MULTIMEDIA FATE MODELLING AND IMPACT OF PHARMACEUTICAL COMPOUNDS ON FRESHWATER ECOSYSTEMS

By

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The present thesis entitled *Multimedia Fate Modelling and Impact of Pharmaceutical Compounds on Freshwater Ecosystems* by Sérgio Alberto Morais has been carried out at the Institute of Environmental Science and Technology (ICTA) at Universitat Autònoma de Barcelona (UAB)

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Abstract

The overall objective of this dissertation is to contribute to the development of best available practices in environmental multimedia fate and effect modelling for ecosystem impacts assessment of pharmaceutical compounds. The distribution of pharmaceuticals through several environmental media poses a potential toxic hazard to freshwater ecosystems, among other endpoints. The ionising properties of pharmaceuticals represent additional challenges when modelling the multimedia fate, exposure, and effect of this class of chemicals. Large uncertainties are expected when modelling the mobility, as well as the bioavailability for uptake by exposed biota and degradation, of ionising organic chemicals using conventional models. The development and evaluation of alternative approaches that include these issues are essential for the improvement of micropollutants environmental behaviour simulation. Model comparison and quantification of uncertainties of model results are vital for their correct interpretation. Furthermore, the quantification of uncertainties of model results is detrimental to establish priorities for further monitoring, as well as research, the wide number of pharmaceutical active compounds currently in use considering the most important pathways of environmental contamination.

In order to achieve that, the following specific objectives are addressed:

1. Develop a consistent matrix algebra framework for multimedia fate, multipathway exposure and toxicity effects models adapted for pharmaceutical compounds and consistent with life cycle impact assessment models.
2. Develop an approach to quantify the uncertainty of model results, accounting for regression model uncertainty, and identifying the main contributing parameters to overall uncertainty.
3. Compare and quantify the uncertainty of alternative model approaches on the level of characterisation factors as well as of final impact results, contributing to the identification of the best available practices on multimedia fate, exposure and effect modelling of PCs based on current scientific knowledge.
4. Prioritise pharmaceutical compounds on their probabilistic impact on freshwater ecosystems from both WWTP direct emissions and indirect emissions for further monitoring and research.

Chapter 1 puts this dissertation into its context and defines its objectives.

Chapter 2 presents a multimedia fate, exposure, and effect model based on matrix algebra adapted for pharmaceutical compounds and consistent with the UNEP/SETAC consensus model USEtox. An approach to quantify the uncertainty of model results using Monte Carlo analysis is presented. The approach accounts for the uncertainty of regression models and toxicity effects, as well as the variability of environmental parameters and experimental parameter values. The framework is applied to pharmaceuticals detected in biosolids following application on agricultural soils. The most influential parameters of the probabilistic comparative impact assessment were identified, as well as topics for further research for the compounds of most concern.

Chapter 3 is a detailed comparison of the USEtox model with the alternative framework adapted for pharmaceutical compounds. The alternative framework includes regressions to estimate fate parameters that account for the ionized fraction of a molecule. The comparison has been performed at the level of characterisation factors as well as of final impact results for 3 emissions scenarios into different environmental media. The most sensitive model parameters in the estimation of ecotoxicological characterization factors of micropollutants were evaluated by Monte Carlo analysis in both the default USEtox model and in the alternative approach.

Chapter 4 and 5 present a prioritisation of PCs detected in European wastewater treatment plants for further monitoring and research. *Chapter 4* presents the pathway of direct discharge of WWTPs emissions to surface waters. In *Chapter 5* the indirect emissions pathways to the freshwater compartment are addressed. The indirect emission pathways include the application of biosolids from WWTPs and of effluents as reclaimed water for irrigation, both on agricultural areas and landscapes. Research topics were defined by indentifying important gaps of knowledge as well as by computing the contribution of estimated model parameters' uncertainty to the impact variance.

Chapter 6 presents general conclusions on the research outlined and will provide recommendations for future research.

Keywords: Multimedia fate model, Uncertainty analysis, Pharmaceuticals, Micropollutants, Dissociating organics, Freshwater ecotoxicity, Wastewater treatment plants, Biosolids, Land application, Reclaimed water, Probabilistic comparative impact, Risk Assessment, LCA, USEtox.

Resumen

Esta tesis tiene como objetivo principal contribuir para el desarrollo de las mejores prácticas disponibles en la modelación del destino multimedia y de los efectos de compuestos farmacéuticos para evaluar su impacto en los ecosistemas. La distribución de fármacos a través de los distintos compartimentos ambientales representa un riesgo potencial de toxicidad para los ecosistemas acuáticos, entre otros. La capacidad de ionización de muchos de estos compuestos en el medio ambiente es un reto para la modelación de su destino multimedia, de su exposición y efectos. El uso de modelos convencionales no polares representa un elevado nivel de incertidumbre en la modelación de la movilidad de compuestos orgánicos ionizables, y en la modelación de su biodisponibilidad para la exposición a organismos y para la degradación en el medio ambiente. El desarrollo y la evaluación de modelos alternativos que incluyan estos puntos son esenciales para mejorar la simulación del comportamiento ambiental de microcontaminantes. La comparación de modelos y la cuantificación de la incertidumbre de sus resultados son fundamentales para su correcta interpretación. Además, la cuantificación de estas incertidumbres es necesaria para establecer prioridades de monitoreo y de investigación adicional entre el gran número de fármacos activos en uso actual teniendo en cuenta las diferentes vías de contaminación ambiental.

En este contexto, se consideraron los siguientes objetivos específicos:

1. Desarrollo de un modelo de destino multimedia, exposición y toxicidad con base en álgebra matricial y adaptado a compuestos farmacéuticos, consistente con modelos de evaluación del impacto de ciclo de vida.
2. Desarrollo de un método para la cuantificación de la incertidumbre del modelo, incluyendo la incertidumbre de los modelos de regresión aplicados, y la identificación de los parámetros más pertinentes a la incertidumbre total.
3. Comparar y cuantificar las incertidumbres de los modelos alternativos en términos de los factores de caracterización y de los resultados finales de impacto, contribuyendo a la identificación de las mejores prácticas de modelación del destino multimedia, exposición y efectos de fármacos con base en los conocimientos científicos actuales.
4 Priorización de compuestos farmacéuticos en términos de su impacto probabilístico en los ecosistemas de agua dulce, considerando las emisiones

directas y indirectas de plantas de tratamiento de aguas, para posterior monitorización e investigación adicional.

Capítulo 1 establece el contexto de la tesis y sus objetivos.

Capítulo 2 presenta un modelo de destino multimedia, exposición y efectos con base en álgebra matricial, adaptado a fármacos y consistente con el modelo consensual de la UNEP/SETAC, el modelo USEtox. Se presenta un enfoque para cuantificar la incertidumbre de los resultados del modelo usando el análisis de Monte Carlo. El enfoque incluye la incertidumbre asociada a los modelos de regresión utilizados y a los efectos tóxicos, y la variabilidad asociada a los parámetros ambientales y experimentales. El modelo se aplicó a fármacos detectados en lodos de depuradora, posteriormente aplicados a suelos agrícolas. En relación a los compuestos de mayor relevancia, los parámetros más influyentes en la evaluación probabilística de impacto fueron identificados tal como temas para investigación futura.

El *capítulo 3* presenta una comparación detallada entre el modelo USEtox y el modelo alternativo adaptado a compuestos farmacéuticos. Este modelo alternativo incluye modelos de regresión para estimar parámetros teniendo en cuenta la fracción iónica de una molécula. La comparación se hizo al nivel de los factores de caracterización y al nivel de los resultados finales del impacto teniendo en cuenta tres escenarios de emisiones en distintos compartimientos ambientales. Los parámetros más sensibles de los modelos fueron identificados por análisis de Monte Carlo.

Los *capítulos 4 y 5* presentan una priorización de los fármacos detectados en plantas de tratamiento de aguas residuales europeas al nivel de su monitorización ambiental y de temas para investigación futura. En el Capítulo 4 las emisiones directas de efluentes al compartimiento de agua dulce son estudiadas. En el capítulo 5 se consideran las emisiones indirectas: la aplicación de lodos de depuración y de efluentes en suelos agrícolas como fertilizante y como agua de irrigación, respectivamente. Los temas de investigación futura se definieran tanto por la identificación de lagunas en el conocimiento acerca del comportamiento ambiental de los fármacos, como por la contribución de la incertidumbre de los parámetros estimados del modelo a la varianza de los impactos calculados.

En el *capítulo 6* se presentan las conclusiones generales y recomendaciones para trabajo futuro.

Palabras clave: Modelo de destino multimedia, Análisis de incertidumbre, fármacos, microcontaminantes, compuestos orgánicos ionizables, ecotoxicidad en agua dulce, plantas de tratamiento de aguas residuales, lodos de depuración, agua regenerada, Evaluación de riego, Impacto comparativo probabilístico, Análisis de ciclo de vida, USEtox .

Sumário

Esta tese tem como objectivo principal contribuir para o desenvolvimento de melhores práticas disponíveis em modelação do destino multi-compartimental e dos efeitos de compostos farmacêuticos para a avaliação dos seus impactos em ecossistemas. A distribuição de fármacos através dos vários compartimentos ambientais representa um risco tóxico potencial para os ecossistemas aquáticos, entre outros. A capacidade de muitos fármacos em se ionizarem no meio ambiente representa um desafio para a modelação do comportamento ambiental destes compostos. Elevadas incertezas são expectáveis ao modelar a mobilidade de compostos orgânicos ionizáveis utilizando modelos convencionais não-polares, tal como ao modelar a sua biodisponibilidade para se degradarem nos meios ambientais e para serem tomados por organismos expostos. O desenvolvimento e avaliação de modelos alternativos que incluam estes pontos são essenciais para a melhoria da simulação do comportamento ambiental de micropoluentes. A comparação de modelos e a quantificação das incertezas dos seus resultados é vital para a sua correcta interpretação. Adicionalmente, a quantificação destas incertezas é necessária para estabelecer prioridades de monitorização e de investigação adicional entre vasto número de fármacos activos em uso corrente considerando as diferentes vias de contaminação ambiental.

Neste âmbito, os seguintes objectivos específicos foram considerados:

1. Desenvolvimento de um modelo de destino multi-compartimental, exposição e efeitos tóxicos baseado em matrizes algébricas, adaptado a compostos farmacêuticos e consistente com modelos de avaliação de impacto de ciclo de vida.
2. Desenvolvimento de uma abordagem para a quantificação das incertezas do modelo, incluindo a incertezas dos modelos de regressão aplicados, e identificando os parâmetros de maior relevância para a incerteza total.
3. Comparar e quantificar as incertezas de modelos alternativos ao nível dos factores de caracterização e dos resultados finais de impacto, contribuindo para a identificação das melhores práticas disponíveis em modelação do destino multi-compartimental, exposição e efeitos de fármacos baseadas no conhecimento científico actual.

4. Priorização de compostos farmacêuticos ao nível do seu impacto probabilístico em ecossistemas de água doce, tanto de emissões directas de estações de tratamento de água como de emissões indirectas, para posterior monitorização e investigação adicional.

O *capítulo 1* contextualiza a dissertação e define os seus objectivos.

O *capítulo 2* apresenta um modelo de destino multi-compartimental, exposição e efeitos baseado em matrizes algébricas, adaptado a compostos farmacêuticos e consistente com o modelo consensual da UNEP/SETAC, o modelo USEtox. Uma abordagem utilizando a análise de Monte Carlo para a quantificação das incertezas dos resultados do modelo é apresentada. A abordagem inclui a incerteza associada aos modelos de regressão utilizados e aos efeitos tóxicos e a variabilidade associada aos parâmetros ambientais e experimentais. O modelo foi aplicado a fármacos detectados em lamas de depuração e posteriormente aplicadas em solos agrícolas. Os parâmetros mais influentes da avaliação probabilística de impacto foram identificados, tal como tópicos para investigação futura relativamente aos compostos de maior relevância.

No *capítulo 3* é apresentada uma comparação detalhada entre o modelo USEtox e o modelo alternativo adaptado a compostos farmacêuticos. Este modelo alternativo inclui regressões para estimar parâmetros considerando a fracção iónica de uma molécula. A comparação foi realizada ao nível dos factores de caracterização e ao nível dos resultados finais de impacto, considerando 3 cenários de emissão em diferentes meios ambientais. Os parâmetros mais sensíveis dos modelos foram identificados através de análise de Monte Carlo.

Os *capítulos 4* e 5 apresentam uma priorização de fármacos detectados em estações de tratamento de água europeias para posterior monitorização e investigação. No capítulo 4 são estudadas as emissões directas de efluentes para o compartimento de água doce. No capítulo 5 são consideradas as emissões indirectas: aplicação de lamas de depuração e de efluentes de estações de tratamento de água em solos, como fertilizante e como água de rega, respectivamente. Tópicos para investigação futura foram definidos, tanto pela identificação de lacunas de conhecimento, como pela contribuição da incerteza dos parâmetros estimados para a variância do impacto.

O capítulo 6 apresenta conclusões generais e recomendações para trabalho futuro.

Palavras-chave: Modelo de destino multi-compartimental, Análise de incerteza, Fármacos, Micropoluentes, Compostos orgânicos ionizáveis, Ecotoxicidade em água doce, Estações de tratamento de água, Lamas de depuração, Água reciclada. Impacto comparativo probabilístico, Avaliação de Risco, Avaliação de ciclo de vida, USEtox.

1. Introduction

1.1 Context

The release of chemicals into the environment takes place as part of either natural or human activity. These chemicals, depending on several factors, can pose a risk to both humans and ecosystems and the knowledge and the quantification of such risks are pivotal for preventive action. The measurement of environmental concentrations is a very important step to identify potentially hazardous concentrations of chemicals in environmental media, such as air, water, soil, or sediment. However, only when there are evidence of contamination and availability of resources these measurements are practical. Methods that can simulate the fate of a chemical, i.e., the distribution of a chemical after its release into the environment, as well as to predict the exposure level of the target under protection (e.g. human population, or ecosystems) and which effects the chemical will cause, are therefore necessary. Such methods are referred to as environmental multimedia fate, multipathway exposure and effect models. The application of these models is a necessary solution when measurements of environmental concentrations are not practicable; for example, when large areas are under toxic stress or a predictive estimation of the potential hazard of an emission, e.g. of a new chemical design, is necessary in for a decision-making process.

In the last decades there has been an increasing interest in life cycle and comparative risk approaches, focusing on the prevention of emissions in opposition to end-of-pipe solutions, in order to design environmentally friendlier products or services (Rosenbaum, 2006). These environmental management approaches need methods that link the product development chains to the corresponding emissions and eventually impacts on human health and ecosystems. Such approaches can provide informed decisions whenever choices affecting a product, service, or activity and its impact in the environment have to be made.

In recent years, the focus of environmental pollution by organic chemicals is being enlarged to include organic micropollutants, i.e. organic chemicals which are detected in environmental media at trace amounts, belonging to diverse classes of chemicals such as pesticides, pharmaceuticals and personal care products (PPCPs). For example, in Europe, approximately 4000 different pharmaceutical active compounds can reach every environmental compartment (Mompelat et al., 2009). Whenever choices affecting products, services, or activities involving these ubiquitous pollutants, life cycle and comparative risk assessments are needed to support decisions regarding, for example,

the definition of environmental contamination monitoring programmes, the comparison of agricultural practices, emission reduction technologies and scenarios, or new chemical designs to be introduced in the market.

1.2 Problem setting

Pharmaceutical compounds (PCs) are one of the chemical classes of micropollutants whose detection in environmental media has raised concern in recent years. The most common environmental contamination pathways are the emission of pharmaceutical compounds (PCs) from wastewater treatment plants (WWTPs) after urinal and faecal excretion and the application of livestock manure as a top soil dressing containing veterinary pharmaceuticals. The pathways of contamination after excretion and passage through municipal sewage systems include 1) the infiltration of sewage from leakages in drains, 2) the application of biosolids from WWTPs on agricultural areas and landscapes, and, due to incomplete removal, 3) the disposal of WWTP effluents and raw sewage into surface waters and 4) as reclaimed water into agricultural fields and landscapes by irrigation. The distribution of PCs through several environmental media poses a potential toxic hazard to terrestrial organisms, humans, and freshwater ecosystems; however, the scope of the present thesis is restricted to the ecotoxicity impact of PCs on freshwater ecosystems.

Ecotoxicity refers to the potential for biological, chemical, or physical stressors to affect ecosystems (Van Zelm, 2010a). The term was first outlined by Truhaut (1977), who defined it as "the branch of toxicology concerned with the study of toxic effects, caused by natural or synthetic pollutants, to ecosystems, animals (including human beings), plants, and microbial communities". Ecotoxicology research is being used to set environmental regulations, given that legal environmental criteria are derived from ecological and human risk assessments, which establishes generic risk limits for toxic compounds for different environmental media.

Methods addressing ecotoxicity to be applied either in life cycle or comparative risk assessments need to be improved regarding the chemical coverage and environmental relevance (Larsen and Hauschild, 2007a). In the case of PCs, large uncertainties may be attached to the ecotoxicity modelling as estimated data must used at a great extent, given that reliable fate, exposure, and effect data are not always available. Furthermore, compared to most bulk chemicals, pharmaceuticals are often large and chemically

complex molecules with basic and acidic functionalities. Under environmental conditions, PCs can be neutral, cationic, anionic, or zwitterionic. In conventional multimedia fate and exposure models, the sorption of the ionic fraction of ionised organic chemicals is not adequately modelled because conventional non-polar partitioning models to estimate partitioning coefficients are applied. Therefore, large uncertainties are expected when modelling the mobility, as well as the bioavailability for uptake by exposed biota and degradation, of dissociating organic chemicals using the conventional models.

The quantification and communication of uncertainties related to model results is vital for their correct interpretation and use (Steen, 1997). Such analysis is often hindered by the difficulty to assign uncertainty distributions to the usually numerous parameters of a model as required by most methods of uncertainty assessment. Frequently, this leads to complete omission of this important and integral aspect of any model result, while potentially it might influence or even change the main result of such a comparative study (Rosenbaum, 2006). This problem is even more apparent when modelling large sets of chemicals as usually done in comparative risk or life cycle assessment. In this context, potential important sources of uncertainty in a model result, such as regression models used for parameter estimation and toxicity effects, are usually neglected in comparative risk or life cycle assessments. The identification of important contributors of uncertainty in a model results applied to micropollutants is needed in order to develop alternative, simpler approaches of uncertainty estimation, given that conventional uncertainty analysis are rather resource intensive, especially when modelling large sets of chemicals. Moreover, the quantification of uncertainty related to different model approaches covering the full source-to-impact chain is necessary in order to identify the best available practices on multimedia fate, exposure and effect modelling based on current scientific knowledge.

Conventional multimedia fate, exposure and effect models have been applied on the topic of emissions of PCs from WWTPs in order to prioritise compounds for further monitoring or additional research. In this context, quite a large body of work has been conducted, however studies have generally been limited to single WWTPs (Verlicchi et al., 2012) and rarely account for the quantification of the uncertainty of model results. Moreover, these studies are either limited to a few therapeutic classes, or do not account for spatial variations of the environmental landscape, nor do most of them account for the dissociating properties of PCs (e.g., Sandersonn et al., 2004; Besse and Garric, 2008; Christen et al., 2010). Most of those studies, therefore, lack spatial differentiation

given that the spatial resolution is neglected. This limitation can be overcome by the use of regional grids within a model's geographic scale, which is rather resource intensive, or by including spatial variations of landscape characteristics in the model using uncertainty analysis. Furthermore, as stated above, because many PCs contain ionising functional groups, their charge changes with environmental pH, which displays great variability with a given geographic scale, and thus, their transport behaviour and bioavailability may be affected. In addition, the indirect emission pathways to the freshwater compartment from WWTPs, such as the application of biosolids from WWTPs and of effluents as reclaimed water for irrigation on agricultural areas and landscapes, are neglected when examining the prioritisation of PCs for further monitoring or additional research.

1.3 Objectives and structure of the thesis

The overall objective of this thesis is to contribute to the development of best available practice in environmental multimedia and multipathway modelling for ecosystem impacts of pharmaceutical compounds, addressing several important aspects. In order to achieve that, the following specific objectives are addressed:

1. Develop a consistent matrix algebra framework for multimedia fate, multipathway exposure and toxicity effect models adapted for pharmaceutical compounds and consistent with life cycle impact assessment models.
2. Develop an approach to quantify the uncertainty of model results, accounting for regression model uncertainty, and identifying the main contributing parameters to overall uncertainty.
3. Compare and quantify the uncertainty of alternative model approaches on the level of characterisation factors as well as of final impact results, contributing to the identification of the best available practices on multimedia fate, exposure and effect modelling of PCs based on current scientific knowledge.
4. Prioritise pharmaceutical compounds on their probabilistic impact on freshwater ecosystems from both WWTP direct emissions and indirect emissions for further monitoring and research. Research topics will be defined by indentifying important gaps of knowledge as well as by computing the contribution of estimated model parameters' uncertainty and variability to the impact variance.

The chapters in this thesis are all written as journal articles. The literature review is thus performed at the beginning of each chapter. In each introduction, specific objectives related to the overall thesis topic are expanded. Since journal articles must be self-contained there is some degree of repetition in this thesis.

Chapter 2 presents a multimedia fate, exposure, and effect model based on matrix algebra adapted for pharmaceutical compounds and consistent with the UNEP/SETAC consensus model USEtox. An approach to quantify the uncertainty of model results using Monte Carlo analysis is presented. The approach accounts for the uncertainty of regression models and toxicity effects, as well as the variability of environmental parameters and experimental parameter values. The framework is applied to pharmaceuticals detected in biosolids following application on agricultural soils. Emphasis is laid upon interpretation of the physical meaning of different elements within the fate matrix, such as the transfer fractions of PCs from biosolids to the freshwater compartment and their residence time on the freshwater compartment. The most influential parameters of the probabilistic comparative impact assessment were identified, as well as topics for further research for the compounds of most concern.

Chapter 3 is a detailed comparison of the USEtox model with the alternative framework adapted for pharmaceutical compounds. The alternative framework includes regressions to estimate fate parameters that account for the ionised fraction of a molecule. The comparison has been performed at the level of characterisation factors as well as of final impact results for 3 emissions scenarios into different environmental media. The most sensitive model parameters in the estimation of ecotoxicological characterization factors of micropollutants were evaluated by Monte Carlo analysis in both the default USEtox model and in the alternative approach.

Chapter 4 and 5 present a prioritisation of PCs detected in European wastewater treatment plants for further monitoring and research. *Chapter 4* presents the pathway of direct discharge of WWTPs emissions to surface waters. In *Chapter 5* the indirect emissions pathways to the freshwater compartment are assessed. The indirect emission pathways include the application of biosolids from WWTPs and of effluents as reclaimed water for irrigation, both on agricultural areas and landscapes. The analysis includes the occurrence of 85 PCs detected in influents and effluents of 179 WWTPs. Research topics were defined by indentifying important gaps of knowledge as well as

by computing the contribution of estimated model parameters' uncertainty to the impact variance.

Finally, *Chapter 6* presents general conclusions on the research outlined and will provide recommendations for future research.

2. Multimedia Fate Modelling and Comparative Impact on Freshwater Ecosystems of Pharmaceuticals from Biosolids-Amended Soils

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2.1 Abstract

This study modelled the impact on freshwater ecosystems of pharmaceuticals detected in biosolids following application on agricultural soils. The detected sulfonamides and hydrochlorothiazide displayed comparatively moderate retention in solid matrices and, therefore, higher transfer fractions from biosolids to the freshwater compartment. However, the residence times of these pharmaceuticals in freshwater were estimated to be short due to abiotic degradation processes. The non-steroidal anti-inflammatory mefenamic acid had the highest environmental impact on aquatic ecosystems and warrants further investigation. The estimation of the solid-water partitioning coefficient was generally the most influential parameter of the probabilistic comparative impact assessment. These results and the modelling approach used in this study serve to prioritize pharmaceuticals in the research effort to assess the risks and the environmental impacts on aquatic biota of these emerging pollutants.

