsona	Súria	Manresa	Monistrol	Abrera	Igualada	Capellades	Piera	St Sarduní	Masquefa	Martorell	Terrassa	Rubí	St Feliu
Scenario S2																		
highest conc	Berga	Sallent	Moià	St Fruitos	Solsona	Súria	Manresa	Monistrol	Abrera	Igualada	Capellades	Piera	St Sarduní	Masquefa	Martorell	Terrassa	Rubí	St Feliu
median conc	Berga	Sallent	Moià	St Fruitos	Solsona	Súria	Manresa	Monistrol	Abrera	Igualada	Capellades	Piera	St Sarduní	Masquefa	Martorell	Terrassa	Rubí	St Feliu
lowest conc	Berga	Sallent	Moià	St Fruitos	Solsona	Súria	Manresa	Monistrol	Abrera	Igualada	Capellades	Piera	St Sarduní	Masquefa	Martorell	Terrassa	Rubí	St Feliu
Scenario S3																		
highest conc	Berga	Sallent	Moià	St Fruitos	Solsona	Súria	Manresa	Monistrol	Abrera	Igualada	Capellades	Piera	St Sarduní	Masquefa	Martorell	Terrassa	Rubí	St Feliu
median conc	Berga	Sallent	Moià	St Fruitos	Solsona	Súria	Manresa	Monistrol	Abrera	Igualada	Capellades	Piera	St Sarduní	Masquefa	Martorell	Terrassa	Rubí	St Feliu
lowest conc	Berga	Sallent	Moià	St Fruitos	Solsona	Súria	Manresa	Monistrol	Abrera	Igualada	Capellades	Piera	St Sarduní	Masquefa	Martorell	Terrassa	Rubí	St Feliu
Scenario S4																		
highest conc	Berga	Sallent	Moià	St Fruitos	Solsona	Súria	Manresa	Monistrol	Abrera	Igualada	Capellades	Piera	St Sarduní	Masquefa	Martorell	Terrassa	Rubí	St Feliu
median conc	Berga	Sallent	Moià	St Fruitos	Solsona	Súria	Manresa	Monistrol	Abrera	Igualada	Capellades	Piera	St Sarduní	Masquefa	Martorell	Terrassa	Rubí	St Feliu
lowest conc	Berga	Sallent	Moià	St Fruitos	Solsona	Súria	Manresa	Monistrol	Abrera	Igualada	Capellades	Piera	St Sarduní	Masquefa	Martorell	Terrassa	Rubí	St Feliu

Figure A 16. Optimal set of WWTP upgrades for each scenario of diclofenac consumption, 3 uncertainty levels, environmental flows and EQS 10 and 100