Keywords: Biosolids, Freshwater ecotoxicity, Land application, Multimedia fate modelling, Pharmaceuticals, Probabilistic comparative impact.

2.2 Introduction

The application of municipal biosolids to agricultural soils as a source of crop nutrients and organic matter is a common farming practice. Seven EU member states spread >50% of their biosolids on agricultural soils (Müller, 2007). Persistent pharmaceuticals that partition into organic matter during the sewage treatment process are present in sludge and ultimately in biosolids (Edwards et al., 2009; Sabourin et al., 2009; Wu et al., 2010). These emerging pollutants have been detected in biosolids-amended soils (Furczak and Joniec, 2007; Kinney et al., 2008). Recent research has shown the potential of several pharmaceuticals to migrate offsite in runoff water following land application of biosolids (Lapen et al., 2008; Topp et al., 2008; Wu et al., 2010).

However, few studies have experimentally characterized the fate and transport of these pharmaceuticals and the risks of contaminating adjacent surface waters (Barron et al., 2010). Furthermore, in Europe, approximately 4000 different pharmaceutical active compounds (PhACs) can reach every environmental compartment (Mompelat et al., 2009). The wide range of properties of pharmaceuticals and the lengthy analytical processes required for field-scale experiments make chemical fate modelling a valuable tool for screening and prioritizing pharmaceuticals in research efforts to understand their environmental behaviour.

The aims of this study were 1) to model the environmental fate of pharmaceuticals detected in dewatered municipal biosolids (DMB) applied to agricultural soils, accounting for their dissociating properties, 2) to estimate their comparative impact on freshwater ecosystems, and 3) to identify and prioritize those compounds that warrant further investigation as well as the most sensitive fate processes, i.e., those that contribute to variance of impact results to a higher extent. For other endpoints, such as terrestrial ecosystems and humans, other modelling challenges need to be investigated and are currently out of the scope of this research. Almost no experimental data on terrestrial ecotoxicity effects are available, as well as, in human exposure routes, quantitative structure activity relationship (QSAR) models to estimate biotransfer factors for milk and meat and bioaccumulation in roots and leaves of dissociating compounds or degradation data in the vegetation compartment are also not available.

2.3 Methodology

In a previous study, 43 pharmaceuticals were targeted in DMB samples, and 28 were either absent or present in concentrations below the method detection limit (Rodríguez-Rodríguez et al., 2011). The wastewater treatment plant (WWTP) in this study is located in El Prat de Llobregat, near Barcelona, Spain, and it has a treatment capacity of two million equivalent habitants. Table 1 show the concentrations of detected pharmaceuticals in the DMB analysis, which did not account for human or veterinary metabolites of parent compounds.

The concentration of pharmaceuticals is higher immediately following sludge application at the beginning of the growing season and lower at the end of the year due to removal processes. However, for screening purposes, steady-state conditions and first-order kinetics for the degradation processes are assumed.

The modelled system consists of five compartments: biosolids, agricultural soil, air, freshwater, and freshwater sediment (Figure 1). The landscape and environmental parameters of the regional scale European Union System for the Evaluation of Substances model (EUSES v2.1.1) (EC, 2004) were chosen to mimic a typical densely populated region in the EU with an area of 40 400 km^2 and applied in this assessment. After biosolids have been applied to a soil, pharmaceuticals can desorb and thereby become bioavailable in the agricultural soil matrix. They can then undergo leaching and runoff in surface water. Conversely, they can remain highly bound and unavailable. To account for differences in the sorption, desorption, and degradation of compounds between the biosolid and soil matrices, the biosolids-amended soil compartment was modelled as a biosolids compartment nested in the agricultural soil compartment. The volume of the biosolids compartment was calculated for an application rate of 5000 kg dry weight per hectare per year, assumed to be typical for EU regional agricultural practices (EC, 2004), and 1.5 $kg.L^{-1}$ density of dry biosolids (EC, 2004).

In the model, the environmental compartments are assumed to be homogeneous and well mixed. Once emitted, chemicals are assumed to be instantaneously dispersed throughout the entire compartment. Therefore, spatial variations in properties of the medium and spatial differences in concentrations are disregarded. The mass distribution estimation in the five-compartment model requires a mass balance solution with five simultaneous differential equations.

Table 1: Structures, molecular acidity, and concentrations of detected pharmaceuticals in dewatered municipal biosolids

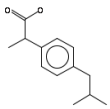
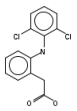
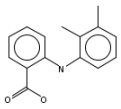
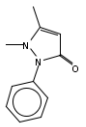
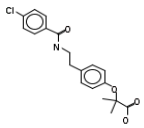
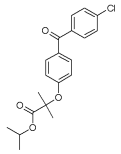
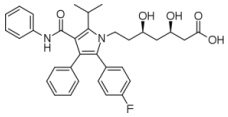
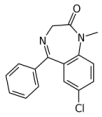
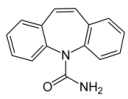
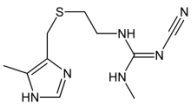
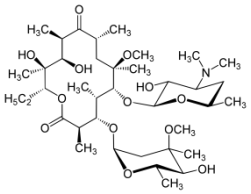
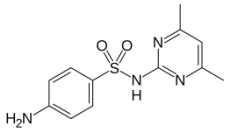
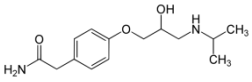
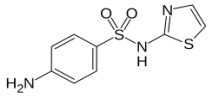
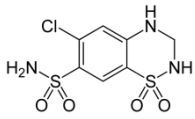
Compound	**CAS** [a]	**Structure**	**Usage**	**p*K*a** [b]	**Concentration ng g^{-1} (±SD)** [c]
Ibuprofen	15687-27-1		Anti-inflammatory	4.91	85.9 (± 9.2)
Diclofenac	15307-86-5		Anti-inflammatory	4.15	60.3 (± 9.6)
Mefenamic acid	644-62-2		Anti-inflammatory	4.2	17.9 (± 2.1)
Phenazone	60-80-0		Analgesic and antipyretic	1.4	9.6 (± 2.2)
Bezafibrate	41859-67-0		Antilipemic	3.73 [d] 0.36 [e]	4.5 (± 0.1)
Fenofibrate	49562-28-9		Antilipemic	-	4.2 (± 0.6)
Atorvastatin	134523-00-5		Statin	4.46 [d, g] 0.14 [e]	37.8 (± 3.5)
Diazepam	439-14-5		Anticonvulsant, anxiolytic and sedative	3.4	19.3 (± 2.8)
Carbamazepine	298-46-4		Anticonvulsant	13.9[f]	25.6 (± 5.0)

Table 1 (continued)

Compound	CAS[a]	Structure	Usage	p*Ka*	Concentration ng g^{-1} (±SD) [c]
Cimetidine	51481-61-9		Antihistaminic	4.17	11.4 (± 0.6)
Clarithromycin	81103-11-9		Antibiotic	8.89	21.0 (± 2.2)
Sulfamethazine	57-68-1		Anti-infective	7.4[d, h] 2.65[e, h]	20.4 (±1.4)
Atenolol	29122-68-7		β-adrenergic blocker	9.6	13.6 (± 2.2)
Sulfathiazole	72-14-0		Anti-Infective	7.2[d] 2.66[e]	71.1 (± 9.0)
Hydrochlorothiazide	58-93-5		Diuretic	7.9	26.7 (± 3.1)

[a] Chemical Abstract Service
[b] SPARC v4.5, except carbamazepine, sulfamethazine, and pKa_{acid} of atorvastatin.
[c] (Rodríguez-Rodríguez et al., 2011)
[d] pKa_{acid}
[e] pKa_{base}
[f] (Röhricht et al., 2009)
[g] (Wu et al., 2000)
[h] (Lertpaitoonpan et al., 2009)

In the present study, a simple approach based on matrix algebra, which can guide higher tier assessments, was used initially to assess the fate of pharmaceuticals. Matrix algebra provides a straightforward and transparent solution for the visualization and solution of *n* differential equations for an *n*-compartment model (Pennington et al., 2005; Rosenbaum et al., 2007). This method has been used to assess chemical fate in multimedia models such as the Simple Box (Brandes et al., 1996), USES-LCA (Huijbregts, 1999), IMPACT 2002 (Pennington et al., 2005) and USEtox (Rosenbaum et al., 2008) models. The fate matrix $\overline{FF}$ links the quantity released to the environmental compartments to the chemical masses or concentrations in a given compartment. It

accounts for multimedia transport (e.g., air, water, and soil) and loss processes in a given compartment (e.g., abiotic and biotic degradation or advective transport outside the modelled scale). A detailed description of the framework applied in this research is provided in Appendix A, Section A1.

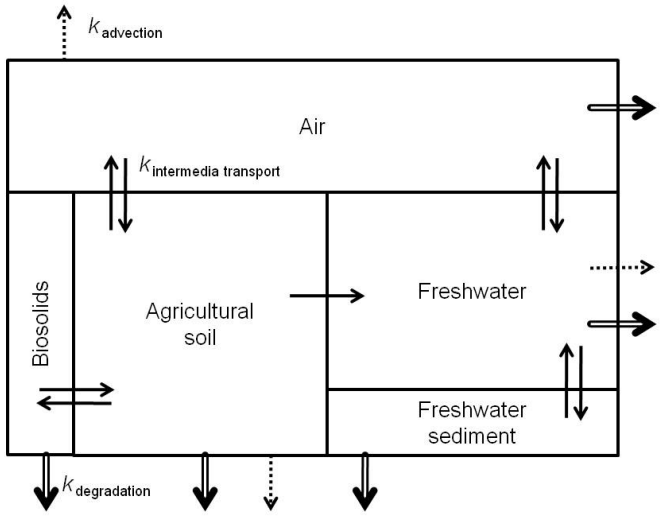


Figure 1: Five-compartment system for the dissipation of pharmaceuticals from biosolids-amended soils. In a given environmental compartment, bold arrows represent intermedia transport rates, dashed arrows represent advective transportation rates out the system, and double-line arrows represent degradation rates.

2.3.1 Intermedia transport and loss processes

The modelled diffusive intermedia mass transfer mechanisms include absorption of the chemical from the gaseous phase by water or soil, volatilization from water or soil, and sorption and desorption to and from biota, soil, sediment and biosolids. These mechanisms are reversible, while advective mass transfer mechanisms are irreversible. Chemicals are transported by a physical medium from one compartment to another. The advective intermedia mass transfer mechanisms include deposition of the chemical associated with aerosol particles, deposition of the chemical in rainwater, sedimentation and resuspension of the chemical associated with sediment particles, run-off and erosion to surface waters. Loss mechanisms include abiotic and biotic degradation, burial in deep sediment layers, advective transport by plant uptake, advective transport in air and water out of the modelled region, and leaching to groundwater, which is regarded as a loss process because groundwater is not part of the system, as modelled in the European Commission Technical Guidance Document (TGD) on Risk Assessment (EC, 2003).

To determine the intermedia transport, leaching, burial, and advective transport rates to outside the regional scale, equations from the USEtox model were applied (Rosenbaum et al., 2008). These equations use mass-transfer coefficients, partition coefficients and environment characteristics as inputs. Mass-transfer coefficients and the environment characteristics were set according to the EUSES 2.1.1 European regional model (EC, 2004). Experimental data of physic-chemical properties to obtain partition coefficients of compounds are preferred in present model, except in the cases described in Appendix A, Section A2. If experimental data was not available, the partition coefficients were estimated according to the routines described in the same section. For a given environmental compartment pH, a different degree of anion, cation, and neutral molecule sorption can be expected; therefore, the applied regressions to estimate solid-water partition coefficients account for the dissociating properties of pharmaceuticals. Such approach has been shown to outperform the application of conventional non-polar partitioning regressions, reducing substantially the uncertainty of ecotoxicity impact results of indirect emissions to the freshwater compartment (Morais et al., 2013). In the USEtox model, plant uptake is modelled as a human exposure pathway for non-dissociating compounds; therefore, it was not applicable in this study. The modelling description of plant uptake is provided in Appendix A, Section A3.

For degradation in the environment, substance-specific degradation rates are preferred in the model calculations (Appendix A, Section A4). However, degradation data are usually lacking for one or more compartments. Therefore, several models and assumptions were applied in this study. In any environmental compartment, the overall degradation rate constant is given by the sum of degradation rate constants for the various transformation processes.

Degradation in air

The most effective elimination process in the troposphere for most substances is reaction with photochemically generated OH-radicals, although for some substances, reaction with ozone and nitrate radicals may be also important (EC, 2004). Volatilization from water and soil surfaces is not expected to be an important fate process based on estimated Henry's Law constants; therefore, degradation by reaction with ozone and nitrate radicals and direct photolysis were disregarded. The specific pseudo-first-order degradation rate constant of a substance with ˙OH radicals ($k_{deg,\ air}$ in

s^{-1}) was determined by multiplying the compound-specific hydroxyl radical rate constant (k_{OH} in $cm^3.molec^{-1}.s^{-1}$) to the OH-radical concentration in the atmosphere, according to EUSES2.0 (EC 2004). The k_{OH} values were estimated using the software program AOPWIN v1.92a (USEPA 2008). The default [•OH] was 2.0×106 molecules (radicals)/cm^3 for 12 hours of daylight (Atkinson and Arey, 2003).

Degradation in water

The ultimate aerobic biodegradation probabilities in freshwater were estimated using the Biowin3 model in the software program Biowin v4.10™ (USEPA, 2009). Biowin has been shown to outperform other models in the predictive screening of a variety of chemicals (Raymond, Rogers et al. 2001). Biodegradation probabilities were converted to biodegradation rates ($k_{biodeg,water}$ in s^{-1}) according to Aronson et al. (Aronson et al., 2006). For compounds reported as recalcitrant in the literature, half-lives of 180 days were assigned (Aronson et al., 2006).

Photodegradation rates for pharmaceuticals depend on the intensity of solar irradiation, eutrophic conditions, water depth, organic matter composition, latitude and season (Boreen et al., 2003; Vione et al., 2009). Experimental photolysis half-lives based on the literature may not reflect consistently a regional model due to differences in experimental conditions, thus introducing uncertainty. Therefore, in the present study, average full day direct photolysis rates for winter and summer seasons were calculated by GCSOLAR (USEPA, 1999) for a well-mixed water layer of 50cm thickness (Tixier et al., 2002), after providing experimental molar absorption coefficients in function of the UV/VIS wavelength range (ελ, in $L.mol^{-1}.cm^{-1}$) (Ulvi, 1998; Doll and Frimmel, 2003; Boreen et al., 2004; Werner et al. 2005; Liu and Williams, 2006; Vione et al., 2009; Yuan et al., 2009; Baeza and Knappe, 2011; Calisto et al., 2011; Razavi et al., 2011) and quantum yields of pharmaceuticals (Appendix A, Section A4). Absorption attenuation coefficients of pure water in function of wavelength were assumed for the water body, as well as a depth of 3 m (EC, 2003), the latitude range of 40°-60°, and assuming a perfectly clear sky. Ozone layer thickness values were obtained from satellite data (NASA, 2011).

Indirect photolysis reactions proceed due to the presence of chemical transients such as hydroxyl, alkyl peroxy, and carbonate radicals, single oxygen, aqueous electrons, and coloured dissolved organic matter (cDOM) in its excited triplet state, which are

generated by natural water constituents and can react with organic compounds. The hydroxyl radical, ˙OH, is the most reactive of the aforementioned intermediates due to its non-selective and highly electrophilic nature (Lam and Mabury, 2005) and the only transient considered in this study, although for some pharmaceuticals other transients may have a large impact on the rate of degradation (Lam et al., 2003). Bimolecular rate constants (k_{OH}, in $M^{-1}s^{-1}$) for the reaction between pharmaceuticals and ˙OH (Appendix B, Section A4) were converted to pseudo-first order rate constants by multiplication by the hydroxyl radical concentration (in M). The concentration of ˙OH is reported to be present at 10^{-14}–10^{-17} M in surface waters (Lam et al., 2003).

The importance of hydrolysis degradation rates is normally limited for pharmaceuticals (Khan and Ongerth, 2002). For pharmaceuticals that reach the freshwater compartment, there is a lack of hydrolysable functional groups, or these compounds are generally resistant to hydrolysis, or other mechanisms of degradation are the limiting ones (Lyman et al., 1990; West, 2007; Liu et al., 2009).

Degradation in soil and sediment

The main route for the degradation of pharmaceuticals in soils is aerobic soil biodegradation (Kümmerer et al., 2005). Division factors of 1:2:9 were used to extrapolate biodegradation rates from fresh water to the soil and sediment compartments ($k_{biodeg, soil}$ and $k_{biodeg, sed}$ in s^{-1}), respectively, as suggested in the EPI Suite™ and applied in the USEtox model (Huijbregts et al., 2010). Photodegradation is likely to occur only in the top layer of the soil surface; hence, the formation and persistence of photodegradable substances is dependent on farming practices such as the timing and depth of ploughing (Boxall, 2008), which are virtually impossible to determine. This degradation route was therefore neglected for the screening purposes of this study.

Degradation in biosolids

Biodegradation is also the primary degradation route for most pharmaceuticals in biosolids (Wu et al., 2009). Minor impacts from sunlight irradiation on degradation were reported for 8 pharmaceuticals, including carbamazepine and clarithromycin (Wu et al., 2008). Presently, the understanding of the effects of the biosolid matrix on the persistence of compounds in agricultural soils is limited (Monteiro and Boxall, 2009). Amendment with biosolids increases organic matter and phosphorous content, which

have been reported to increase microbial activity (Furczak and Joniec, 2007). Conversely, studies have shown that high soil organic matter (SOM) content may inhibit the degradation of organic compounds due to increased adsorption of chemicals and reduced bioavailabity (Xu et al., 2009a). In addition, SOM may serve as an alternative nutrition source for microorganisms involved in the degradation (Alvey and Crowley, 1995). The type of digestion may also influence biodegradation in biosolids matrices in opposing ways. Monteiro and Boxall (2009) suggested that aerobically digested biosolids may hasten degradation rates, whereas anaerobically digested biosolids show opposite effects, possibly as a result of differences in microbial communities and properties. Moreover, interactions between pharmaceuticals and other contaminants can affect the fate of pharmaceuticals in biosolids. For example, the presence of antibacterial compounds, such as sulfamethazine, is likely to reduce bacterial populations (Thiele-Bruhn and Beck, 2005) and, therefore, influence microbial degradation. We pragmatically estimated biodegradation rates in biosolids amended to soils by extrapolation from biodegradation rates in soils and by assessing the influence of different extrapolation factors on the comparative impact results by Monte Carlo analysis (Appendix A, Section A6).

2.3.2 Freshwater ecosystem impacts

The impact of a chemical on freshwater ecosystems due to an emission flow from biosolids-amended soils, $EI_{aqu,b}$ in PAF·m^3.d, is given by

$$EI_{aqu,b} = M_b \cdot FF_{b,fw} \cdot FR_{fw,fw} \cdot EF_{aqua,fw} \quad (2.1)$$

where M_b is the mass emitted from biosolids amended to soils, in kg per kg of dry weight biosolids, and $FF_{b,fw}$ is the fate factor that represents the mass increase in freshwater due to an emission flow from biosolids and is estimated by means of the fate matrix (Appendix A, Section A1). It is equivalent to the fraction transferred from biosolids to freshwater ($f_{b,fw} = FF_{b,fw}/FF_{fw,fw}$), multiplied by the residence time in freshwater ($FF_{fw,fw}$). $FR_{fw,fw}$ is the environmental exposure factor for freshwater, equivalent to the fraction of chemical dissolved in freshwater (Appendix A, Section A5). $EF_{aqua,fw}$ is the ecotoxicity factor in water, which expresses the change in the Potentially Affected Fraction (PAF) species that experiences an increase in stress for a change in contaminant concentration, in PAF·m^3·kg^{-1}. $EF_{aqua,fw}$ is calculated according to the AMI method (Jolliet et al. 2003; Payet 2004), which is based on the Hazardous

Concentration (HC) of a chemical affecting 50% of a tested species over their chronic Effect Concentration affecting 50% of tested individuals (EC50), also called $HC50_{EC50}$. A detailed description of the procedure used to calculate effect factors is provided in Appendix A, Section A5. The AMI method may be limited in comparative risk assessments for pharmaceuticals. This approach and all risk assessments are based on the effects of single compounds. However, pharmaceutical mixtures have been shown to exhibit effects different from those of single compounds (Backhaus et al., 2008; Quinn et al., 2009). Moreover, the ecological relevance of sub-lethal responses is unknown for some compounds. Particularly, the relevance of non-standard endpoints, which may introduce bias in the comparative results, is unknown. Furthermore, acute-chronic ratios are based on industrial chemicals, and although the acute-chronic ratios of pharmaceuticals for crustacean and algae do not differ from those reported elsewhere for industrial chemicals, differences of several orders of magnitude were observed between acute and chronic data in fish for endocrinologically active compounds (Webb, 2004, Han et al., 2010) .

2.3.3 Monte Carlo Analysis

To characterize the comparative impact of pharmaceuticals on freshwater ecosystems, Monte Carlo analysis was conducted on the impact estimates. The analysis includes 1) the experimental parameter values (partition coefficients, biodegradation half lives in water and soil, and bimolecular hydroxyl radical rate constants); the geometric mean and the geometric standard deviation of experimental values were set as uncertainty parameters assuming a lognormal distribution; 2) the extrapolation of parameter values from one compartment to another (biodegradation rates in biosolids); 3) the uncertainties associated with the regression equations adopted in the model; 4) the uncertainty of ecotoxicological impact characterization, and 5) the variability of environmental parameters (pH and f_{OC} of agricultural soil, concentration of hydroxyl radical in freshwater, and rain rate) and direct photolysis rates. The parameters included in the Monte Carlo analysis are described in Appendix A, Section A6.

The training and validation sets used to derive the regressions adopted in the model (estimation of partition coefficients, bioconcentration factors, and biodegradation rates) were used to derive residual estimation errors between estimated and experimental data. The mean error and their probability distribution were fit into the regressions as

uncertainty parameters. Uncertainty distributions of $HC50_{EC50}$ values were estimated according to Payet parametric method (Payet 2004), which is based on the Student distribution for calculating the confidence interval on the mean. For each pharmaceutical, the maximum and minimum of the uniformly distributed photodegradation rate parameter were obtained considering the GCSOLAR results for the winter and summer seasons, the latitudes of 40 and 60°, and the maximum and minimum experimental quantum yields.

2.4 Results and discussion

2.4.1 Transport to freshwater compartment

Figure 2 shows the overall transfer fraction of pharmaceuticals to freshwater from biosolids-amended soils in function of the overall soil-water partitioning coefficient normalized by the organic carbon content, K_{OC}. Pharmaceuticals with large log K_{OC} values are strongly sorbed to solid matrices and are less likely to leach and runoff due to their low availability for transport in the solution phase. Generally, the studied compounds can be considered to have low mobility in solid matrices. However, hydrochlorothiazide and the sulfonamides sulfathiazole and sulfamethazine display moderate retention comparatively to the other compounds. For the mean agricultural soil pH 7, approximately 11% of hydrochlorothiazide appears in the anionic form, which displays reduced sorption capacity due to the negatively charged surface of organic colloids at relevant environmental pH values. Moreover, the neutral form of hydrochlorothiazide is highly hydrophilic (log K_{OW} = -0.07). The same reasoning is applied to sulfathiozole, 39% of which appears in the anionic form, and its neutral form also displays high hydrophilicity (log K_{OW} = 0.72), and to sulfamethazine, 18% in the anionic form and high hydrophilicity of its neutral form (log K_{OW} = 0.76). A zwitterionic form of sulfathiozole exists along with the anionic and neutral forms at agricultural soil pHs (for example, ≈20% at pH 7). The sorption behaviour of this form could not be estimated by the procedure adopted for the estimation of partition coefficients.

The mobility of the sulfonamides and of hydrochlorothiazide increase for higher soil pHs because the fraction of their anionic forms increases accordingly; further, the electronegativity of colloid surfaces due to ionization of hydroxides and phenolic groups also increases. However, these compounds display comparatively high

photodegradation rates in surface waters, thus short residence times in that compartment (Figure 3). As shown in Figure 4, the potential increase in the comparative impact results would be negligible for these compounds even at higher soil pHs according to the Monte Carlo analysis. Moreover, for the freshwater compartment, experimental molar absorption coefficients were obtained generally at the mean agricultural soil pH 7 except for sulfamethazine (pH=3.9) and sulfathiazole (pH=3.6). At those pH values these sulfa drugs are in their neutral form. The anionic form of these pharmaceuticals were reported to exhibit higher degradation rates than the neutral form (Boreen et al., 2004; Baeza and Knappe, 2011), therefore the freshwater impact results may be overestimated for these compounds.

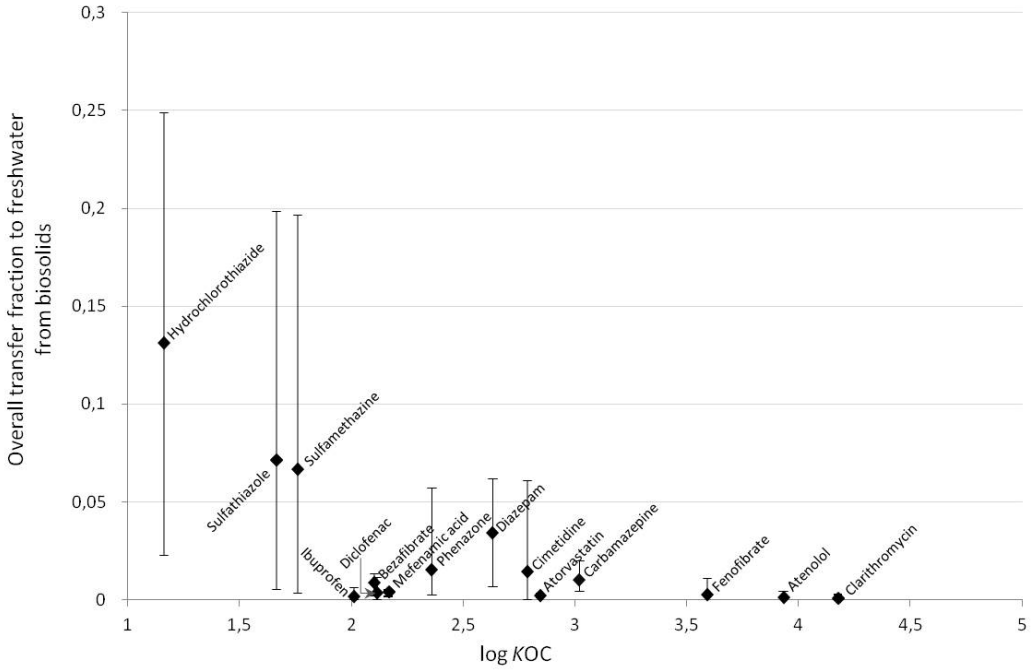


Figure 2: Probability distribution mean and 90% confidence interval of overall transfer fraction to freshwater of the detected pharmaceuticals in function of the probability distribution mean of logK_{OC}.

It should be noted that the influence on the direct and indirect photolysis rates of the dissociating properties of pharmaceuticals was disregarded in Monte Carlo analysis due to lack of data. For the interval of freshwater pHs that may be found on European surface waters, between 5.52-8.5 (Heijerick et al., 2005), the influence of dissociation on the photodegradation of the detected pharmaceuticals is yet unclear in the present study.

2.4.2 Probabilistic comparative impact results

Figure 4 shows the comparative impacts of pharmaceuticals on freshwater ecosystems. The non-steroidal anti-inflammatory mefenamic acid is the pharmaceutical with the highest probabilistic distribution mean of freshwater ecosystem impact. In a context of land application of biosolids, more knowledge on biodegradation and sorption and desorption profiles in different solid matrices, possibly based on field-scale studies, is required. Mefenamic acid is a widely used non-steroidal anti-inflammatory, and it is commonly found in effluents and biosolids (Barron et al. 2009; Kim et al. 2009a; Radjenovic et al., 2009).

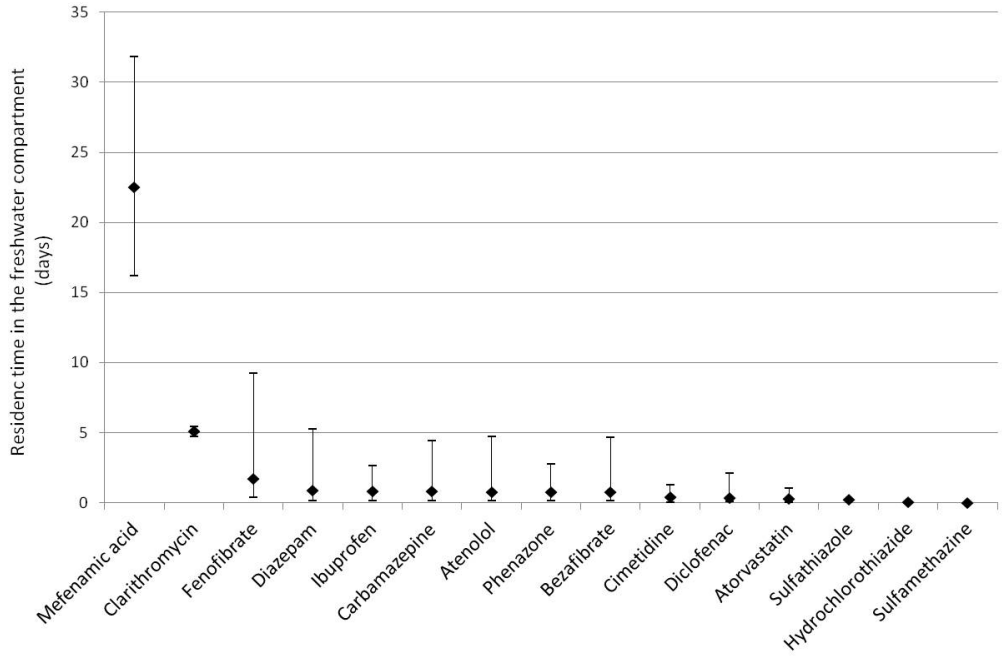


Figure 3: Probability distribution mean and 95% confidence interval of the residence time in the freshwater compartment of the detected pharmaceuticals.

In previous studies, mefenamic acid displayed high ecological risks to aquatic environments based on its actual concentration in comparison with the predicted no effect concentration (PNEC) for direct emissions to water via sewage effluent (Jones, Voulvoulis et al. 2002, Tauxe-Wuersch, De Alencastro et al. 2005). For this route of entrance in the environment, Tauxe-Wuersch et al (2005) reported a predicted environmental concentration in surface water (PEC_{sw}) for mefenamic acid of 2173 $ng.L^{-1}$, according to the scenario proposed by EMEA (2001), and a risk quotient (PEC_{sw}/PNEC) of 5 for a PNEC of 430 $ng.L^{-1}$. According to our model a PEC_{sw} of 22.8

$ng.L^{-1}$ was estimated for the biosolid-amended soils route and, by applying the same PNEC, a risk quotient of 0.05, below the threshold level of 1 for surface water according to EMEA/CHMP (2006). However, the results of the present study represent a particular geographical region in terms of detected micropollutants and mass loads in biosolids. A more comprehensive assessment is necessary to conclude about the relevance of this particular contamination route in a risk assessment context.

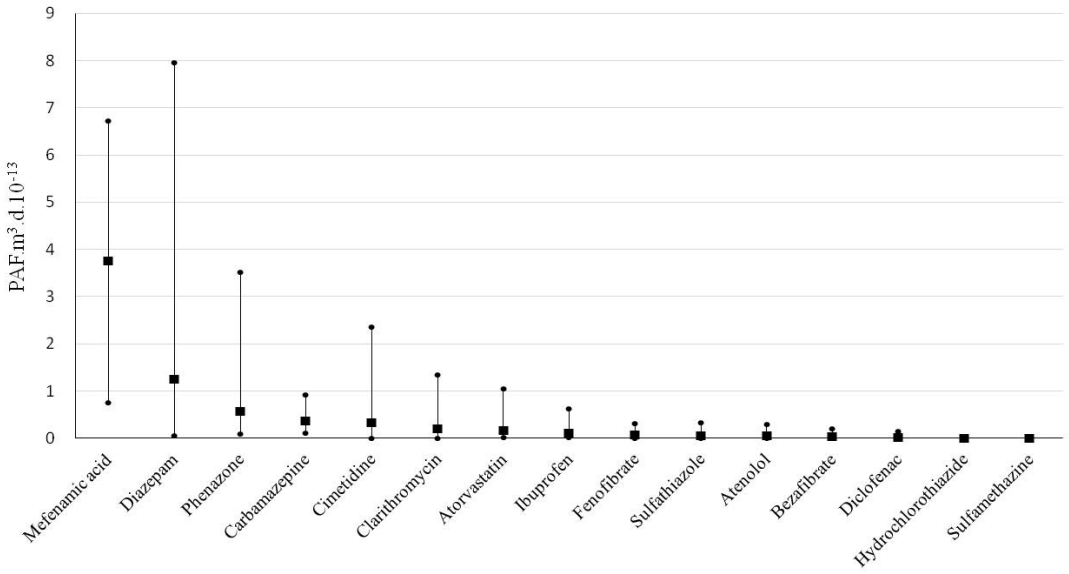


Figure 4: Probability distribution mean and 95% confidence interval of the impact on freshwater ecosystems from the detected pharmaceuticals per m^3 of dry weight biosolids.

The relevance of mefenamic acid aquatic impacts can be related to the comparatively high residence time in freshwater (Figure 3), due to a relatively slower overall removal rate, and to its high toxicity to tested species compared to other pharmaceuticals (Appendix A, Section A5). However, Werner et al. (2005) suggest that photosensitization by the excited triplet-sate DOM can contribute to the environmental degradation of mefenamic acid. The influence on the comparative impact results of this degradation mechanism is yet unknown, therefore the output results may be overestimated for these pharmaceutical. The same reasoning may be applied to atorvastatin since Razavi et al. (2011) state that the reaction with the excited state of DOM has a major significance on the photodegradation of this pharmaceutical, therefore the comparative impact result may also be overestimated for this compound. However, according to the results, atorvastatin is not a significant pharmaceutical in terms of comparative impact. The results from the sensitivity analysis suggest that the impact of mefenamic acid may be comparatively higher for higher rain rates (Table 2).

This compound is an acidic pharmaceutical that exists almost entirely in the anionic form at agricultural soil pHs, therefore displays higher availability for transport in the solution phase.

Diazepam impact results are especially sensitive to the hydroxyl radical concentration (Table 2). This suggests that the impact of this pharmaceutical may be comparatively very significant in poor nitrate-containing waters; conversely the impact would be negligible in case of high nitrate-containing waters (Figure 4). The fraction of organic carbon on agricultural soil is the most influential parameter in the estimation of phenazone impact (Table 2). The increased mobility in SOM-poor soils displayed by phenazone increases its comparative relevance to freshwater ecosystem impacts. Although this increased mobility is generally estimated for all the detected pharmaceuticals, especially for basic pharmaceuticals, phenazone shows high toxicity to tested species compared to other pharmaceuticals (Appendix A, Table 11); therefore a high comparative impact is estimated for this compound in SOM-poor soils.

This study did not account for the abiotic and biotic derivatives of parent compounds. Nevertheless, microbial transformations and abiotic degradations may produce by-products that are more harmful than the parent compounds (Andreozzi et al., 2003; Boreen et al., 2003; Isidori et al, 2005). For example, Schmitt-Jansen et al. (2007) suggested a higher toxicity potential for phototransformation products compared to diclofenac. The effects of including abiotic and biotic derivatives on the results of this study are yet unclear. Moreover, human or animal metabolism of parent compounds may also affect the overall toxicity of pharmaceuticals (Escher et al., 2006).

2.4.3 Contribution to variance of impact results

Generally, for most compounds the comparative impact results are more sensitive to the uncertainty of environmental fate properties estimation, particularly K_{OC}, and of ecotoxicological impact characterization ($HC50_{EC50}$ values) rather than of the variability of environmental characteristics, such as agricultural soil pH or rain rate (Table 2). Narrower estimates may be possible by increasing the number of species tested in the calculation of ecotoxicity factors, that is, by increasing the degrees of freedom of the Student uncertainty distribution of $HC50_{EC50}$ values, especially for mefenamic acid, atorvastatin and clarithromycin. However, the results of the uncertainty analysis of the model indicate that the estimation of K_{OC} was found influential for most compounds.

Table 2: Contribution of model parameters to impact results variance for each compound. Negative indices indicate that an increase in the parameter is associated with a decrease in the output result. *Exp* denotes experimental values.

	Sensitivity indices for the comparative impact results for each compound (in %)														
Parameter	Ibuprofen	Diclofenac	Mefenamic acid	Phenazone	Bezafibrate	Fenofibrate	Atorvastatin	Diazepam	Carbamazepine	Cimetidine	Clarithromycin	Sulfamethazine	Atenolol	Sulfathiazole	Hydrochlorothiazide
$k_{biodeg,\ water}$	-	0.0	-	-1.6	-0.5	-1.5	-11.6	-	-	-0.8	-3.7	-0.3	-9.2	-0.5	0.0
$k_{biodeg,\ soil}$	-	-	0.0	-4.1	0.0	0.0	-0.2	-4.1	-	0.0	-0.2	0.0	-0.1	-0.2	0.0
$k_{biodeg,\ biosolids}$	-2.4	-0.1	0.0	-0.2	0.0	-1.0	-1.4	0.0	0.0	-0.2	-1.7	0.0	-1.0	0.0	-1.0
$k_{photodegradation,\ water}$	0.0	-33.4	-5.6	-0.1	0.0	-	-2.4	0.0	0.0	-	-6.7	-40.8	0.0	-45.1	-66.6
K_{OW} (KOWWIN v1.67a)	-	-	-	-	0.0	0.0	0.0	-	-	0.0	-	-3.6	-4.9	-	-0.3
K_{OC} *(*KOCWIN v2.0)	-	-	-	-	-	-85.9	-	-	-	-66.7	-	-	-	-0.7	-3.9
K_{OC} (acids regression)	-	-45.9	-30.3	-	-22.7	-	-	-	-	-	-	-30.9	-	-42.8	-20.5
K_{OC} (bases regression)	-	-	-	-0.1	-	-	-	-	-	-1.8	-62.2	-	-55.2	-	-
BCF_{fish} (BCFBAF v3.00)	-	-	-	-	-	0.0	-	-	0.0	-	-	-	-	-	-
BCF_{fish} (acids regression)	0.0	0.0	0.0	-	0.0	-	0.0	-	-	-	-	0.0	-	0.0	-0.1
BCF_{fish} (bases regression)	-	-	-	0.0	-	-	-	0.0	-	0.0	0.0	-	0.0	-	-
$HC50_{EC50}$	-12.3	-12.8	-25.2	0.0	-3.3	-4.6	-51.9	-8.5	-4.6	-1.2	-20.8	-6.9	-11.1	0.0	0.0
exp K_{OC}	0.0	-	-	0.0	-	-	0.0	-3.9	-1.2	-	-	-	-	-	-
exp $k_{biodeg,\ water}$	0.0	-	-0.8	-	-	-	-	-	0.0	-	-	-	-	-	-
exp $k_{biodeg,\ soil}$	-66.9	0.0	-	-	-	-	-	-	0.0	-		-	-	-	-
exp $k_{OH,\ water}$	0.0	-	-	0.0	-0.8	0.0	0.0	-1.0	-9.9	0.0	-	-	0.0	-	0.0
[˙OH] in water	0.0	-	-	0.0	-69.3	0.0	0.0	-68.9	-60.4	0.0	-	-	-14.5	-	0.0
pH $_{agricultural\ soil}$	0.0	2.6	10.0	0.0	0.9	0.0	0.0	0.0	-	-18.3	0.0	9.6	0.0	1.8	-1.0
foc $_{agricultural\ soil}$	-17.4	-5.1	-4.7	-91.0	-2.4	-5.9	-23.7	-14.1	-23.8	-9.8	-4.8	-7.5	-3.8	-8.6	-6.5
Rain rate	0.4	0.0	22.5	2.7	0.0	0.9	8.7	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0

This suggests the limited predictive power of the regressions used to describe the pH dependence of the K_{OC} of dissociating compounds, at least in the particular context of this study, particularly in case of basic pharmaceuticals with like clarithromycin and atenolol. The driving force behind the strong sorption of cations may be electrical attraction since, at the same lipophilicity, the sorption of cations is stronger than of neutral bases, making it unlikely that the process behind is lipophilic sorption (Franco and Trapp, 2008). These regressions are not sufficiently accurate to predict pH-dependent sorption of organic bases because they suffer from the following limitations: 1) they do not consider unusual ratios of organic carbon to clay or other adsorbent materials because the method assumes correlated amounts of clay and organic carbon; 2) they do not address the effects of complexation, i.e. the binding of organic ions to ligands of opposite charge, and 3) they consider the impact of pH on the speciation of the molecule (sorbate), but they do not consider the impact on the soil surface chemistry (sorbent), where the surface of organic colloids is negatively charged because of ionization of hydroxides and phenolic groups. The more complex behaviour of bases and the difficulty of improving model predictions have already been observed (Kah and Brown, 2007; Franco et al., 2009). It should be noted that others sources of uncertainty not included in the analysis may be important. Issues such as the influence on the direct and indirect photolysis rates of the dissociating properties of pharmaceuticals, already referred in Section 2.4.1, the acute-to-chronic data extrapolation, and the application of a linear dose-response curve for aquatic ecotoxicity effect factors calculation are yet unclear in the present study regarding their uncertainty. Moreover, the assumption of homogenous compartments for such complex media as soil or water represents a further uncertainty, as a chemical entering these compartments is assumed to immediately dilute perfectly within the volume.

2.5 Conclusions

Treatment lines in conventional WWTPs do not adequately remove PhACs. These microcontaminants are found not only in the aqueous phase but also in the solid phase. The application of biosolids to land represents another input to the environment. This study modelled the environmental fate and ranked the potential impact on aquatic ecosystems of pharmaceuticals, accounting for their dissociating properties, detected and quantified in biosolids which are used as soil amendments on agricultural fields.

Generally, the pharmaceuticals were considered to have low mobility in the regional EU model. The detected sulfonamides and hydrochlorothiazide displayed comparative moderate retention in solid matrices and, therefore, higher transfer fractions from biosolids to the freshwater compartment. However, the residence times of these pharmaceuticals in freshwater were estimated to be short due to abiotic degradation processes. The non-steroidal anti-inflammatory mefenamic acid had the highest probabilistic distribution mean of freshwater ecosystem impact and warrants further investigation.

The estimation of the solid-water partitioning coefficient was generally the most influential parameter of the probabilistic comparative impact assessment. Nevertheless the addition of estimated uncertainties, pharmaceuticals of greater potential of concern may be identified, depending on the geographical conditions of pollutant mass loads in biosolids, as well as the most sensitive fate processes.

This approach, starting from the most complex route in terms of fate modelling, pretends to be straightforward and transparent solution that can be applied to all routes of entrance in the environment of micropollutants, probably more relevant in terms of ecological risk. In this trend, it should be noted that freshwater ecosystem impacts of micropollutants in case of using reclaimed effluent water in agricultural soils can be assessed with Equation 1 by applying the fate factor to freshwater from an emission to agricultural soil, $FF_{ag,fw}$, calculated by means of the fate matrix in Appendix A, Section A1. Likewise, freshwater ecosystem impacts of pharmaceuticals in wastewater treatment effluents can be assessed by applying $FF_{fw,fw}$. Moreover, the overall procedure is consistent with life cycle impact assessment methods (LCIA), such as USEtox, and can be adapted for life cycle assessment purposes. Advanced effluent treatments and alternative biosolids applications can also be compared by means of LCA, as well as the entire life cycle of a pharmaceutical can be compared with that of new chemical designs.

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3. Accounting for the dissociating properties of organic chemicals in LCIA: an uncertainty analysis applied to micropollutants in the assessment of freshwater ecotoxicity

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3.1 Abstract

In Life Cycle Impact Assessment (LCIA) models, the sorption of the ionic fraction of dissociating organic chemicals is not adequately modelled because conventional non-polar partitioning models are applied. Therefore, high uncertainties are expected when modelling the mobility, as well as the bioavailability for uptake by exposed biota and degradation, of dissociating organic chemicals. Alternative regressions that account for the ionized fraction of a molecule to estimate fate parameters were applied to the USEtox model. The most sensitive model parameters in the estimation of ecotoxicological Characterization Factors (CFs) of micropollutants were evaluated by Monte Carlo analysis in both the default USEtox model and the alternative approach. Negligible differences of CFs values and 95% confidence limits between the two approaches were estimated for direct emissions to the freshwater compartment; however the default USEtox model overestimates CFs and the 95% confidence limits of basic compounds up to three orders and four orders of magnitude, respectively, relatively to the alternative approach for emissions to the agricultural soil compartment. For three emission scenarios, LCIA results show that the default USEtox model overestimates freshwater ecotoxicity impacts for the emission scenarios to agricultural soil by one

order of magnitude, and larger confidence limits were estimated, relatively to the alternative approach.

Keywords: USEtox, LCA, Freshwater ecotoxicity, Micropollutants; Dissociating organics, Risk Assessment

3.2 Introduction

Sorption of chemicals released to the environment to solid surfaces is a dominating process driving their distribution in soil, surface waters and sediments. Therefore, the solid-water partitioning coefficient, K_d, is a key parameter to model the mobility and fate of chemicals in the environment. Many transport processes in environmental systems, as well as bioavailability for uptake by exposed biota and degradation, are directly related to K_d. Experimental K_d values are often not available in the literature. For example, in the USEtox LCIA model eighty-three percent of the chemicals present in the organic chemicals database have estimated K_d values. The estimation of this parameter in LCIA models, such as IMPACT2002+, USES-LCA, EDIP 2003 or USEtox, is based on conventional non-polar partitioning models correlated only to the octanol–water partition coefficient, K_{OW}, that do not adequately model the mechanism of sorption of dissociating organic chemicals to organic colloids in soil, which consists of organic matter and inorganic clay minerals. These correlations are particularly true for lipophilic compounds, however, the driving force behind the sorption of cations may be electrical attraction to the negatively charged sorption sites in soil since, at the same lipophilicity, the sorption of cations is stronger than of neutral bases, making it unlikely that the process behind is lipophilic sorption (Franco and Trapp, 2008). Recently, Droge and Gross (2012) cited an ample number of recent studies that have shown that the dominant sorption process for organic cations is cation-exchange at negatively charged sorption sites in natural organic matter and whole soils/sediments. The sorption of anions generally is moderate but not negligible, even for very hydrophilic anions (Franco et al., 2009). Therefore, a different degree of anion, cation, and neutral molecule sorption can be expected, with cations showing the highest potential for sorption. Moreover, other fate parameters depend upon the dissociation of the molecule, such as the Bioconcentration Factors (BFs) or the partitioning coefficient between dissolved organic carbon and water, K_{DOC}.