Environmental flows																		
EQS 640																		
Scenario S1	5	15	16	17	21	25	26	29	31	38	40	41	47	49	51	52	53	55
highest conc	Berga	Sallent	Moià	St Fruitos	Solsona	Súria	Manresa	Monistrol	Abrera	Igualada	Capellades	Piera	St Sarduní	Masquefa	Martorell	Terrassa	Rubí	St Feliu
median conc	Berga	Sallent	Moià	St Fruitos	Solsona	Súria	Manresa	Monistrol	Abrera	Igualada	Capellades	Piera	St Sarduní	Masquefa	Martorell	Terrassa	Rubí	St Feliu
lowest conc	Berga	Sallent	Moià	St Fruitos	Solsona	Súria	Manresa	Monistrol	Abrera	Igualada	Capellades	Piera	St Sarduní	Masquefa	Martorell	Terrassa	Rubí	St Feliu
Scenario S2																		
highest conc	Berga	Sallent	Moià	St Fruitos	Solsona	Súria	Manresa	Monistrol	Abrera	Igualada	Capellades	Piera	St Sarduní	Masquefa	Martorell	Terrassa	Rubí	St Feliu
median conc	Berga	Sallent	Moià	St Fruitos	Solsona	Súria	Manresa	Monistrol	Abrera	Igualada	Capellades	Piera	St Sarduní	Masquefa	Martorell	Terrassa	Rubí	St Feliu
lowest conc	Berga	Sallent	Moià	St Fruitos	Solsona	Súria	Manresa	Monistrol	Abrera	Igualada	Capellades	Piera	St Sarduní	Masquefa	Martorell	Terrassa	Rubí	St Feliu
Scenario S3																		
highest conc	Berga	Sallent	Moià	St Fruitos	Solsona	Súria	Manresa	Monistrol	Abrera	Igualada	Capellades	Piera	St Sarduní	Masquefa	Martorell	Terrassa	Rubí	St Feliu
median conc	Berga	Sallent	Moià	St Fruitos	Solsona	Súria	Manresa	Monistrol	Abrera	Igualada	Capellades	Piera	St Sarduní	Masquefa	Martorell	Terrassa	Rubí	St Feliu
lowest conc	Berga	Sallent	Moià	St Fruitos	Solsona	Súria	Manresa	Monistrol	Abrera	Igualada	Capellades	Piera	St Sarduní	Masquefa	Martorell	Terrassa	Rubí	St Feliu
Scenario S4																		
highest conc	Berga	Sallent	Moià	St Fruitos	Solsona	Súria	Manresa	Monistrol	Abrera	Igualada	Capellades	Piera	St Sarduní	Masquefa	Martorell	Terrassa	Rubí	St Feliu
median conc	Berga	Sallent	Moià	St Fruitos	Solsona	Súria	Manresa	Monistrol	Abrera	Igualada	Capellades	Piera	St Sarduní	Masquefa	Martorell	Terrassa	Rubí	St Feliu
lowest conc	Berga	Sallent	Moià	St Fruitos	Solsona	Súria	Manresa	Monistrol	Abrera	Igualada	Capellades	Piera	St Sarduní	Masquefa	Martorell	Terrassa	Rubí	St Feliu
EQS1700																		
Scenario S1																		
highest conc	Berga	Sallent	Moià	St Fruitos	Solsona	Súria	Manresa	Monistrol	Abrera	Igualada	Capellades	Piera	St Sarduní	Masquefa	Martorell	Terrassa	Rubí	St Feliu
median conc	Berga	Sallent	Moià	St Fruitos	Solsona	Súria	Manresa	Monistrol	Abrera	Igualada	Capellades	Piera	St Sarduní	Masquefa	Martorell	Terrassa	Rubí	St Feliu
lowest conc	Berga	Sallent	Moià	St Fruitos	Solsona	Súria	Manresa	Monistrol	Abrera	Igualada	Capellades	Piera	St Sarduní	Masquefa	Martorell	Terrassa	Rubí	St Feliu
Scenario S2																		
highest conc	Berga	Sallent	Moià	St Fruitos	Solsona	Súria	Manresa	Monistrol	Abrera	Igualada	Capellades	Piera	St Sarduní	Masquefa	Martorell	Terrassa	Rubí	St Feliu
median conc	Berga	Sallent	Moià	St Fruitos	Solsona	Súria	Manresa	Monistrol	Abrera	Igualada	Capellades	Piera	St Sarduní	Masquefa	Martorell	Terrassa	Rubí	St Feliu
lowest conc	Berga	Sallent	Moià	St Fruitos	Solsona	Súria	Manresa	Monistrol	Abrera	Igualada	Capellades	Piera	St Sarduní	Masquefa	Martorell	Terrassa	Rubí	St Feliu
Scenario S3																		
highest conc	Berga	Sallent	Moià	St Fruitos	Solsona	Súria	Manresa	Monistrol	Abrera	Igualada	Capellades	Piera	St Sarduní	Masquefa	Martorell	Terrassa	Rubí	St Feliu
median conc	Berga	Sallent	Moià	St Fruitos	Solsona	Súria	Manresa	Monistrol	Abrera	Igualada	Capellades	Piera	St Sarduní	Masquefa	Martorell	Terrassa	Rubí	St Feliu
lowest conc	Berga	Sallent	Moià	St Fruitos	Solsona	Súria	Manresa	Monistrol	Abrera	Igualada	Capellades	Piera	St Sarduní	Masquefa	Martorell	Terrassa	Rubí	St Feliu
Scenario S4																		
highest conc	Berga	Sallent	Moià	St Fruitos	Solsona	Súria	Manresa	Monistrol	Abrera	Igualada	Capellades	Piera	St Sarduní	Masquefa	Martorell	Terrassa	Rubí	St Feliu
median conc	Berga	Sallent	Moià	St Fruitos	Solsona	Súria	Manresa	Monistrol	Abrera	Igualada	Capellades	Piera	St Sarduní	Masquefa	Martorell	Terrassa	Rubí	St Feliu
lowest conc	Berga	Sallent	Moià	St Fruitos	Solsona	Súria	Manresa	Monistrol	Abrera	Igualada	Capellades	Piera	St Sarduní	Masquefa	Martorell	Terrassa	Rubí	St Feliu

Figure A 17. Optimal set of WWTP upgrades for each scenario of naproxen consumption, 3 uncertainty levels, environmental flows and EQS 640 and 1,700