In the USEtox model (Rosenbaum et al., 2008), an ecotoxicological Characterization Factor (CF) of a chemical in freshwater is the product between a fate factor, that represents the persistence in the environment described by processes such as degradation and inter-compartment transfer, an exposure factor, that represents the bioavalability (i.e, the fraction of chemical dissolved in the freshwater compartment), and an effect factor. Twenty-one percent of chemicals in the USEtox organics database are fifty percent or more in ionic phase at physiological pH (i.e., acids $pK_a < 7.4$, bases $pK_a > 7.4$). Therefore, CFs of these chemicals are labelled in the model as interim whereas relatively high uncertainty is expected. Moreover, forty-five percent of chemicals, at least those for which pK_a values are available, suffer any degree of dissociation at the environmental pH interval of the model's continental scale (3.2-8.5 (Reuter et al., 2008)).

The aims of this study were 1) to apply to the USEtox model alternative regressions that account for the ionized fraction of a molecule to estimate fate parameters 2) to identify the most sensitive model parameters in the estimation of CFs by Monte Carlo analysis in both the default USEtox model and the alternative approach, and 3) to propagate uncertainties and compare both approaches in the impact assessment of different emissions scenarios to different environmental compartments.

3.3 Methodology

Three emission scenarios to freshwater were considered in the this study: a) direct emission to the freshwater compartment of a Wastewater treatment plant (WWTP) effluent, b) direct emission to agricultural soil by using WWTP effluent as reclaimed water, and c) emission to agricultural soil by using WWTP biosolids as soil amendment. The inventory data were gathered from a Neptune FP6 Project report [(Larsen et al. 2010a) (Appendix B, Table 13). It contains twenty micropollutants, thirteen of which are acidic compounds, six basic compounds and one neutral compound (carbamazepine). For the biosolids-amended soil scenario, in order to account for differences in the sorption, desorption, and degradation of compounds between the biosolid and soil matrices, the biosolids-amended soil compartment was modelled as a biosolids compartment nested in the agricultural soil compartment (Figure 1).

The multimedia model USEtox was chosen in the present study because it results from a consensus building effort, under the auspices of UNEP and SETAC, amongst modellers

and, hence, the underlying principles reflect common and agreed recommendations from these experts; furthermore it is the recommended LCIA model by the ILCD (International Reference Life Cycle Data System) Handbook of the European Union (EU, 2011). In the USEtox model, the ecotoxicity factor (effect factor), which expresses the change in the Potentially Affected Fraction (PAF) species that experiences an increase in stress for a change in contaminant concentration, in $PAF \cdot m^3 \cdot kg^{-1}$, is based on the Hazardous Concentration (HC) of a chemical affecting 50% of a tested species over their chronic Effect Concentration affecting 50% of tested individuals (EC50), also called $HC50_{EC50}$. Experimental EC50s were gathered from the ECOTOX database (USEPA, 2007) and literature reports. To complete missing experimental data, it was included Quantitative Structure Activity Relationship (QSAR) data using the software program ECOSAR v1.00 (Nabholz and Mayo-Bean, 2009).

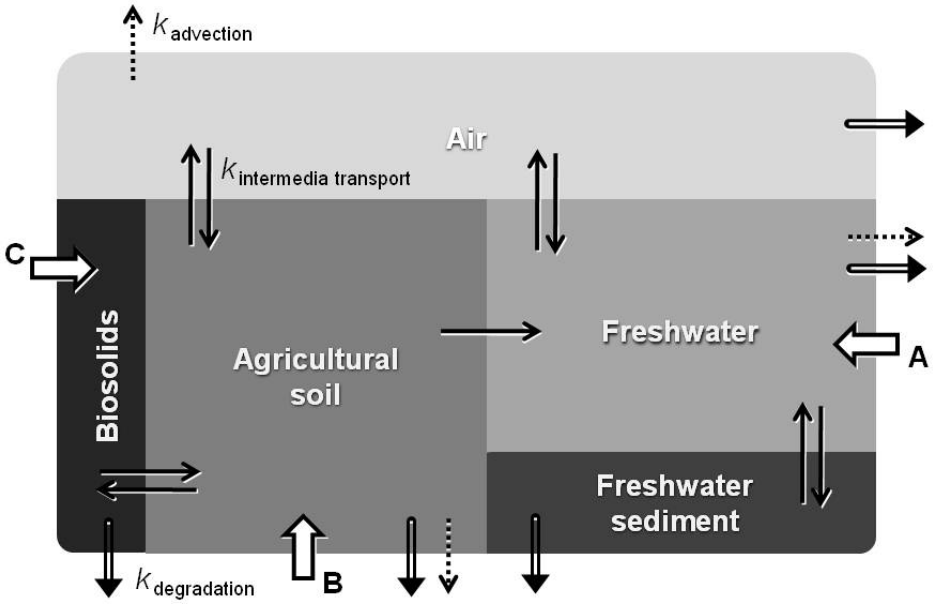

Figure 5: Five-compartment system for the dissipation of micropollutants from A) direct emission to freshwater of WWTP effluent, B) emission to agricultural soil of WWTP effluent as reclaimed water, C) emission to agricultural soil of biosolids as soil-amendment. In a given environmental compartment, bold arrows represent intermedia transport rates, dashed arrows represent advective transportation rates out the system, and double-line arrows represent degradation rates.

The alternative regressions applied in the alternative approach, as well as estimation routines of abiotic degradation rates for both approaches, and the parameters included in the Monte Carlo analysis are described in sections below.

3.3.1 Partition coefficients

In the USEtox model v1.01 the values of experimental octanol–water partition coefficient, K_{OW}, are obtained from the Estimation Programs Interface (EPI) Suite™ (USEPA, 2008) and, in case unavailability, they are estimated by the software KOWWIN v1.67a (USEPA, 2008), which estimates K_{OW} values corrected for the neutral species ($K_{OW,n}$). A different approach was followed for the alternative approach in the case of dissociating compounds. K_{OW} values published in the literature are often the sum of the K_{OW} values of neutral and ionic molecules at the experimental pH, that is, they apparent K_{OW} values (D_{OW}). Therefore, to treat the ionic and neutral fractions separately, experimental K_{OW} values of the neutral species requires a correction of the pH at which D_{OW} was determined, often not reported explicitly. Therefore, for dissociating compounds at environmental pH, estimated values are preferred to measured values. The software KOWWIN v1.67a™ (USEPA, 2008) was used to estimate K_{OW} values corrected for the neutral species since the regressions applied in the present study to estimate other partition coefficients are correlated to $K_{OW,n}$.

The soil-water partitioning coefficient normalized by the organic carbon content, K_{OC} in $l \cdot kg^{-1}$, is estimated in the USEtox model, if no experimental data is available, by KOCWIN v2.0™ using the first-order Molecular Connectivity Index (MCI) (USEPA, 2009), which is applicable to neutral compounds or to the neutral fraction of dissociating compounds as long as $K_{OW,n}$ is used in the regression. In our study experimental K_{OC} values were preferred for neutral and, in case of dissociating compounds, only if these remain essentially in one charged state or neutral the environmental relevant pHs (Appendix B, Table 14). Otherwise, due to the variability of the fractions of neutral and ionic species, such K_{OC} values obtained at a given environmental pH would not be suitable for the interval of environmental pH values considered in this study. For these compounds the soil-water partitioning coefficients are correlated to $K_{OW,n}$, pK_a and pH by using the Franco and Trapp regression equations (Franco and Trapp, 2008):

$$K_{OC} = f_n \cdot 10^{(0.54 \log K_{OW,n} + 1.11)} + (1 - f_n) \cdot 10^{(0.11 \log K_{OW,n} + 1.54)} \text{ for acids} \quad (3.1)$$

$$K_{OC} = f_n \cdot 10^{(0.37 \log K_{OW,n} + 1.70)} + (1 - f_n) \cdot 10^{\left(pK_a^{0.65} \cdot f^{0.14}\right)} \text{ for bases} \quad (3.2)$$

where pK_a is the negative logarithm ($\log_{10}$) of the dissociation constant, f is $K_{OW,n}$ /($K_{OW,n}$ +1), and f_n is the fraction of neutral molecules according to the *Henderson-Hasselbalch* equation:

$$f_n = \frac{1}{1 + 10^{i(\mathrm{pH} - \mathrm{p}Ka)}} \qquad (3.3)$$

where i is the valence number, which is +1 for acids and -1 for bases. The above equations are applicable only to monovalent acids and bases; for compounds with two cationic or anionic dissociating groups, only the first dissociation was considered. p*K*a values were taken from the EPI Suite™ (USEPA, 2008). For compounds without experimentally verified pK_a values, values were estimated using the SPARC software program (Carreira et al., 2009), in which pK_a values are given for –OH, -COOH, or the highest NH_x functional group.

In the USEtox model the partitioning coefficient of organic pollutants between dissolved organic carbon and water, K_{DOC} in l·kg^{-1}, is estimated using the predictive relationship of $K_{DOC} = 0.08 \times K_{ow}$ for non-ionic compounds (Burkhard, 2000). In the alternative approach, for dissociating substances, it is assumed a K_{DOC}/K_{OC} ratio of solutes equal to one. This assumption is valid when the nature of the dissolved organic matter released from the soil/sediment bulk organic matter is similar to that of the soil/sediment bulk organic matter (Ding and Wu, 1995).

3.3.2 Bioconcentration factor in fish

Uptake by exposed biota in environmental systems is a relevant fate process in a human toxicological impact or risk assessment. However, bioconcentration factor in fish, BCF_{fish} in l·kg^{-1}, is a parameter used in the USEtox model to calculate the exposure factor, i.e., the fraction of chemical dissolved in the freshwater compartment. Therefore, it was included in the analysis. BCF_{fish} is the concentration of a chemical in the fish divided by the dissolved concentration of the chemical in the surrounding water. In the USEtox model the estimation of BCF_{fish} is obtained using K_{OW} regression-based estimates from the BCFBAF v3.00 software program (USEPA, 2008). In our study, for dissociating compounds at the freshwater environmental pH interval, the regression equations of Fu et al. (Fu et al., 2009) were applied because they allow variations in the environmental pH:

$$\mathrm{BCF} = f_n \cdot 10^{(0.64 \log K_{OW,n} - 0.12)} + f_d \cdot 10^{(0.37 \log K_{OW,n} + 0.06\, \mathrm{p}Ka - 0.51)} \text{ for acids} \qquad (3.4)$$

$$\mathrm{BCF} = f_{\mathrm{n}} \cdot 10^{(0.62 \log K_{\mathrm{OW,n}} - 0.15)} + f_{\mathrm{d}} \cdot 10^{(0.28 \log K_{\mathrm{OW,n}} + 0.84 \; - 0.07 \; \mathrm{p}Ka)} \text{ for bases (3.5)}$$

The equations are valid in the range -0.36 < p*K*a < 10.61. Therefore, the minimum or maximum p*K*a values outside the calibrated range were applied.

3.3.3 Degradation

Abiotic degradation mechanisms in the freshwater compartment are important elimination processes for most compounds present in the inventory. The USEtox model does not address estimation routines for these mechanisms, therefore the following models and assumptions were applied in both the alternative approach and the default USEtox to estimate direct and indirect photodegradation rates.

Experimental photolysis half-lives based on the literature may not reflect consistently a given geographical scale due to differences in experimental conditions, whereas photodegradation rates depend on the intensity of solar irradiation, water depth, organic matter composition, eutrophic conditions, latitude and season (Boreen et al., 2003; Vione et al., 2009), thus introducing uncertainty. In the present study, average full day direct photolysis rates for winter and summer seasons were calculated by GCSOLAR (USEPA, 1999). Experimental molar absorption coefficients in function of the UV/VIS wavelength range (ελ, in L.mol-1.cm-1) were gathered in the literature (Doll and Frimmel, 2003; Packer et al., 2003; Werner et al., 2005; Liu and Williams, 2006; Pereira et al. 2007; Vione et al., 2009; Baeza and Knappe, 2011; Razavi et al., 2011; Luo et al., 2012) as well as experimental quantum yields of compounds (Appendix A, Section A4). Rates were estimated for a well-mixed water layer of 50cm thickness (Tixier et al., 2002). Absorption attenuation coefficients of pure water in function of wavelength were assumed for the water body, as well as a depth of 3m (EC, 2003), the latitude range of 40°-60°, and assuming a perfectly clear sky. Ozone layer thickness values were obtained from satellite data (NASA, 2011). For compounds without experimental quantum yields available (atenolol), maximum and minimum possible direct photolysis rates were estimated by assuming quantum yield equal to one and zero, respectively.

Indirect photolysis reactions occur due to the presence of chemical transients generated by natural water constituents. The hydroxyl radical, ˙OH, is the most reactive of those

intermediates due to its non-selective and highly electrophilic nature (Lam and Mabury, 2005) and the only transient considered in this study. Pseudo-first order rates were calculated by multiplying bimolecular rate constants (k_{OH}, in M-1s-1) for the reaction with ˙OH (Appendix B, Table 14) by the hydroxyl radical concentration, reported to be present at 10^{-14}–10^{-17} M in surface waters (Lam et al., 2003).

Currently, the understanding of the effects of the biosolid matrix on the persistence of compounds in agricultural soils is limited (Monteiro and Boxall, 2009), therefore, for the scenario of emission to agricultural soil from biosolids application as soil amendment, biodegradation rates in biosolids were estimated by extrapolation from biodegradation rates in soils. The calculation of the probabilistic characterization factors includes an interval of extrapolation factors (Table 3).

3.3.4 Monte Carlo Analysis

Monte Carlo analysis was conducted on the estimation of characterization factors in both approaches. The parameters included in the Monte Carlo analysis are described in Table 3. The analysis includes:

1) the variability of environmental parameters (fraction of organic carbon, f_{OC}, in agricultural soil, pH of freshwater and agricultural soil, concentration of hydroxyl radical in freshwater, and rain rate) and of direct photolysis rates in the USEtox continental scale.
2) the uncertainty of ecotoxicological impact characterization. Uncertainty distributions of $HC50_{EC50}$ values were estimated according to Payet parametric method (Payet 2004) which is based on the Student distribution for calculating the confidence interval on the mean.
3) the uncertainties associated with the regression equations adopted in the model to estimate partition coefficients, BCFs and biodegradation rates.
4) the extrapolation of parameter values from one compartment to another (biodegradation rates in biosolids) and from other parameter values (K_{DOC} from K_{OC}).
5) The experimental parameter values (partition coefficients, biodegradation half lives in water and soil, and bimolecular hydroxyl radical rate constants). The geometric mean and the geometric standard deviation of experimental values were set as uncertainty parameters assuming a lognormal distribution.

The training and validation sets used to derive the regressions adopted in the model were used to derive residual estimation errors between estimated and experimental data (Franco and Trapp, 2008; USEPA, 2008; Fu et al., 2009; USEPA, 2009). The training and validation sets of Franco and Trapp (Franco and Trapp, 2008) used to derive regression to predict K_{OC} of acids and bases were used to generate residual estimation errors of the KOCWIN software applied to dissociating substances in the default USEtox model (parameters *a6* and a*7* in Table 3). Likewise, the training and validation sets of Fu et al. (Fu et al., 2009) used to derive regression to predict BCF_{fish} of acids and bases were used to generate residual estimation errors of the BCFBAF software applied to dissociating substances in the default USEtox model (parameters *a11* and a*12* in Table 3). The mean error and their probability distribution were fit into the regressions as uncertainty parameters (parameters *a3* to *a15* in Table 3). It should be noted that experimental K_{OC} values on the Franco and Trapp training and validation sets were obtained at the pH 4.5 for bases and 5.8 for acids. Nevertheless, it is assumed constant uncertainty parameters for the environmental pH interval. Experimental biodegradation rates gathered in the literature of micropollutants were used to derive residual estimation errors of the procedure adopted in USEtox to estimate biodegradation rates.

In the USEtox model, uncertainty parameters on the estimation of the partitioning coefficient between dissolved organic carbon and neutral organic pollutants in water, K_{DOC} in $l \cdot kg^{-1}$, are provided by Burkhard (Burkhard, 2000). For dissociating substances, it is assumed a K_{DOC}/K_{OC} ratio of solutes equal to one. However, if the dissolved organic matter is more hydrophilic than the soil/sediment bulk organic matter, they tend to escape from soil/sediment particles to the aqueous phase, and the ratios of K_{DOC}/K_{OC} of these solutes will be less than one (Ding and Wu, 1995). In addition, when the sources and nature of the dissolved organic matter and soil/sediment organic matter are different, the ratios of K_{DOC}/K_{OC} of solutes will have a broad range. The broader range of K_{DOC}/K_{OC} ratios estimated by Ding and Wu (1995) is assumed in the Monte Carlo analysis (parameter *a16*). The environmental variability of suspended matter and dissolved organic carbon concentration in freshwater was found to be negligible in terms of sensitivity to CFs values.

In ecotoxicological impact characterization, the inherent uncertainty of QSAR data from the software program ECOSAR was not included on the overall uncertainty of ecotoxicological impact characterization.

Table 3: Probability distributions for the 16 regression error parameters (*a1-a16*), experimental K_{OC} values, experimental biodegradation rates ($k_{biodeg, water}$, $k_{biodeg, soil}$), experimental bimolecular ˙OH rate constants in water ($k_{OH, water}$), and environmental parameters (pH and *foc* in agricultural soil, [˙OH] in freshwater, and rain rate) included in the Monte Carlo simulation. The relation of the calibration coefficients to the actual model parameter values is shown in the last column. S*Dev* denotes standard deviation, *exp* denotes experimental values, *CI* denotes confidence interval, and *DF* denotes degrees of freedom. Asterisks (*) denote base case parameter values.

Parameter	Distribution	Mean	Spread	Relation to model parameters
a1	Uniformal	1	[0.5, 1.5]	$k_{biodeg, biosolids} = k_{biodeg, soil} \times a1^{-1}$
a2	Normal	-3.18×10^{-7}	*Sdev*=2.63×10^{-7}	$k_{biodeg, soil} = k_{biodeg, soil}^{*} \pm a2$
a3	Normal	1.26×10^{-7}	*Sdev*=4.25×10^{-8}	$k_{biodeg, water} = k_{biodeg, water}^{*} \pm a1$
a4	Normal	-3.15×10^{-4}	*Sdev*= 4.41×10^{-1}	log K_{OW}= log $K_{OW}^{*} \pm a4$ (KOWWIN v1.67a)
a5	Normal	-9.84×10^{-2}	*Sdev*= 5.48×10^{-1}	log K_{OC}= log $K_{OC}^{*} \pm a5$ (KOCWIN v2.0, neutral compounds)
a6	Normal	-1.61×10^{-2}	*Sdev*= 1.13×10^{0}	log K_{OC}= log $K_{OC}^{*} \pm a6$ (KOCWIN v2.0, acidic compounds)
a7	Normal	-7.64×10^{-1}	*Sdev*= 1.19×10^{-0}	log K_{OC}= log $K_{OC}^{*} \pm a7$ (KOCWIN v2.0, basic compounds)
a8	Normal	2.23×10^{-2}	*Sdev*= 5.36×10^{-1}	log K_{OC}= log $K_{OC}^{*} \pm$ ***a8*** (acids regression)
a9	Normal	4.45×10^{-2}	*Sdev*= 4.74×10^{-1}	log K_{OC}= log $K_{OC}^{*} \pm a9$ (bases regression)
a10	Normal	1.13×10^{-3}	*Sdev*= 5.11×10^{-1}	log BCF_{fish} = log $BCF_{fish}^{*} \pm a10$ (BCFBAF v3.00, neutral compounds)
a11	Normal	4.50×10^{-1}	*Sdev*= 8.97×10^{-1}	log BCF_{fish} = log $BCF_{fish}^{*} \pm a11$ (BCFBAF v3.00, acidic compounds)
a12	Normal	5.54×10^{-1}	*Sdev*= 2.01×10^{-1}	log BCF_{fish} = log $BCF_{fish}^{*} \pm a12$ (BCFBAF v3.00, basic compounds)
a13	Normal	5.15×10^{-2}	*Sdev*= 5.41×10^{-1}	log BCF_{fish} = log $BCF_{fish}^{*} \pm a13$ (acids regression)
a14	Normal	2.65×10^{-2}	*Sdev*= 6.61×10^{-1}	log BCF_{fish} = log $BCF_{fish}^{*} \pm a14$ (bases regression)
a15	Normal	-1.11	*Sdev*= 6.59×10^{-1}	log K_{DOC} = log $K_{DOC}^{*} \pm a15$ (Burkhard regression, neutral compounds)
a16	Uniformal	1	[0.04, 5.9]	$K_{DOC} = K_{OC} \times a16$ (dissociating compounds)
$k_{photodegradation, water}$	Uniformal		[min, max]	
$logHC50_{EC50}$	Student	$logHC50_{EC50}$	95%*CI* = $\pm \frac{1}{\sqrt{n}} \times t_{n-1}^{0.05} \times Sdev$(LogEC50) [a] *DF*= n-1, where *n* is the size of sample (or number of species tested)	
exp K_{OC}	Lognormal		*b*	
exp $k_{biodeg, water}$	Lognormal		*c*	
exp $k_{biodeg, soil}$	Lognormal		*c*	
exp $k_{OH, water}$	Lognormal		*c*	
[˙OH] in water (M)	Uniformal		$[10^{-14}, 10^{-17}]$ (min, max)	
pH $_{agricultural soil}$	Triangular	7	[3.2, 8.5] (min, max) (Reuter et al., 2008)	
pH $_{freshwater}$	Triangular	7	[5.5, 8.3] (min, max) (Heijerick et al., 2005)	
foc $_{agricultural soil}$	Triangular	0.02	[0.01, 0.1] (min, max) (Jones et al., 2005)	
Rain rate (mm/year)	Triangular	700	[250, 1500] (min, max)	

[a] $t_{n-1}^{0.05}$ is the *t* value from the student table for a 95% confidence interval with *n-1* degree of freedom, and *Sdev* is the Standard deviation of the logEC50s.
[b] Experimental values are shown in Appendix B, Table 14.
[c] Experimental values are shown as half-lives in Appendix B, Table 14.

The uncertainties of GCSOLAR model estimates were not treated in the study but rather the variability of direct photodegradation rates considering the geographical scale. Therefore, the maximum and minimum of the uniformly distributed photodegradation rate parameter was obtained considering the GCSOLAR results for the winter and summer seasons, the latitudes of 40° and 60°, and the maximum and minimum experimental quantum yields.

3.4 Results and Discussion

Table 4 shows the CFs results and the $95^{\%}$ confidence interval for the three emission scenarios and for both approaches. Minor differences of CFs values and of 95% confidence limits between the two approaches are estimated for direct emissions to the freshwater compartment. However, the default USEtox model overestimates CFs of basic compounds relatively to the alternative approach for emissions to the agricultural soil compartment. The differences are as large as 3 orders of magnitude for metropopol and propanolol and 2 orders of magnitude for atenolol and clarithromycin. Larger 95% confidence limits are estimated for basic compounds in the default USEtox model. In the upper endpoint, an increase of 4 orders of magnitude is estimated for propanolol, 3 orders of magnitude for metropropol and 2 orders of magnitude for atenolol, clarithromyin and clindamycin. In the lower endpoint, a decrease of 3 orders of magnitude is estimated for clarithromyin, metropropol and for the acidic pharmaceutical naproxen.

Freshwater ecotoxicity probabilistic CF values of direct emissions to freshwater are mainly sensitive to the variability of abiotic degradation rates and to the uncertainty of ecotoxicological impact characterization ($HC50_{EC50}$ values) (Appendix C, Table 15). The uncertainty of sorption partitioning coefficients and BCFs estimation is negligible and explains the minor differences of CFs values and 95% confidence limits between the two approaches for direct emissions. However, for indirect emissions, CF results are more sensitive to the uncertainty of environmental fate properties estimation, particularly K_{OC}, and of $HC50_{EC50}$ values rather to the variability of experimental fate properties or environmental characteristics (Appendix C, Table 16, sensitivity indices are not shown for emission scenario from biosolids because they do not differ significantly). The results of the Monte Carlo analysis of both approaches indicate that the estimation of K_{OC} was found influential for most compounds, particularly in the case

of the default USEtox model. This suggests the limited predictive power of regressions that do not account for the sorption of the cationic fraction of organic bases, particularly in case of basic compounds with p*K*a>4 (bases for which the cation dominates the sorption). The underestimation of sorption to solid matrices in case of indirect emissions to freshwater, which overestimates the availability for transport in the solution phase, largely overestimates CFs of basic compounds relatively to the alternative approach and results in larger confidence limits.

Figure 6 shows the freshwater ecotoxicity impacts for the three emission scenarios and for both approaches. For a direct emission to freshwater, as expected from estimated CF values, negligible differences between approaches are estimated. Nevertheless, the USEtox model overestimates approximately by one order of magnitude the impacts of indirect emissions relatively to the alternative approach. Moreover, confidence limits are substantially reduced in the alternative approach (Table 5). In the case of emission to agricultural soil of WWTP effluent as reclaimed water, USEtox impact results are mainly sensitive to the propagation of the uncertainty and variability of the basic compounds clarithromycin and propanolol CFs (sensitivity indices of 43.9% and 24.6%, respectively). On the other hand, by estimating the electrical adsorption of the cationic species in the fate and transport modelling of these compounds, which are almost completely dissociated at environmental relevant pH's, the total impact results of the alternative approach are one order of magnitude lower and the confidence limits are mainly sensitive to the propagation of the uncertainty and variability of the acidic compounds sulfamethazole and primidone CFs (sensitivity indices of 53.7% and 24.5%, respectively). Moreover, in the alternative approach, ecotoxicity impacts are entirely dominated by the anionic compounds and by the neutral carbamazepine. Therefore, in freshwater ecotoxicity assessment, it may be more realistic to neglect indirect emissions of basic compounds with pKa>4, which is the case for the bases present in the inventory data, when using LCIA models that do not account for the dissociating properties of compounds.

The overestimation of impacts and the larger 95% confidence limits associated with the default USEtox model might or might not result in large uncertainties in outputs from LCA applications employing this model or others that do not account for the dissociating properties of compounds.

Table 4: Probabilistic characterization factors of freshwater ecotoxicity for three emission scenarios in PAF.m^3.day.kg$_{emitted}^{-1}$. Uncertainty intervals are log-normally distributed. Values in parenthesis denote default USEtox values.

	Direct emission to Water			Emission to agricultural soil			Emission from biosolids to agricultural soil		
	Mean	95% confidence interval		Mean	95% confidence interval		Mean	95% confidence interval	
Atenolol	6,19E+00 (5,55E+00)	2,02E-01 (2,21E-01)	4,29E+01 (3,52E+01)	7,38E-03 (7,46E-01)	3,55E-05 (1,33E-03)	4,08E-02 (4,72E+00)	5,42E-03 (7,24E-01)	2,87E-06 (7,88E-04)	2,95E-02 (4,51E+00)
Bezafibrate	1,64E+01 (1,56E+01)	2,36E+00 (2,37E+00)	9,82E+01 (9,99E+01)	1,36E-01 (9,51E-02)	7,43E-03 (2,99E-04)	8,34E-01 (6,32E-01)	1,41E-01 (9,99E-02)	6,71E-03 (1,51E-05)	8,95E-01 (5,89E-01)
Carbamazepine	2,09E+01 (2,10E+01)	2,98E+00 (2,97E+00)	1,27E+02 (1,29E+02)	2,31E-01 (2,20E-01)	2,07E-02 (2,04E-02)	1,44E+00 (1,28E+00)	2,15E-01 (2,15E-01)	1,94E-02 (1,94E-02)	1,27E+00 (1,33E+00)
Clarithromycin	8,14E+02 (8,38E+02)	3,66E+01 (3,92E+01)	4,30E+03 (4,69E+03)	8,21E-01 (3,81E+01)	8,20E-03 (1,96E-01)	5,45E+00 (2,19E+02)	5,99E-01 (3,73E+01)	9,43E-04 (1,05E-01)	4,12E+00 (2,27E+02)
Clindamycin	7,56E-01 (8,06E-01)	7,12E-02 (7,32E-02)	3,49E+00 (3,60E+00)	1,38E-03 (8,85E-02)	1,97E-05 (5,05E-04)	8,65E-03 (4,53E-01)	1,16E-03 (8,79E-02)	2,60E-06 (2,35E-04)	7,38E-03 (4,50E-01)
Clofibric acid	6,81E+00 (6,16E+00)	6,42E-01 (6,28E-01)	4,28E+01 (3,65E+01)	5,97E-01 (3,03E-01)	4,26E-03 (4,22E-04)	1,33E+00 (1,99E+00)	2,13E-01 (3,07E-01)	3,82E-03 (1,14E-04)	1,42E+00 (2,09E+00)
Diatrizoate	5,66E-03 (5,59E-03)	9,50E-04 (9,34E-04)	3,06E-02 (3,01E-02)	5,02E-04 (8.47E-04)	1,37E-05 (3.93-06)	2,92E-03 (5.20E-03)	1,50E-05 (8,38E-04)	1,37E-06 (2,85E-06)	3,11E-03 (5,07E-03)
Diclofenac	1,12E+01 (1,12E+01)	1,24E+00 (1,20E+00)	6,83E+01 (6,70E+01)	3,98E-02 (4,26E-02)	5,51E-04 (1,96E-05)	2,50E-01 (2,84E-01)	4,11E-02 (3,78E-02)	2,03E-04 (7,98E-08)	2,81E-01 (2,75E-01)
Erythromycin	7,99E+01 (7,48E+01)	7,53E+00 (7,72E+00)	4,84E+02 (4,43E+02)	1,14E+00 (1,76E+00)	1,37E-02 (1,74E-03)	7,61E+00 (1,20E+01)	1,06E+00 (1,74E+00)	8,51E-03 (9,55E-05)	6,95E+00 (1,20E+01)
Ibuprofen	2,01E+01 (2,02E+01)	1,93E+00 (1,93E+00)	1,29E+02 (1,34E+02)	4,26E-02 (3.83E-02)	1,16E-03 (1,20E-03)	2,61E-01 (2.35E-01)	3,29E-02 (2,93E-02)	5,83E-04 (6,30E-04)	2,10E-01 (1,84E-01)
Iohexol	2,99E-03 (3,04E-03)	3,60E-05 (3,52E-05)	2,19E-02 (2,15E-02)	4,13E-04 (4,25E-04)	2,95E-06 (2,32E-07)	2,98E-03 (3,11E-03)	4,20E-04 (4,25E-04)	3,00E-06 (2,32E-07)	2,90E-03 (3,11E-03)
Iopamidol	1,32E-03 (1,30E-03)	1,90E-04 (1,90E-04)	7,88E-03 (7,79E-03)	1,70E-04 (1,86E-04)	5,36E-06 (3,53E-07)	1,08E-03 (1,16E-03)	1,74E-04 (1,86E-04)	5,69E-06 (3,53E-07)	1,16E-03 (1,16E-03)
Iopromide	3,69E-01 (6,38E-01)	2,50E-02 (2,46E-02)	2,26E+00 (2,35E+00)	4,94E-02 (6,10E-02)	9,19E-04 (1,17E-04)	3,04E-01 (3,31E-01)	4,49E-02 (6,44E-02)	8,90E-04 (6,69E-05)	2,85E-01 (3,14E-01)
Metoprolol	1,08E+01 (1,03E+01)	6,82E-01 (6,75E-01)	5,81E+01 (5,51E+01)	9,26E-04 (3.37E-01)	8,72E-06 (2,16E-04)	5,63E-03 (2.26E+00)	3,25E-04 (3,56E-01)	5,63E-08 (3,28E-05)	1,63E-03 (2,18E+00)
Naproxen	1,11E+00 (1,44E+00)	1,78E-01 (1,86E-01)	3,85E+00 (3,73E+00)	7,53E-02 (1,97E-02)	6,61E-04 (1,85E-05)	1,15E-01 (1,10E-01)	2,52E-02 (2,01E-02)	4,50E-04 (6,89E-07)	1,13E-01 (1,07E-01)
Primidone	1,49E+02 (1,50E+02)	5,00E+01 (5,02E+01)	3,57E+02 (3,59E+02)	6,22E+00 (9,90E+00)	1,66E-01 (1,06E-02)	3,19E+01 (4,99E+01)	6,07E+00 (9,65E+00)	1,28E-01 (1,07E-03)	3,18E+01 (4,85E+01)
Propranolol	9,38E+03 (9,58E+03)	7,53E+01 (6,77E+01)	6,43E+04 (6,49E+04)	6,16E-02 (2,15E+01)	2,21E-04 (2,03E-03)	4,46E-01 (1,72E+02)	2,19E-01 (1,73E+01)	3,59E-07 (9,35E-06)	1,64E-02 (1,37E+02)
Roxithromycin	8,00E+01 (8,80E+01)	1,24E-01 (1,16E-01)	5,20E+02 (5,66E+02)	2,06E-01 (1,74E+00)	8,18E-05 (7,63E-05)	1,20E+00 (9,80E+00)	1,99E-01 (1,66E+00)	2,94E-05 (4,78E-06)	1,23E+00 (8,74E+00)
Sotalol	1,96E-01 (1,93E-01)	8,88E-04 (7,59E-04)	1,43E+00 (1,42E+00)	1,64E-02 (1.72E-02)	2,62E-05 (2.75E-06)	1,14E-01 (1.18E-1)	1,56E-02 (1,73E-02)	2,37E-05 (8,46E-07)	1,14E-01 (1,26E-01)
Sulfamethoxazole	5,18E+01 (4,95E+01)	5,41E+00 (5,47E+00)	3,05E+02 (3,03E+02)	1,70E+00 (2,64E+00)	1,29E-02 (1,14E-03)	1,13E+01 (1,88E+01)	1,59E+00 (2,67E+00)	9,03E-03 (7,84E-05)	1,05E+01 (1,93E+01)
Trimethoprim	5,50E+00 (4,29E+00)	7,48E-01 (7,78E-01)	1,71E+01 (1,59E+01)	2,45E-02 (2,79E-01)	3,17E-04 (2,91E-04)	1,65E-01 (1,63E+00)	2,02E-02 (3,05E-01)	9,55E-05 (5,52E-05)	1,43E-01 (1,70E+00)

These uncertainties will be dependent upon the inventory data, the relevance on the LCA model of indirect mass emissions to freshwater, or upon the non-availability of experimental partitioning coefficients. Metals dominate the freshwater ecotoxicological impacts in past LCA studies on sewage treatment technologies when compared to micropollutants (Hospido et al. 2010; Larsen et al., 2010b), although other LCIA models were applied on those studies, therefore it may be expected a negligible influence on those LCA applications of the overall uncertainty and variability analyzed in this study of dissociating organic pollutants CFs. Moreover, compared to most bulk chemicals, pharmaceuticals are often large and chemically complex molecules with basic and acidic functionalities, therefore the number of dissociating compounds, and the extent of their dissociation at environmental relevant pHs, present in the inventory data used in this study may not be representative of a typical industrial emission. Nevertheless, many pharmaceuticals, antibiotics, surfactants, illicit drugs, pesticides, biocides, and dyes contain nitrogen moieties that are permanently or partially positively charged (cationic) in aqueous and soil environments (Droge and Goss, 2012). In LCA or risk assessment applications where indirect emissions of bases have a relevant contribution to outputs, the alternative approach is consistent with and probably superior to the default USEtox model.

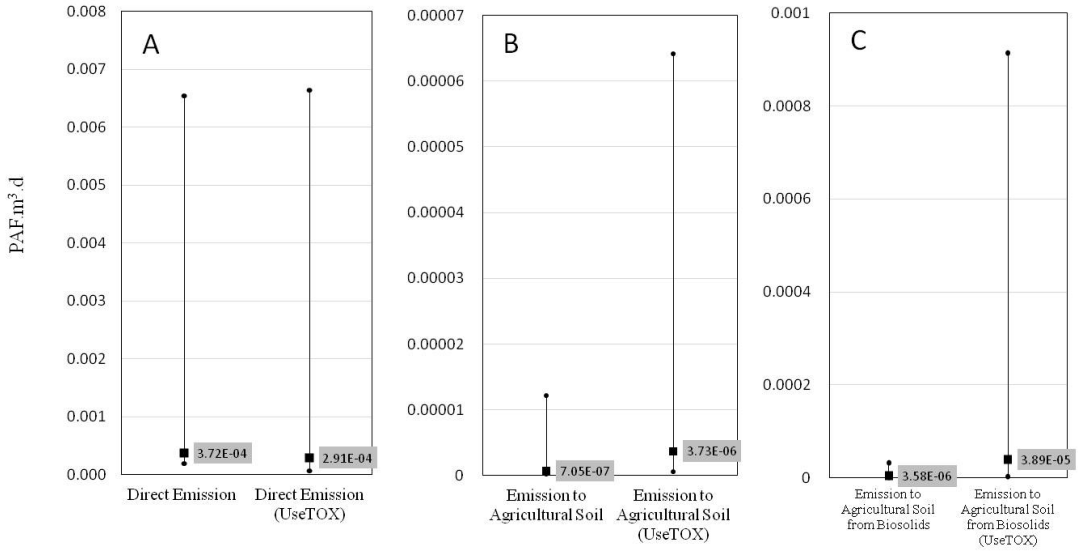

Figure 6: Probability distribution median and 95% confidence interval of ecotoxicity impacts on freshwater, in PAF.m^3.day, for: A) direct emission of micropollutants to freshwater per m^3 of WWTP effluent, B) emission of micropollutants to agricultural soil per m^3 of WWTP effluent as reclaimed water, C) emission of micropollutants to agricultural soil per kg of biosolids as soil-amendment.

The uncertainty and variability analysis performed in the present study does not account for other factors that may influence its outcome. In the case of regressions for dissociating compounds applied in the alternative approach, it is assumed constant uncertainty parameters for the environmental pH interval. That is, although the regressions consider the impact of pH on the speciation of the molecule, the impact of pH on the regressions uncertainty parameters is disregarded. Focusing in the case of the K_{OC} regression for bases (the most influential parameter on the estimated differences between approaches) and due to the more complex behaviour of bases and difficulty of improving model predictions (Kah and Brown, 2007; Franco et al., 2009), one can assume that the overall uncertainty is mainly due to the cationic species sorption, therefore, considering that the regression for bases was obtained at pH 4.5 and the base case environmental pH is 7, for higher pH values the fraction of cations decreases and so should the regression confidence limits. However, pH influences the speciation of the molecule (sorbate) as well as the soil surface chemistry (sorbent). For bases, the impact of pH on speciation and on the sorbent surface chemistry has contrasting effects on the total sorption (Franco et al., 2009). The surface of organic colloids in soil (organic matter and clay) is negatively charged because of ionization of hydroxides and phenolic groups. Cations are electrically attracted by the negative surface of natural colloids in soil. At higher pH, the fraction of cations decreases, but the deprotonation of hydroxides and phenolic groups at the sorbing surface increases the potential for cation exchange. Therefore, the uncertainty parameters of the K_{OC} regression for bases may be both over- and underestimated for other pH values in environmental pH interval. The same reasoning is applied for default USEtox model in terms of uncertainty parameters, but since the regressions do not consider the impact of pH on the speciation of the molecule, the Monte Carlo analysis does not account for the variability of pH on the estimation of K_{OC}, therefore confidence limits of the USEtox results may be underestimated.

It should be noted that the influence on the direct and indirect photolysis rates of the dissociating properties of compounds was disregarded in Monte Carlo analysis due to lack of data. The anionic form of some micropollutants were reported to exhibit higher degradation rates than the neutral form (Boreen et al. 2004; Baeza and Knappe, 2011). The influence of freshwater pH on the photodegradation of compounds, and by extension on the ecotoxicological impacts, is unclear in the present study.

Table 5: Summary of differences of USEtox results relatively to the alternative approach.

	Median	95% Confidence Interval
$CFs_{\text{direct emission}}$	Negligible differences	Negligible differences
$CFs_{\text{indirect emission}}$	Overestimation of up to 3 orders of magnitude for basic compounds	• Overestimation of up to 4 orders of magnitude for basic compounds in the upper endpoint • Overestimation of up to 3 orders of magnitude for basic compounds in the lower endpoint
$Impact_{\text{direct emission}}$	Negligible differences	Negligible differences
$Impact_{\text{indirect emission}}$	Overestimation of 1 order of magnitude	• Overestimation of up to a factor of 30 in the upper endpoint • Overestimation of up to a factor of 3 in the lower endpoint

3.5 Conclusions

The influence on the freshwater ecotoxicity impact results of using pH dependent-regressions to estimate fate properties of dissociating compounds was analyzed, as well as the sensitivity of model parameters on the outcome of the impact assessment, and compared to the default USEtox model for three different emissions scenarios of micropollutants to two environmental compartments. Negligible differences of CFs values and 95% confidence limits between the two approaches were estimated for direct emissions to the freshwater compartment; however the default USEtox model overestimates CFs of basic compounds up to three orders of magnitude relatively to the alternative approach for emissions to the agricultural soil compartment. For CFs of those indirect emissions, the results of uncertainty and variability analysis of both approaches indicate that the estimation of K_{OC} was found influential for most compounds, particularly in the case of the default USEtox model. The underestimation of sorption of cations to solid matrices in the USEtox model overestimates freshwater ecotoxicity impacts for the emission scenarios to agricultural soil by one order of magnitude and larger confidence limits were estimated relatively to the alternative approach. Depending upon the inventory data, the relevance of indirect mass emissions to freshwater on an LCA model and upon the non-availability of experimental partitioning coefficients, there might be considerable uncertainties on outputs from a given LCA study.

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4. An Uncertainty Analysis Applied to the Prioritisation of Pharmaceuticals as Surface Water Contaminants from Wastewater Treatment Plant Direct Emissions

This paper was submitted to *Water Research*, under the same title.

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4.1 Abstract

In this study, the concentration probability distributions of 82 pharmaceutical compounds detected in the effluents of 179 European wastewater treatment plants were computed and inserted into a multimedia fate model. The comparative impact of the direct emission of these compounds from wastewater treatment plants on freshwater ecosystems was assessed to rank compounds based on priority. As many pharmaceuticals are acids or bases, the multimedia fate model accounts for regressions to estimate pH-dependent fate parameters. An uncertainty analysis was performed by means of Monte Carlo analysis, which included the uncertainty of fate and ecotoxicity model parameters, as well as the spatial variability of landscape characteristics on the European continental scale.

Several pharmaceutical compounds were identified as being of greatest concern, including 7 analgesics/anti-inflammatories, 3 β-blockers, 3 psychiatric drugs, and 1 each of 6 other therapeutic classes. Most of these compounds have little or no experimental fate or ecotoxicity data available, as well as a limited reported occurrence in effluents. The contribution of estimated model parameters to the variance of output results, as well as the lack of experimental abiotic degradation data for most compounds, helped to establish priorities for further testing. Generally, the effluent concentration and the

ecotoxicity effect factor were the model parameters with the most significant effect on the uncertainty of output results.

Keywords: Pharmaceuticals, Multimedia fate model, Freshwater ecotoxicity, Dissociating organics, Uncertainty analysis, Wastewater treatment plants

1.1 Introduction

The presence of medicinal residues in the environment and their potential to induce adverse biological effects have been known for many years (Tabak and Bunch, 1970; Aherne and Briggs, 1989). The most common environmental contamination pathways are the emission of pharmaceutical compounds (PCs) from wastewater treatment plants (WWTPs) after urinal and faecal excretion and the application of livestock manure as a top soil dressing (without previous wastewater treatment) containing veterinary drugs that are likely to contaminate the soil and groundwater, which, after rainfall incidents, can reach surface waters from contaminated soil by run-off. Other less important sources of contamination include industrial wastewater and drugs disposed of with domestic waste in landfill sites, which could lead to groundwater contamination by leaching (Ternes, 1998). The pathways of contamination after excretion and passage through municipal sewage systems include the infiltration of sewage from leakages in drains, the application of biosolids from WWTPs on agricultural areas and landscapes, and, due to incomplete removal, the disposal of WWTP effluents and raw sewage into surface waters and as reclaimed water into agricultural fields and landscapes by irrigation. Regarding the emission pathways from WWTPs, we distinguish between direct and indirect emissions to the freshwater compartment; the application of biosolids and effluents into agricultural soils and landscapes can also lead to the migration of contaminants to surface waters via run-off (Sabourin et al., 2009; Borgman and Chefetz, 2013).

Although much research has been conducted on the topic of direct emissions of PCs from WWTPs, studies have generally been limited to single WWTPs (Verlicchi et al., 2012). Moreover, past studies examining the prioritisation of pharmaceuticals (e.g., (Sanderson et al., 2004; Besse and Garric, 2008; Christen et al., 2010) do not account for spatial variations of the environmental landscape, nor do most of them account for the dissociating properties of PCs or include a comprehensive uncertainty analysis of the results.

To provide a holistic view of the PCs of greatest concern, we collected data concerning PC occurrence in 179 WWTPs in Europe. A multimedia model was applied to prioritise PCs according to their probabilistic impact on freshwater ecosystems from WWTP direct emissions. Generally, experimental fate parameters, such as partitioning coefficients or degradation rates, and ecotoxicity data are scarce for most PCs; therefore, estimation methods must be applied in their assessment. Research topics were prioritised for the compounds of most concern by indentifying important gaps of knowledge, as well as by computing the contribution of estimated model parameters' uncertainty and variability to the impact variance. Currently, a similar assessment is being performed concerning indirect emissions to the freshwater compartment.

1.2 Methodology

A survey of the occurrence of PCs in the effluents of European WWTPs was performed to compute concentration probability distributions. The survey is based on a recent review conducted by Verlicchi et al. (2012) on the global occurrence of PCs in urban wastewater. For this Europe-focused study, 54 peer-reviewed publications were collected from the cited review covering 179 WWTPs located in Austria, Denmark, Finland, France, Germany, Greece, Italy, Spain, Sweden, Switzerland, and the UK, with capacities ranging from 6 000 to 2 500 000 population equivalents. Effluent concentration data included 82 drugs pertaining to 15 different classes: 19 analgesics/anti-inflammatories (including 1 metabolite), 15 antibiotics, 12 β-blockers, 7 psychiatric drugs, 7 lipid regulators (including 2 metabolites), 4 hormones, 4 β-agonists, 3 receptor antagonists, 3 antineoplastics, 2 antihypertensives, 2 diuretics, 1 proton-pump inhibitor, 1 antiseptic, 1 contrast agent, and 1 antifungal (Appendix C, Table 17). The quality of effluent concentration data reported in the literature has been confirmed according to the EC Technical Guidance Document (TGD) on Risk Assessment (EC, 2003). Therefore, the references included in the survey feature a description of the analytical methodology and the quality assurance programme used for sampling, analysis and elaboration. The geometric mean and the geometric standard deviation of the effluent concentration of each compound, assuming a lognormal distribution and weighted by the population served in each WWTP, were computed and inserted into a multimedia fate and transport model, assuming steady-state concentrations, to assess the comparative impact to freshwater ecosystems.

The applied model is based on the multimedia model USEtox (Rosenbaum, Bachmann et al. 2008) and is described in detail in (Morais et al., 2013ab); a notable difference is the inclusion of regressions to estimate pH-dependent fate parameters, such as partitioning coefficients, if no suitable experimental values are available. Over 60% of PCs are acids or bases that are fully or partially dissociated at environmental pH (Avdeef, 2003); hence, conventional non-polar regressions cannot be applied without considering the speciation of pharmaceuticals (Tarazona et al., 2010; Escher, Baumgartner et al., 2011). For the environmental compartments evaluated, the landscape characteristics of the USEtox European continental scale were applied. The model accounts for inter-media transport processes, intramedia partitioning and degradation in the environment (Figure 1).

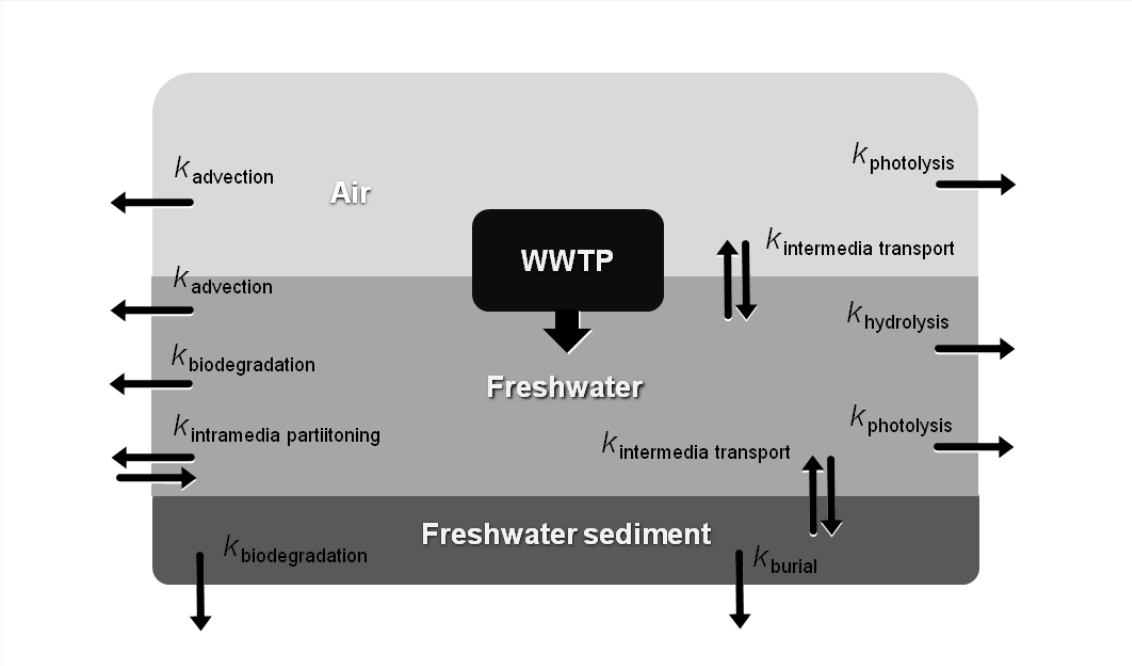

Figure 7**:** Three-compartment system for the dissipation of pharmaceuticals from direct emissions to freshwater of WWTP effluents.

Abiotic degradation mechanisms in the freshwater compartment are important elimination processes for PCs (Andreozzi et al. 2003; Doll and Frimmel, 2003). However, the USEtox model does not address estimation procedures for these mechanisms; therefore, to estimate direct and indirect photodegradation rates, a number of models and assumptions were applied and are described in detail in (Morais et al., 2013ab). In short, the average full day direct photolysis rates for winter and summer were calculated by GCSOLAR (USEPA, 1999) for the latitude range of 40-60° by providing, if available in the literature for the compounds under study, quantum yields

and molar absorption coefficients as a function of the UV/VIS wavelength range (Appendix C, Table 18). For indirect photolysis, bimolecular rate constants (k_{OH}, in $M^{-1}s^{-1}$) for the reaction between a substance and ˙OH (Appendix C, Table 18), the most reactive chemical transient, were converted to pseudo-first order rate constants by multiplication by the hydroxyl radical concentration in surface waters (in M).

1.2.1 The ecotoxicity effect factor

In comparative impact assessment methodologies, the conversion of emissions to ecotoxicological impacts comprises a fate and an effect analysis step (van Zelm et al., 2007). The fate factor describes the marginal increase in environmental concentration per unit of emission. The ecotoxicity effect factor (EEF) addresses the marginal increase in effect (toxic pressure on ecosystems) per unit of chemical concentration. An assessment factor (AF) based on the predicted no effect concentration (PNEC) approach is recommended in generic risk assessment according to the TGD (EC, 2003); however, a potentially affected fraction (PAF) of species approach based on the average toxicity was considered in the present study as a basis for the EEF calculation, as adopted in the USEtox model. Both approaches have advantages and drawbacks (Larsen and Hauschild, 2007ab); however, a PAF-based approach has two main advantages that better serve the purposes of this study: 1) a PNEC approach targets the protection of the most sensitive species; therefore, the risk of bias is high when scarce ecotoxicity data are available, which is the case for PCs; and 2) the assessment of the mean impact (AMI) on ecosystems method, a PAF-based approach, allows the quantification of uncertainty, giving an indication of the reliability of the results. The AMI method is based on the hazardous concentration (HC) at which the effect concentration (with an endpoint of, for example, mortality) affecting 50% of tested individuals (EC50) is exceeded for 50% of the included species; this is also called $HC50_{EC50}$ (Payet, 2004; Payet, 2005; Payet and Jolliet, 2005). Two statistical estimators can be used to estimate the toxicity of a substance to biological species and the associated confidence interval: a non-parametric estimator using the median as the $HC50_{EC50}$ combined with bootstrap statistics to estimate its uncertainty (Payet and Jolliet, 2005) or a parametric estimator based on the assumption of a lognormal distribution of data using the geometric mean as $HC50_{EC50}$ and Student's t-statistics for its confidence interval (Payet, 2004; Payet, 2005).

The EEF indicator, i.e., $0.5/HC50_{EC50}$, focuses on the trophic structure by including the EC50 values of at least 3 trophic levels: primary producers (algae), primary consumers (crustaceans), and secondary consumers (fish) (Appendix C, Table 19). The low environmental concentrations but constant introduction to the environment indicate that PCs are more likely to have chronic rather than acute toxic effects on aquatic biota (Carlsson et al., 2006; Fent et al., 2006; Quinn et al., 2008); hence, chronic EC50 values are preferred as well as, due to the comparative context of the assessment, standard tests/test conditions and standard test organisms. However, the ecotoxicological data on PCs remain scarce, and there are not enough chronic experimental ecotoxicity data available to perform an assessment (Escher et al., 2011). An acute-chronic ratio of 2 was applied to extrapolate chronic $HC50_{EC50}$ values from acute $HC50_{EC50}$ values, as recommended by (Larsen and Hauschild, 2007b), and was applied in the USEtox model (Huijbregts et al., 2010). However, best estimate AFs for this extrapolation have not yet been developed, and research is needed in this area (Larsen and Hauschild, 2007b), particularly in the context of micropollutants. Even acute ecotoxicity data are only available for a very limited set of pharmaceuticals (Escher et al., 2011); therefore, EC50 values are completed by extrapolation from the lowest observed effect concentration (LOEC) or no observed effect concentration (NOEC) values, according to the best-estimate AFs from (Payet 2004). To determine missing experimental data, quantitative-structure activity relationship (QSAR) data were included using the software program ECOSAR v1.00 (Nabholz and Mayo-Bean, 2009). For estimated data, a conservative approach was followed by considering the chemical class with the highest potency (i.e., the lowest concentration predicted to cause the toxic effect), except in the case of the neutral organics class if a compound is completely dissociated at environmentally relevant pH values.

The baseline toxicity, or narcosis, is the addressed toxic mode of action (TMoA) in most generic risk assessment or impact assessment methodologies. Previous studies have shown that most PCs produce their environmental adverse effect via narcosis (Sanderson and Thomsen, 2007). However, some pharmaceuticals, which are designed to be bioactive (with the exception of contrast agents), also exhibit a therapeutic effect in non-target aquatic life, such as the estrogenic effects caused by hormones in fish (Santos et al., 2010), or they act via a specific TMoA, such as the inhibition of photosynthesis caused by β-blockers in algae (Escher et al., 2006). As a change in sex ratio apparently relates directly to the reproduction of a fish population, this endpoint is

considered more relevant than vitellogenin in an impact assessment context (Larsen et al., 2010b). Hence, the endpoints used for the average toxicity calculation include the inhibition of growth and photosynthesis for algae, mortality or immobility (*Daphnia)* for invertebrates, and mortality or change in sex ratio for fish.

1.2.2 Uncertainty analysis

The propagation of the uncertainty and variability of model parameters in the output results was quantified by Monte Carlo analysis. The parameters included in the analysis are described in the Appendix C, Table 20. The analysis includes the following factors:

(1) The variability of effluent concentrations, direct photolysis rates and continental-scale environmental parameters (freshwater pH, rainfall, freshwater concentration of suspended matter, dissolved organic carbon, and ˙OH).

(2) The uncertainty of the EEF. Uncertainty distributions of $HC50_{EC50}$ values were estimated according to the parametric estimator, as recommended by (Payet 2004). Moreover, the parametric estimator is based on the geometric mean, which is the most robust average estimator for $HC50_{EC50}$ (Larsen and Hauschild, 2007b). However, the uncertainty of extrapolating average chronic toxicity, i.e., chronic $HC50_{EC50}$, from average acute toxicity was not addressed in the present study, nor was the uncertainty of extrapolating and estimating individual endpoints.

(3) The uncertainties associated with the regression equations adopted in the model to estimate partition coefficients, bioconcentration factors and biodegradation rates. The procedure to compute the uncertainty parameters of estimated fate parameters is described in detail in Morais et al. (2013ab). In short, the training and validation sets used to derive the regression methods applied in the present study (Franco and Trapp, 2008; USEPA, 2008; Fu et al., 2009; USEPA, 2009) were used to derive mean residual errors and their probability distributions and were fit into the regressions.

(4) The experimental parameter values (partition coefficients, biodegradation half-lives, and k_{OH}). The geometric mean and the geometric standard deviation of experimental values were set as uncertainty parameters, assuming a lognormal distribution.

1.3 Results and discussion

Figure 8 shows the comparative ecotoxicological impact of PCs emitted directly from WWTP effluents to the freshwater compartment. A general condition for impact assessment methodologies is that the impact indicator be additive (Hauschild 2007). Hence, the contribution of each PC's uncertainty to the variance of the total ecotoxicity can be computed; these results are shown in Figure 9. The total ecotoxicity impact is 6.51×10^{-2} PAF·m^3·d per m^3 of effluent (95% confidence interval = 2.84×10^{-2}–6.61×10^{-1}), and to rank PCs for further discussion, it is assumed that the PCs of most concern are those totalling a 90% contribution to the total impact variance. For the PCs of most concern, the contribution of model parameters to the variance of the results of Figure 8 is shown in Figure 10. The contribution to the variance provides an approximation of the percentage of the variance or uncertainty of an output result caused by the variability or uncertainty of a given model parameter. The contribution is calculated by squaring the correlation coefficients between model parameters and impact results, for a given number of trials, and normalising them to 100%. Generally, for the substances of most concern, the HC50 parameter is the most relevant one for the statistical spread of impact results shown in Figure 2. For most substances, the parametric quantification of HC50 uncertainty is based on only 3 data values, which typically produces wide confidence limits (Larsen and Hauschild, 2007a), making the statistical differentiation between substances ambiguous.

1.3.1 Antineoplastics

The antineoplastic tamoxifen displays the highest median ecotoxicity impact (Figure 8). The uncertainty of the HC50 parameter contributes 93.8% of the variance of the tamoxifen impact results (Figure 4). Only 2 experimental acute EC50 values, covering 1 trophic level, were obtained in the present study (Appendix C, Table 19). The ecotoxicological datum on algae was estimated by ECOSAR. The quantification of this QSAR method's uncertainty is not considered in the present study, as stated above; therefore, its influence on impact results is unclear. In addition, the EC50 value for crustaceans was extrapolated from the NOEC. The inherent uncertainty of extrapolating ecotoxicological endpoints is also not considered in the present study. Overall, a more comprehensive ecotoxicological study is needed. Moreover, the calculated impact of tamoxifen is based on very limited data on measurements in WWTP effluents. Roberts

and Thomas (2006) reported concentrations ranging from 0.146 to 0.369 µg/l in a WWTP in the UK, and Coetsier et al. (2009) reported detected concentrations ranging from 0.053 to 0.102 µg/l in a WWTP in France. According to the outcome of the present study, tamoxifen should be subject to monitoring in WWTP effluents for more conclusive results. The neutral form of tamoxifen, with an estimated log K_{OW} of 6.30 (USEPA, 2008), is highly hydrophobic. Moreover, tamoxifen is predominantly found in the basic form at pH 7 (pK_a = 8.52); therefore, electrostatic interactions may play a significant role in its partitioning into negatively charged sorption sites of particles and, consequently, in its removal from WWTPs. The environmental occurrence of tamoxifen is, however, relatively common. It was detected in all samples from the Ebro River in Spain and from its tributaries at mean concentrations of 18.9 and 22.7 ng/l, respectively (López-Serna et al., 2012). In the River Tyne, UK tamoxifen concentrations ranged from 27 to 212 ng/l, with a median concentration of 53 ng/l (Roberts and Thomas, 2006). Thomas and Hilton (2004) reported similar values in 5 UK estuaries. Another issue of concern, and a subject for further study, is the depletion of tamoxifen, which may be underestimated in the aquatic environment because no data on indirect photolysis are available in the literature. Nevertheless, this compound, which has double bonds and aromatic rings, may react with chemical transients generated by natural water constituents under sunlight, especially with the extremely reactive hydroxyl radical that can abstract hydrogen from saturated organics, add to double bonds or add to aromatic rings. In contrast, the chronic ecotoxicity of tamoxifen derivatives produced by direct photolysis revealed no significant differences in comparison to the parental compound (DellaGreca et al., 2007); therefore, the overall impact of tamoxifen may be underestimated, given that photoproducts were not included in the present study.

1.3.2 Analgesics/anti-inflammatories

Mefenamic acid is a widely used non-steroidal anti-inflammatory compound and is commonly found in effluents (e.g., Tauxe-Wuersch et al., 2005; Barron et al., 2009; Kim et al., 2009a; Radjenovic et al., 2009; Rosal et al., 2010a). Literature data on mefenamic acid concentrations in WWTP effluents vary by 3 orders of magnitude, from 0.005 (Kasprzyk-Hordern et al., 2009) to 3.0 µg/l (Tauxe-Wuersch et al., 2005). The variability of the effluent concentration contributes 97.7% of the variance of the impact of mefenamic acid. However, the calculated effect of this anti-inflammatory may be

overestimated, given that Werner et al. (2005) suggested that photosensitisation by excited triplet-state DOM may contribute to the environmental degradation of mefenamic acid. The influence of this degradation mechanism on the calculated effect remains unknown in the present study. Concerning environmental occurrence, mefenamic acid was not detected in samples from the Ebro River, Spain, or its tributaries (López-Serna et al. (2012). In contrast, it was detected in 2 rivers in South Wales, UK at a maximum concentration of 33 ng/l (Kasprzyk-Hordern et al., 2009).

The calculated impact of aminopyrine is based on estimated ecotoxicological data. Even excluding the uncertainty of ecotoxicity data estimation, the HC50 parameter has a contribution of 97.4% to the variance of the impact of aminopyrine. Moreover, this compound is not commonly detected in WWTP effluents. Ternes (1998) reported the detection of aminopyrine at a maximum concentration of 1.0 µg/l in 3 WWTP effluents during monitoring of 16 WWTPs in Germany. Andreozzi et al. (2003) reported detection in a WWTP in France at a concentration of 0.43 µg/l; however, the same authors reported no detection in another WWTP effluent in France, 3 WWTPs in Italy, 1 WWTP in Sweden and another WWTP in Greece. Poor sorption to particles in WWTPs may be expected, given that the predominant neutral form of this basic compound at pH 7 (pK_a = 5.0) has an estimated log K_{OW} of 0.6 (USEPA, 2008). Therefore, depending on the role of its biodegradation in WWTPs, a very low influent concentration or non-existent discharge may have been observed in the studied WWTPs in which aminopyrine was not detected in the effluents; however, no data on influent concentrations were reported in the referred studies. In fact, the human clinical use of aminopyrine is widely banned due to the risk of agranulocytosis and due to its potential to produce carcinogenic nitrosamines (U.N., 2003); hence, its presence in WWTP discharges may be caused by low levels of application in veterinary medicine or by industrial release (Ternes, 1998). No abiotic degradation data are available; however, aminopyrine is expected to be susceptible to indirect photolysis. In addition, it contains chromophores that absorb at wavelengths >290 nm and may therefore also be susceptible to direct photolysis; hence, the residence time of aminopyrine in the aquatic environment may be overestimated. Concerning its occurrence in the environment, aminopyrine was not detected in 20 rivers in Germany (Ternes, 1998).

The concentration reported in the literature on the occurrence of the opiate codeine in WWTP effluents varies by 3 orders of magnitude (Gómez et al. 2007; Wick et al., 2009), from 0.022 to 15.59 µg/l. This variability of the effluent concentration

contributes 66.6% of the variance of impact results. The HC50 parameter contributes 32.8%; furthermore, estimated data were applied. Codeine is expected to be susceptible to indirect photolysis and contains chromophores that absorb at wavelengths >290 nm; therefore, it may also be susceptible to direct photolysis.

The concentration of tramadol in WWTP effluents reported in the literature varies by 3 orders of magnitude, from 0.02 to 97.62 µg/l (Kasprzyk-Hordern et al., 2009, Wick et al., 2009). The effluent concentration of tramadol contributes 75.3% to the impact variance. The HC50 parameter represents 24.1% of the tramadol impact result variance; furthermore, for experimental EC50 values of 2 trophic levels, crustaceans and fish, the species were not specified in the literature. In terms of environmental occurrence, tramadol was detected in 2 rivers in South Wales, UK at a maximum concentration of 5970 ng/l (Kasprzyk-Hordern et al., 2009).

1.3.3 β-blockers

The HC50 parameter contributes between 70-86% to the impact results for variance of the β-blockers betaxolol, oxprenolol, and propanolol. Moreover, oxprenolol ecotoxicity data have been estimated for all trophic levels, and in the case of betaxolol, only 1 acute EC50 value is experimental. Propanolol is commonly measured in WWTP effluents (e.g., Maurer et al., 2007; Wick et al., 2009; Alder et al., 2010); however, limited data are available on the occurrence of oxprenolol and betaxolol in WWTP effluents. The former was detected in a range of 0.01 to 0.05 µg/l in 2 WWTPs in Italy, 2 WWTPs in France and 1 WWTP in Greece (Andreozzi et al., 2003). The same authors reported no detection in the effluent of a Swedish WWTP. Among 29 WWTPs that were studied in Germany, betaxolol was detected in 50% of the WWTPs at a maximum concentration of 0.19 µg/l and a median concentration of 0.057 µg/l (Ternes, 1998). In contrast, it was not detected in 3 WWTPs in Italy, 2 WWTPs in France, 1 WWTP in Sweden, 1 WWTP in Greece (Andreozzi et al., 2003) or 1 WWTP in Germany (Wick et al., 2009). In terms of environmental occurrence, no literature data on oxprenolol were found; however, betaxolol was not detected in 29 rivers in Germany, even when it was present in WWTP effluents (Ternes, 1998), nor was it detected in the Ebro River in Spain (López-Serna et al., 2012). According to the molecular structures of β-blockers, indirect photolysis may play a role in their persistence in the aquatic environment; however, except for propanolol, no experimental data on photosensitisation were found in the literature.

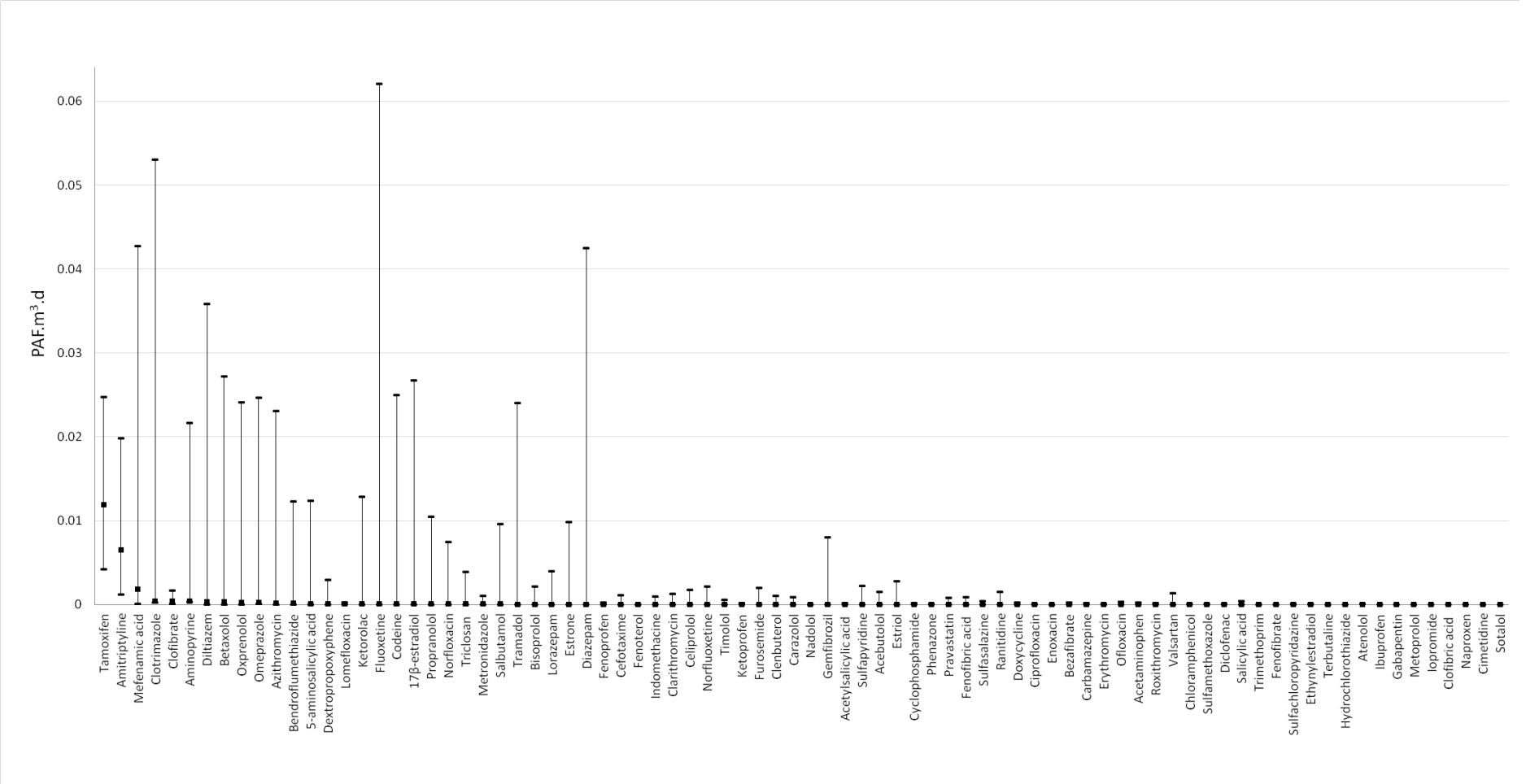

Figure 8: Probability distribution median and 95% confidence interval of ecotoxicity impacts on freshwater, in PAF m^3 day, of PCs per m^3 of WWTP effluent.

1.3.4 Psychiatric drugs

In addition to the high contribution of the HC50 parameter to the variance impact of the tricyclic antidepressant amitriptyline (95.9%), the experimental ecotoxicological data were limited to crustaceans, with chronic EC50 values for 4 species. In the case of other trophic levels, ECOSAR values were applied. Both the high sorption potential of the neutral form, with an estimated log K_{OW} of 4.95 (USEPA, 2008), and the predominance of the basic form at pH 7 (pK_a= 9.4) indicate significant removal in WWTPs. Nevertheless, the literature data (both on measurements of amitriptyline in WWTP effluents and on the fate of amitriptyline in WWTPs) are too limited for conclusive results. Amitriptyline was detected in 2 WWTP effluents from activated sludge treatment at median concentrations of 0.197 and 0.085 µg/l in South Wales, UK, and at a maximum concentration of 17 ng/l in the rivers to which the effluents were discharged (Kasprzyk-Hordern et al. 2009). In addition, according to its molecular structure, amitriptyline may be susceptible to indirect photolysis; hence, its residence time in the aquatic environment may be overestimated in the present study.

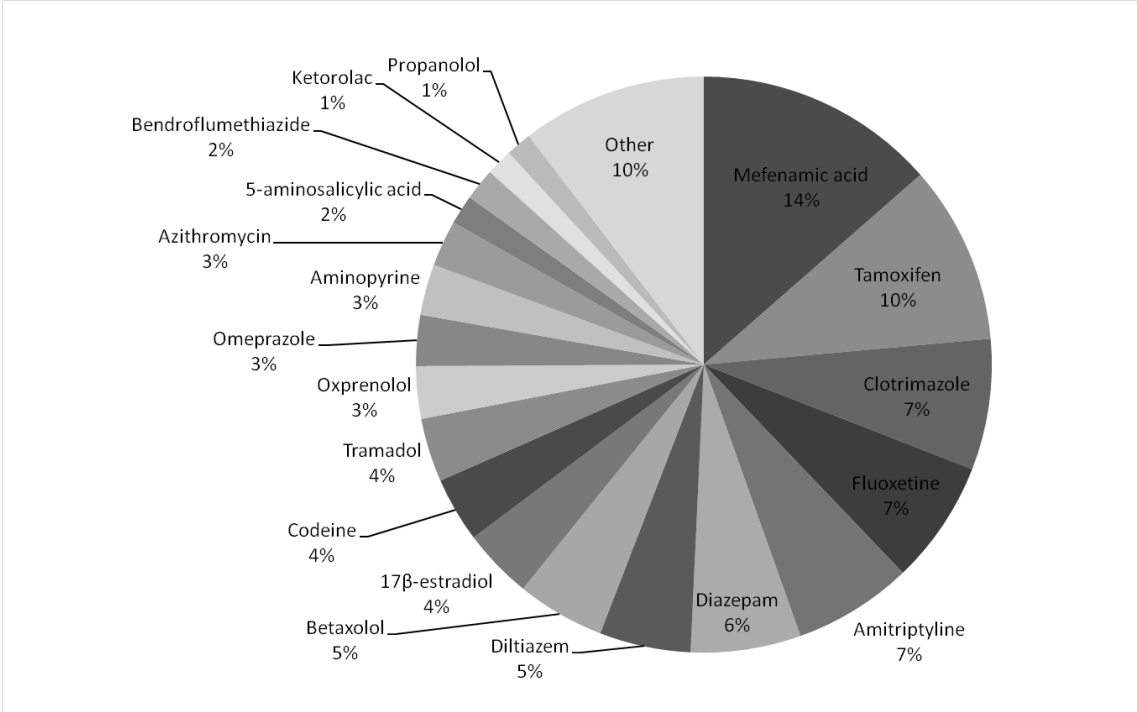

Figure 9: Contribution to variance of total freshwater ecotoxicity impact.

The impact of diazepam is comparatively significant for the higher concentrations in WWTP effluents that have been reported in the literature. This parameter has a contribution of 92.5% to the impact variance. The concentration ranges 3 orders of

magnitude, from 0.04 to 19.3 µg/l (Ternes, 1998; Suárez et al., 2005); however, measurements of this compound in WWTP effluents are very scarce in the literature.

The HC50 parameter contributes 43.3% to impact variance of the serotonin reuptake inhibitor fluoxetine. Three acute experimental HC50s covering 3 trophic levels were applied. An acute LC50 value was applied for fish; however, for fluoxetine, other TMoAs such as endocrine disruption may be relevant, given that Mennigen et al. (2008) suggested that fluoxetine may have the potential to affect sex hormones and modulate genes involved in the reproductive function of fish. The effluent concentration has a contribution of 39.4% to the impact variance. Fluoxetine was found in the range of 0.016-2.0 µg/l in Spanish WWTPs (Munoz et al., 2009; Rosal et al., 2010a), but it was not detected in a Swedish WWTP (Zorita et al., 2009). Although direct photolysis could potentially limit the persistence of fluoxetine in surface waters, Lam et al. (2004) suggested that its degradation by indirect photolysis would be the limiting degradation mechanism.

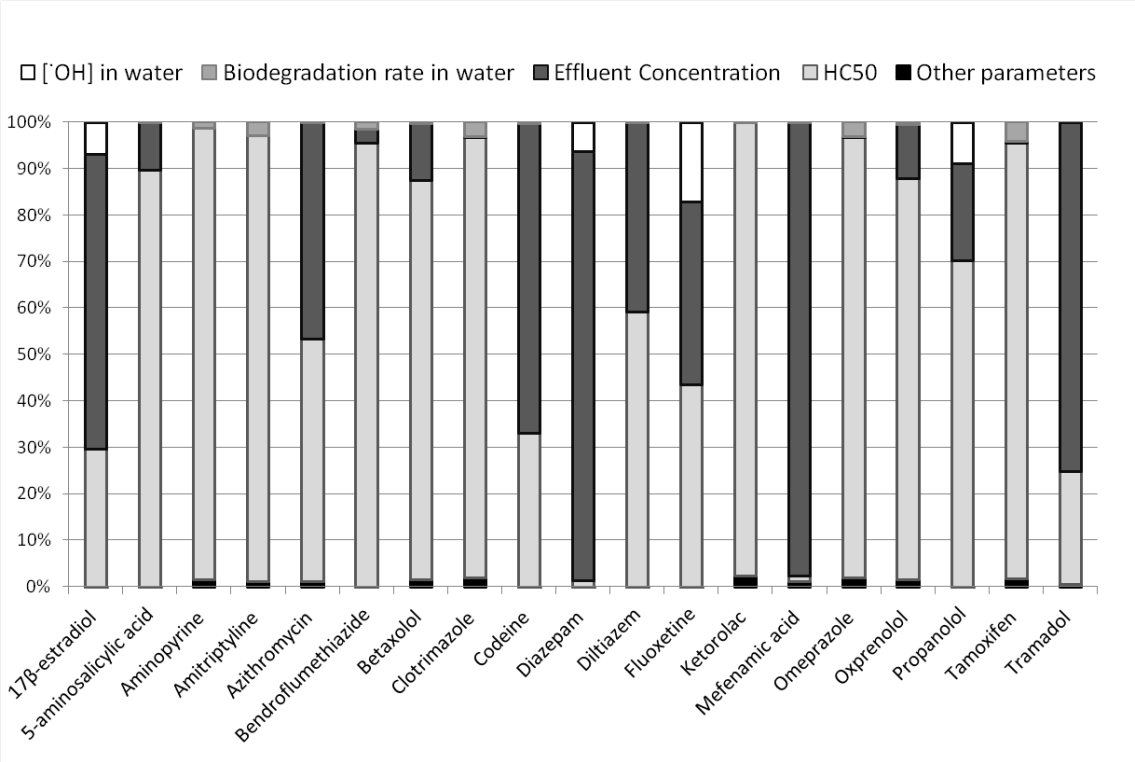

Figure 10: Contribution of model parameters to impact variance of PCs of most concern.

1.3.5 Other therapeutical classes

The statistical spread of the antifungal clotrimazole's impact is also mainly due to the HC50 parameter, with a 95% contribution to the variance; 3 experimental acute EC50

values covering 3 trophic levels were applied. According to its molecular structure, clotrimazole is expected to be susceptible to indirect photolysis; therefore, its residence time in the aquatic environment may be overestimated. The neutral form of clotrimazole, which predominates at pH 7 (pK_a= 5.22), is highly hydrophobic, with an estimated log K_{OW} of 6.26 (USEPA, 2008); therefore, significant partitioning to particles in WWTPs may be observed. There are limited data on the occurrence of this topical product in WWTP effluents at detectable concentrations; however, clotrimazole is a widely used over-the-counter antifungal agent. Clotrimazole was not detected in the WWTP effluent of a former production plant, even when clotrimazole was found in the WWTP influent (OSPAR, 2005). Conversely, Roberts and Thomas (2006) reported concentrations ranging from 0.014 to 0.027 µg/l in a WWTP in the UK, and Kahle et al. (2008) reported concentrations ranging between 0.005 and 0.006 µg/l in the effluents of 2 Swiss WWTPs. In terms of environmental occurrence, clotrimazole was not detected in the Elbe and Saale Rivers in Germany at any of the measured points (OSPAR, 2005). However, it was detected in concentrations ranging from 6 to 34 ng/l, with a median of 21 ng/l, in the River Tyne, UK (Roberts and Thomas, 2006) and was the most frequently detected of 14 pharmaceuticals analysed in UK estuaries, with a maximum concentration of 22 ng/l and a median concentration of 7 ng/l (Hilton and Thomas, 2003).

The HC50 parameter contributes 59% to the impact variance of the antihypertensive receptor diltiazem. This parameter is of even greater concern, given that only 1 experimental EC50 value was found in the literature. Diltiazem was found at concentrations ranging between 0.095 and 1.156 µg/l in 2 WWTP effluents in the UK and at concentrations ranging between 2 and 40 ng/l in the rivers to which those effluents are discharged (Kasprzyk-Hordern et al., 2009). No abiotic degradation data are available. However, diltiazem is expected to be susceptible to indirect photolysis, and because it has chromophores that absorb at wavelengths >290 nm, it has the potential to be degraded by direct photolysis; therefore, the depletion of diltiazem in the aquatic environment may be underestimated.

The HC50 parameter contributes 95% to the impact variance of the proton-pump inhibitor omeprazole. Moreover, only 1 experimental EC50 value was found in the literature. Very limited data on measurements of omeprazole in WWTP effluents are available in the literature; nevertheless, it is one of the most widely prescribed pharmaceuticals. It was detected at a maximum concentration of 0.922 µg/l and an

average concentration of 0.322 µg/l in a WWTP effluent in Spain (Rosal et al., 2010a). Omeprazole is expected to undergo hydrolysis in the environment due to the presence of functional groups that hydrolyse under environmental conditions, and it may also be susceptible to direct and indirect photolysis.

In addition to the high contribution of HC50 to the variance of the macrolide antibiotic azithromycin's impact result (52.2%), EC50 values were estimated. The effluent concentration contributes 46.7% to the impact variance. Azithromycin was detected in a range between 0.040 and 0.400 µg/l in a WWTP in Switzerland (Göbel et al., 2005) and in a range between 0.035 and 0.160 µg/l in a WWTP in Spain (Prieto-Rodríguez et al., 2013). Literature reports of its environmental occurrence are scarce. It was detected in the Ebro River in Spain at a median concentration of 4.57 ng/l (López-Serna et al., 2012). The photodegradation of azithromycin was shown to be enhanced in the presence of nitrates and humic acids (Tong et al., 2011), which indicates the role of indirect photolysis in the persistence of this compound in the environment. However, indirect photodegradation was not included in the present study for this compound; therefore, the impact of azithromycin is most likely overestimated.

Concentrations of the hormone 17β-estradiol in WWTP effluents reported in the literature vary by 2 orders of magnitude (Baronti et al. 2000; Clara et al., 2004), from 0.0007 to 0.0180 µg/l. The variability of effluent concentration represents 63.6% of the impact variance. The HC50 parameter contributes 29.2% to the variance. Experimental acute EC50 values for 6 species were applied; however, the EC50 value for algae was estimated. 17β-estradiol was detected in rivers at levels ranging from 0.002 to 0.006 ng/l (Laganà et al., 2004; Zuehlke et al., 2005).

The diuretic bendroflumethiazide, the anti-inflammatories 5-aminosalicylic acid and ketorolac, and the lipid regulator clofibrate are discussed in the Appendix C (Section 4).

1.3.6 Additional considerations

Table 6 summarises future research topics for the PCs of greatest concern. These topics can be related to 3 issues: a) the fate of PCs in WWTPs, b) substance-specific modelling parameters, and c) lack of spatial and time resolution models. The first topic includes compounds with very limited data on measurements or detection in WWTP effluents, such as tamoxifen or amitriptyline. These substances should be subject to further monitoring in WWTPs, depending on geographical usage patterns, for more conclusive

results. This category should also include compounds whose impact result would be most sensitive to variations of the emission concentration. Ideally, a comparatively well characterised drug from an impact perspective would account for low variance of output results due to environmental fate and transport modelling parameters, either estimated or experimental, and due to EEF characterisation. The uncertainty of its impact result, from a modelling perspective, would be related mainly to the variability of the concentration in WWTP effluents, depending on geographical and seasonal usage patterns, treatment technologies, and operation conditions. The focus of research for these compounds should be detailed ecological risk assessments possibly leading to research and development on the operation and design of WWTPs to improve the reduction of the compounds' effluent concentrations. However, the compounds most sensitive to the emission concentration, such as diazepam or mefenamic acid, have other research priorities either because of limited data on their occurrence or incomplete modelling parameters.

The second issue includes drugs whose impact results are mostly sensitive to the uncertainty of substance-specific environmental fate and transport modelling parameters, such as degradation rates or partitioning coefficients, or to EEF characterisation, as well as drugs whose impact result may be affected by modelling incompleteness, either from the lack of abiotic degradation data (such as for omeprazole or azithromycin) or from the exclusion of degradation products (such as for tamoxifen). These compounds should be subjected to further experimental research according to the most sensitive parameters because of a lack of precise knowledge regarding those parameters. The third issue, the lack of spatial and time resolution models, addresses the variability of landscape parameters, such as freshwater pH or [˙OH], and the seasonal variation of direct photolysis rates. However, for the compounds of greatest concern, only the spatial variability is somewhat significant, and only in the case of [˙OH]. The large scale applied in the present study displays a great variety of landscape characteristics; nevertheless, the uncertainty regarding the HC50 parameter and the variability of the effluent concentration predominate in terms of the contribution of variance to the output results.

Table 6: Research topics for PCs of most concern

	Effluent characterization [a]	Ecotoxicological effect characterization [b]	Parameter incompleteness	
			Abiotic degradation mechanisms [c]	Derivatives toxicity [d]
17β-estradiol	↓↓	↓		↓↓
5-aminosalicylic acid	↓↓↓	↓↓↓	↓↓	↓↓
Aminopyrine	↓↓↓	↓↓↓	↓↓	↓↓
Amitriptyline	↓↓↓	↓↓↓	↓	↓↓
Azithromycin	↓↓↓	↓↓↓	(↓↓)	↓↓
Bendroflumethiazide	↓↓↓	↓↓↓	↓↓	↓↓
Betaxolol	↓↓	↓↓↓	↓	↓↓
Clotrimazole	↓↓↓	↓↓	↓	↓↓
Codeine	↓↓	↓↓↓	↓↓	↓↓
Diazepam	↓↓	↓		↓↓
Diltiazem	↓↓↓	↓↓↓	↓ ↓	↓↓
Fluoxetine	↓↓	↓↓		↓↓
Ketorolac	↓↓↓	↓↓↓	↓ ↓	↓↓
Mefenamic acid	↓↓	↓	(↓↓)	↓↓
Omeprazole	↓↓↓	↓↓↓	↓↓↓	↓↓↓
Oxprenolol	↓↓↓	↓↓↓	↓	↓↓
Propranolol	•	↓		↓↓
Tamoxifen	↓↓	↓↓↓	↓	↓ (↓↓)
Tramadol	↓↓	↓↓		↓↓

[a] •: more than 10 peer-reviewed publications; ↓: between 5 and 10 peer-reviewed publications; ↓↓: between 2 and 5 peer-reviewed publications; ↓↓↓: only one peer-reviewed publication.
[b] ↓: more than 3 acute EC50s covering 3 trophic levels; ↓↓: 3 acute EC50s covering 3 trophic levels; ↓↓↓: at least 1 estimated or extrapolated EC50.
[c] number of possible abiotic degradation mechanisms not included in the assessment (hydrolysis, direct and indirect photolysis); (↓↓) denotes a specific degradation pathway with some evidence of occurrence in the literature but with no data available.
[d] number of possible degradation mechanisms generating derivatives (hydrolysis, photolysis and biodegradation); (↓↓) denotes a specific degradation pathway with evidence of derivatives toxicity in the literature.

1.3.7 Model limitations

It should be noted that other sources of uncertainty not included in the Monte Carlo analysis may be important. Some have already been discussed above, such as the uncertainty of ecotoxicological data estimation, the extrapolation of endpoints, the lack of abiotic degradation data for several compounds, and the exclusion of abiotic and biotic derivatives of parent compounds. This last source of uncertainty may be relevant in the case of tamoxifen, as already mentioned; however, substances that do not appear in the ranking of compounds of most concern may have their comparative impact substantially increased by the inclusion of their derivative impact. For example, some researchers have suggested that the phototransformation products of triclosan,

diclofenac or hydrochlorothiazide have a higher toxicity potential than their parent compounds (Han et al., 2000; Schmitt-Jansen et al., 2007). Nevertheless, the inclusion of phototransformation products impact is possible, if the chemical structures are identified, by applying the method proposed by (van Zelm et al., 2010b).

In addition, the uncertainty of the influence of pH on direct and indirect photolysis rates, the uncertainty of the application of a linear dose-response curve for the calculation of EEFs, and the lack of spatial variation of background impacts in the AMI method remain unclear. For example, for uncertainty of the influence of pH on the abiotic degradation, the literature data on the direct phototransformation of triclosan (pK_a =8.1) applied in the present study are based on its anionic form (Tixier et al., 2002), which is the dominant photochemical degradation pathway. Therefore, by disregarding the influence of pH on the direct photolysis rate, the residence time of triclosan in the freshwater environment may be underestimated for lower pH values.

1.4 Conclusions

Despite the high uncertainties of the PC impact results, which range up to 12 orders of magnitude, and the model's limitations and incompleteness, the outcome of the present study allows priorities to be set for further experimental testing. Notably, some PCs of greatest concern, such as tamoxifen, clotrimazole and oxprenolol, have rarely been investigated previously with regard to their ecotoxicity, their occurrence in WWTPs, or their degradation in the environment. Theoretically, the relevant PCs may be susceptible to abiotic degradation. However, in general, no experimental data are available; hence, the persistence of these PCs in the freshwater compartment is comparatively higher than that of well-researched PCs that were not included on the ranking of priority drugs, such as triclosan, diclofenac or ibuprofen. Ecotoxicity data remain to be the most critical issue affecting impact or risk assessments of PCs. The present assessment is based on only 3 data values for most of priority PCs (only approximately 4% of these compounds have more than 3 EC50 values) that produced wide confidence limits. Moreover, approximately 63% of the PCs of priority have at least 1 estimated or extrapolated EC50. In short, several PCs were identified both for further WWTP monitoring and for testing their ecotoxicity and their persistence in the environment.

1.5 Acknowledgments

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5. An Uncertainty Analysis Applied to the Prioritisation of Pharmaceuticals as Surface Water Contaminants from Wastewater Treatment Plants: the Case of Indirect Emissions from Amendment of Soils with Biosolids and Irrigation with Reclaimed Water

This paper was submitted to *Water Research*, under the same title.

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5.1 Abstract

The comparative impact on freshwater ecosystems of pharmaceutical compounds from indirect emission pathways from wastewater treatment plants was assessed to rank compounds based on priority. The concentration probability distributions of 85 pharmaceutical compounds detected in the effluents of 179 European wastewater treatment plants were computed, their concentrations in biosolids were estimated, and their fates were calculated for the reuse of effluents as irrigation water and for the application of biosolids as a soil amendment, both in agricultural soils. Because many pharmaceutical compounds contain dissociating functional groups, their charges change with solution pH, and thus, their transport behaviour may be affected; therefore, the multimedia fate model uses regressions to estimate pH-dependent fate parameters. An uncertainty analysis was performed using Monte Carlo analysis, which included the uncertainty of the fate and ecotoxicity model parameters and the spatial variability of landscape and meteorological characteristics at the European continental scale.

Several pharmaceutical compounds were identified as being of greatest concern, including 4 analgesics/anti-inflammatories, 3 antibiotics, 2 diuretics, and 1 each of 4 other therapeutic classes. For most of these compounds, few or no experimental fate or

ecotoxicity data are available, and there have been limited reported occurrences in effluents. The contribution of the estimated model parameters to the variance in the output results and the lack of experimental abiotic degradation data for most of the compounds helped to establish priorities for further additional research. The emissions concentration, the ecotoxicity effect factor, and the solid-water partitioning coefficient were the model parameters with the most significant effects on the uncertainty of the output results. The spatial and temporal variation in the environmental characteristics was found to be of minor significance to the output results.

Keywords: Pharmaceuticals, Reclaimed water, Biosolids, Freshwater ecotoxicity, Dissociating organics, Wastewater treatment plants

5.2 Introduction

The presence of pharmaceutical compounds (PCs) in the environment with the potential to induce adverse biological effects has been recognised as a concern for many years (Tabak and Bunch, 1970; Richardson and Bowron, 1985). Some PCs are not fully metabolised in the body, or their metabolites are reconverted into parent compounds; some PCs may be disposed of in sewage systems via flushing and, thereafter, not completely eliminated in conventional wastewater treatment plants (WWTPs). Body metabolisation and excretion followed by wastewater treatment is considered to be the primary pathway by which biologically active PCs enter the environment (Jelic, Gros et al. 2011). WWTP effluents are discharged to surface waters or reused for irrigation, and the biosolids produced are applied to agriculture soil or landscapes as soil amendment or disposed of in landfills. The benefits of effluent reuse and biosolids application in agricultural soils are obvious. The use of WWTP effluents as reclaimed water can increase the water supply in areas in which the water demand by the urbanised population has exceeded the available natural water sources, becoming a limiting factor for agricultural and industrial requirements (Ternes et al., 2007). In addition, the application of biosolids to land, the option favoured internationally for sludge management, contributes positively to recycling nutrients, soil properties, and fertility (Clarke and Smith, 2011). However, several studies have investigated the occurrence and fate of pharmaceuticals in irrigated soils with reclaimed water (e.g., Kinney et al., 2006; Ternes et al., 2007; Borgman and Chefetz, 2013) and in biosolids-amended soils (e.g., Lapen et al., 2008; Wu et al., 2010). In recent years, concern has arisen regarding

the presence of WWTP-derived PCs in runoff and drainage water from cultivated fields, either due to irrigation with reclaimed water and/or biosolids application, and the ability of these PCs to reach the freshwater compartment (Topp et al. 2008; Yang et al., 2012). Many studies regarding the direct emissions of PCs from WWTP effluents to surface waters have been conducted; however, the indirect emission pathways are generally neglected when examining the prioritisation of PCs for further monitoring or additional research, especially in the case of the reclaimed water pathway. Moreover, past studies examining the prioritisation of PCs from biosolids-amended soils do not account for the dissociating properties of PCs (e.g., Eriksen, Amundsen et al., 2009) or are limited to a few therapeutic classes (e.g., Oldenkamp et al., 2013).

In this study, we collected data from literature concerning PC occurrences in 179 WWTPs in Europe to provide a holistic view of the PCs of most concern in the indirect emission pathways to the freshwater compartment. This study focuses on freshwater ecosystems; terrestrial ecosystems and the risk of human exposure are out of the scope of this research. A multimedia model was applied to prioritise PCs according to their probabilistic impact on freshwater ecosystems from indirect emissions from WWTPs. Research topics were prioritised for the compounds of most concern by identifying important gaps in knowledge and by computing the contribution to the impact variance of the uncertainty of the model parameters and the variability. Previously, a similar assessment was performed concerning direct emissions to the freshwater compartment (Morais et al., 2013a).

5.3 Methodology

5.3.1 Emission data

A survey of the occurrence of PCs in European WWTPs was performed to compute the concentration probability distributions in either influents or effluents. This survey was based on a recent review conducted by Verlicchi et al. (2012) on the global occurrence of PCs in urban wastewater. For this Europe-focused study, 54 peer-reviewed publications were collected from the cited review, covering 179 WWTPs located in Austria, Denmark, Finland, France, Germany, Greece, Italy, Spain, Sweden, Switzerland, and the UK, with capacities ranging from 6 000 to 2 500 000 population equivalents. The concentration data included 85 drugs in 15 different classes: 20 analgesics/anti-inflammatories (including 1 metabolite), 15 antibiotics, 12 β-blockers, 8

psychiatric drugs, 7 lipid regulators (including 2 metabolites), 4 hormones, 4 β-agonists, 4 receptor antagonists, 3 antineoplastics, 2 antihypertensives, 2 diuretics, 1 proton-pump inhibitor, 1 antiseptic, 1 contrast agent, and 1 antifungal (Appendix C, Table 17). The quality of the effluent concentration data reported in the literature has been confirmed according to the EC Technical Guidance Document (TGD) on Risk Assessment (EC, 2003). The geometric mean and the geometric standard deviation of the influent and effluent concentrations of each compound were computed, assuming a lognormal distribution and weighted by the population served in each WWTP. The WWTP parameters of the Sewage Treatment Plant (STP) model of the EPI Suite™ (USEPA, 2008) and the biodegradation rates in WWTPs that were estimated by the same model were applied in a mass balance to estimate PC concentrations in biosolids and their confidence intervals, assuming steady-state concentrations (Appendix C, Table 17). However, the estimated concentrations concern the raw sludge, and the potential effects of sludge digestion on the removal of PCs were disregarded in the present study.

5.3.2 Fate and effect

A fate factor describes the marginal increase in the environmental concentration per unit of emission. The fate calculations were performed using the multimedia model USEtox (Rosenbaum et al., 2008) adapted for dissociating compounds (Morais et al., 2013ab). Because many PCs contain dissociating functional groups, their charge changes with solution pH, and thus, their transport behaviour may be affected. The adaptation of the model includes regressions to estimate the pH-dependent fate parameters of the dissociating compounds, such as partitioning coefficients and bioconcentration factors (Franco and Trapp, 2008; Fu et al., 2009), if no suitable experimental values are available in the literature. Moreover, in the biosolids-amended soil pathway, the biosolids-amended soil compartment was modelled as a biosolids compartment nested in the agricultural soil compartment to account for differences in the sorption, desorption, and degradation of the compounds between the biosolids and soil matrices (Morais, Delerue-Matos et al.). The model accounts for inter-media transport processes, intra-media partitioning and degradation in the 5-compartment system (Figure 11), for which the landscape characteristics of the USEtox European continental scale were applied. To estimate direct and indirect photodegradation rates, a number of models and assumptions were applied and are described in detail in Morais et al. (2013ab). Briefly,

average full day direct photolysis rates for winter and summer were calculated using GCSOLAR (USEPA, 1999) for the latitude range of 40-60° by providing, if available in the literature for the compounds under study, quantum yields and molar absorption coefficients as a function of the UV/VIS wavelength range (Appendix C, Table 18). For indirect photolysis, bimolecular rate constants (k_{OH}, in $M^{-1}s^{-1}$) for the reaction between a compound and the most reactive chemical transient (˙OH) (Appendix C, Table 18) were converted to pseudo-first order rate constants by multiplication by the hydroxyl radical concentration in surface waters (in M).

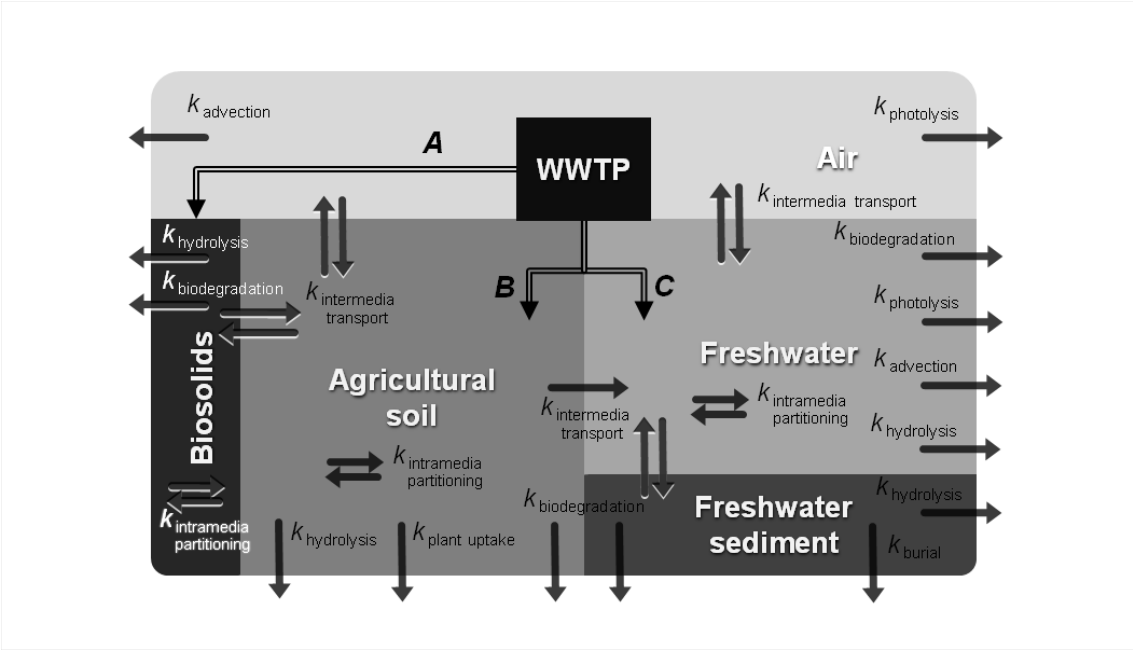

Figure 11**:** Five-compartment system for the dissipation of pharmaceuticals from A) emission to agricultural soil of WWTP biosolids, B) emission to agricultural soil of WWTP effluents, and C) direct emission to freshwater of WWTP effluents. Bold arrows represent rates (*k*) of intermedia transport, intramedia partitioning, and degradation.

The ecotoxicity effect factor (EEF) addresses the marginal increase in effect (toxic pressure on ecosystems) per unit of chemical concentration. A potentially affected fraction (PAF) of species approach based on the average toxicity was considered in the present study as the basis for the EEF calculation, as adopted in the USEtox model. The average toxicity is the hazardous concentration (HC) at which the effect concentration for a given endpoint, affecting 50% of tested individuals (EC50), is exceeded for 50% of the included species, also called $HC50_{EC50}$. As a PAF-based approach, the assessment of the mean impact (AMI) on ecosystems method (Payet, 2004; Payet, 2005; Payet and Jolliet, 2005) was applied, allowing the quantification of uncertainty as two statistical estimators, a parametric and non-parametric estimator, can be used in the AMI method

to estimate the toxicity of a substance to biological species and the associated confidence interval. The average toxicity focuses on the trophic structure by including the EC50 values of at least 3 trophic levels: primary producers (algae), primary consumers (crustaceans), and secondary consumers (fish) (Appendix C, Table 19). Chronic EC50 values were preferred because of the low environmental concentrations and the constant introduction of PCs, indicating that these compounds are more likely to have chronic rather than acute toxic effects on aquatic biota (Carlsson et al., 2006; Fent et al., 2006; Quinn et al., 2008). However, as chronic ecotoxicological data on PCs remain rare, the best estimate assessment factor (AF) to extrapolate the chronic HC50 from the acute HC50, recommended by Larsen and Hauschild (2007b) and adopted in the USEtox model (Huijbregts et al., 2010), was applied in the present study. Furthermore, when acute EC50 values were not available, the best estimates from Payet (2004) for extrapolation from other endpoints were also applied. When no experimental data were available, ECOSAR v1.00 (Nabholz and Mayo-Bean, 2009) was used to predict EC50s for algae, daphnia, and fish. The endpoints used for the average toxicity calculation include the inhibition of growth and photosynthesis for algae, mortality or immobility (*Daphnia)* for invertebrates, and mortality or, for the endocrine disruption toxic mode of action, change in sex ratio for fish.

5.3.3 Uncertainty analysis

The propagation of the uncertainty and variability of the model parameters in the output results was quantified using Monte Carlo analysis (Appendix C, Table 20). The analysis includes the following factors:

1) the variability of the continental-scale environmental and meteorological parameters (agricultural soil and freshwater pH, fraction of organic carbon in soil (f_{OC}), rainfall, freshwater concentration of suspended matter, dissolved organic carbon, and $^{\cdot}OH$);
2) the variability of the direct photolysis rates;
3) the variability of the concentrations of PCs in the effluents in the reclaimed water pathway;
4) the uncertainty of the concentrations if PCs in the biosolids in the biosolids-amended soils pathway;

5) the variability of the experimental parameter values (partition coefficients, biodegradation half-lives, and k_{OH}); the geometric mean and the geometric standard deviation of experimental values were set as uncertainty parameters, assuming a lognormal distribution;
6) the extrapolation of parameter values from one compartment to another (biodegradation rates in biosolids) and from other parameter values (K_{DOC} from K_{OC});
7) the uncertainties associated with the regression equations adopted in the model to estimate the partition coefficients, bioconcentration factors and biodegradation rates; the training and validation sets used to derive the regression methods applied in the present study (Franco and Trapp, 2008; USEPA, 2008; Fu et al., 2009; USEPA, 2009) were used to derive the mean residual errors and their probability distributions and were fit into the regressions, as described in (Morais et al. 2013ab);
8) the uncertainty distributions of the $HC50_{EC50}$ values, according to the parametric estimator as recommended by (Payet, 2004), based on the assumption of a lognormal distribution of data using the geometric mean as $HC50_{EC50}$ and Student's t-statistics for the confidence interval (Payet, 2004; Payet, 2005); the uncertainty of extrapolating chronic $HC50_{EC50}$ from acute chronic $HC50_{EC50}$ was not addressed in the present study, nor was the uncertainty of extrapolating and estimating individual endpoints.

5.4 Results and discussion

5.4.1 The pathway of irrigation with reclaimed water

Figure 12 shows the comparative ecotoxicological impact of PCs on the freshwater compartment for the reclaimed water pathway. The contribution of each PC to the variance of the total ecotoxicity impact is shown in Figure 13. The PCs of greatest concern are those with a 90% contribution to the total impact variance, and these are discussed further. The contribution of the model parameters to the variance of the impact results of these PCs is shown in Figure 14.

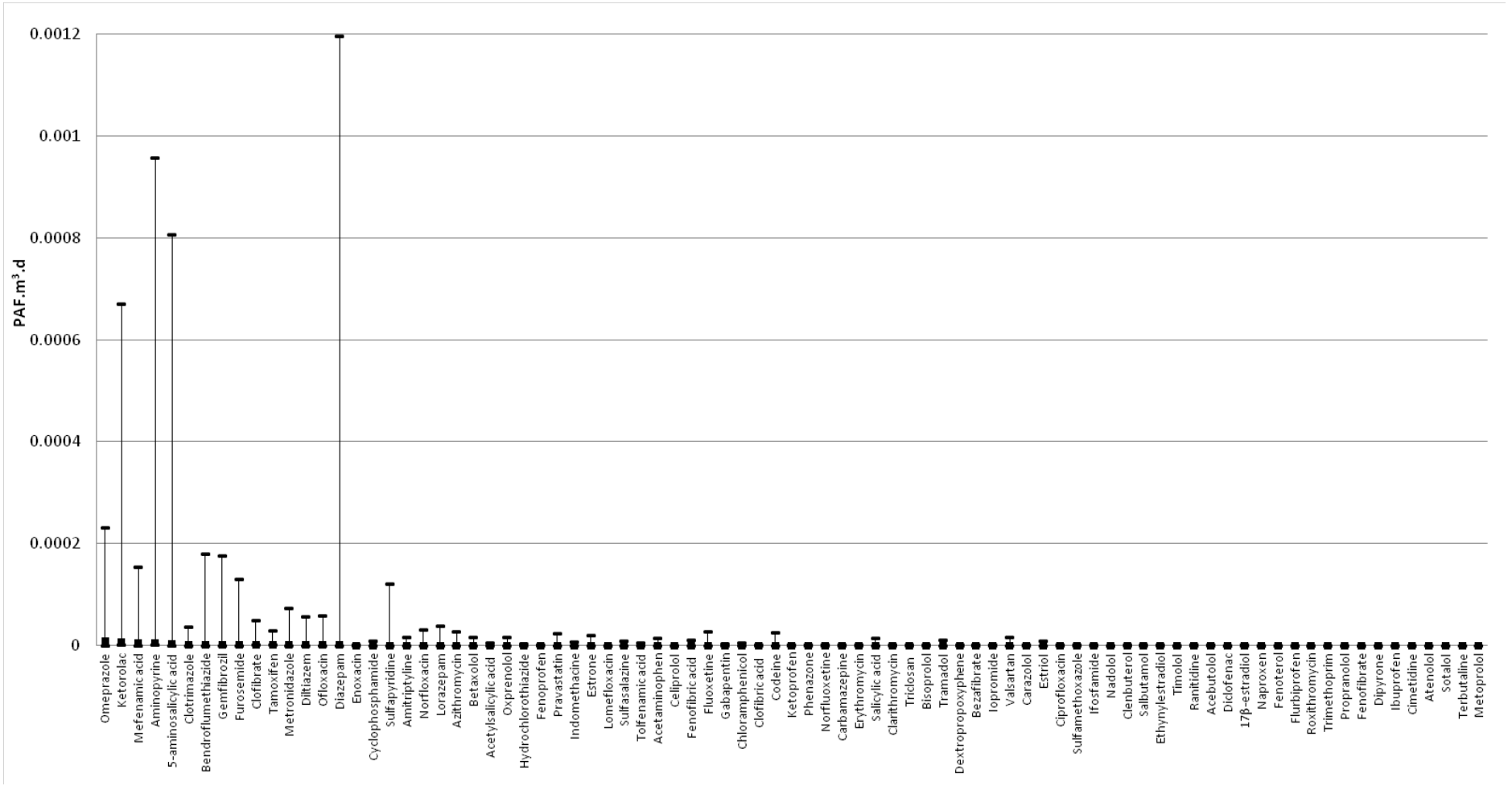

Figure 12: Probability distribution median and 95% confidence interval of ecotoxicity impacts of PC's on freshwater, in PAF m^3 day, per m^3 of WWTP effluent as reclaimed water for irrigation in agricultural soils.

The non-steroidal anti-inflammatory ketorolac displays the highest median impact in this contamination pathway (Figure 2). The HC50 parameter is very relevant to the impact of ketorolac because it contributes 50.0% of the impact variance. In addition, further uncertainty related to the HC50 parameter was not quantified because the EC50 values were estimated. In several European countries, the marketing of ketorolac was withdrawn or the dose and treatment duration were restricted due to several side effects (U.N., 2003). Hence, very limited data regarding ketorolac in WWTP effluents are available in the literature given that, in general, pharmaceuticals with high consumption rates are those selected for further investigation (Escher et al., 2011). Ketorolac was detected at a median concentration of 0.228 µg/l and a maximum concentration of 0.539 µg/l in effluent from a WWTP in Spain (Rosal et al., 2010a). The uncertainty of the K_{OC} estimation of this acidic compound represents 44.0% of the impact variance. Moreover, ketorolac is expected to be susceptible to indirect photolysis, and it may also be susceptible to direct photolysis because it contains chromophores that absorb at wavelengths >290 nm; hence, its impact may be overestimated as no experimental data were found in the literature.

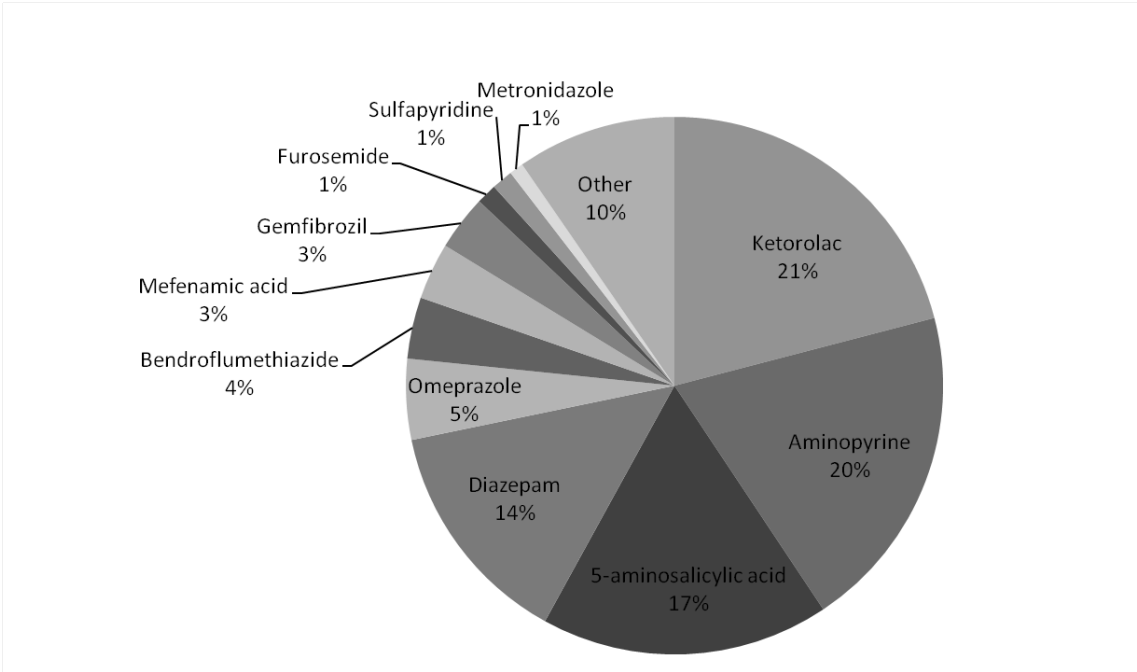

Figure 13: Contribution of PC's to variance of total freshwater ecotoxicity impact for the reclaimed water pathway

The calculated impact of aminopyrine is based on estimated ecotoxicological data. Even excluding the uncertainty of the ecotoxicity data estimation, the HC50 parameter contributes 41.4% of the variance in the impact of aminopyrine. Moreover, this

compound is not commonly detected in WWTP effluents. Ternes (1998) reported the detection of aminopyrine at a maximum concentration of 1.0 µg/l in the effluents of 3 WWTP during monitoring of 16 WWTPs in Germany. Andreozzi et al. (2003) reported detection in a WWTP in France at a concentration of 0.43 µg/l; however, the same authors reported no detection in the effluent from another WWTP in France, 2 WWTPs in Italy, 1 WWTP in Sweden or 1 WWTP in Greece. The human clinical use of aminopyrine is widely banned due to the risk of agranulocytosis and due to its potential to produce carcinogenic nitrosamines (U.N., 2003); hence, its presence in WWTP discharges may be caused by low levels of application in veterinary medicine or by industrial release (Ternes, 1998). The profiles of sorption to solid matrices of this PC warrant further experimental investigation because the estimated K_{OC} contributes 19.4% to the impact variance. In addition, a relevant increase of mobility in SOM-poor soils is estimated for aminopyrine, whether through decreased hydrophobic interactions with organic matter in its neutral form at higher soil pHs or through decreased electrostatic interactions with organic matter in its cationic form at lower soil pHs, given that the f_{OC} parameter contributes 11.5% to its impact variance. No abiotic degradation data are available, but aminopyrine is expected to be susceptible to indirect photolysis and contains chromophores that absorb at wavelengths >290 nm; therefore, aminopyrine may also be susceptible to direct photolysis, and hence, the residence time of aminopyrine in the aquatic environment may be overestimated.

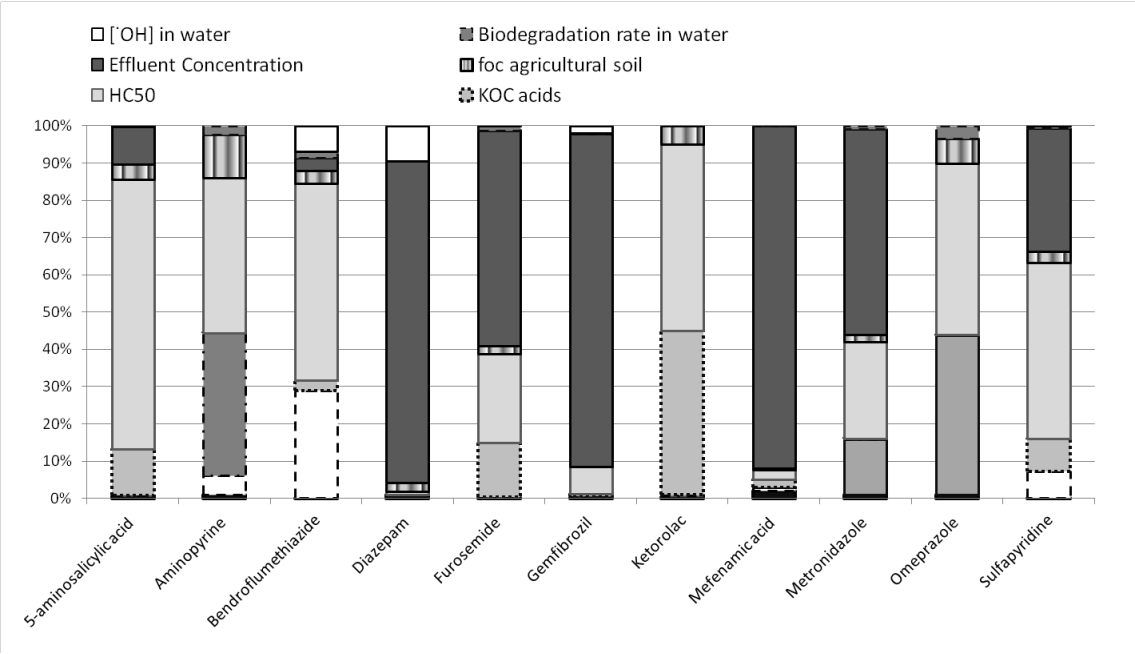

Figure 14: Contribution of model parameters to impact variance of PCs of most concern for the reclaimed water pathway.

The impact results for the anti-inflammatory 5-aminosalicylic acid are primarily sensitive to the HC50 parameter, which contributes 72.4% to the variance of the output results. Moreover, only EC50 values for fish species are available in the literature, and EC50s were estimated for the other trophic levels. Very limited data regarding 5-aminosalicylic in WWTP effluents are available in the literature. It was detected at median concentrations of 0.63 and 21.1 µg/l in the effluents of 2 WWTP that were used in activated sludge treatments in South Wales, UK (Kasprzyk-Hordern et al., 2009). In addition, 5-aminosalicylic contains chromophores that absorb at wavelengths >290 nm and, therefore, may be susceptible to direct photolysis by sunlight and to photosensitisation.

The range of diazepam effluent concentrations reported in the literature varies by 3 orders of magnitude, from 0.04 to 19.3 µg/l (Ternes, 1998; Suárez et al., 2005); however, the occurrence of this compound in WWTP effluents is very rare in the literature. The impact results of diazepam are especially sensitive to the variability of effluent concentration, which contributes 86.4% of the impact variance. Because diazepam displays the highest upper limit of the impact result confidence intervals, the monitoring of this antihypertensive in WWTP effluents is necessary. Its 9.5% contribution to the variance of the concentration of ˙OH radicals in freshwater suggests an increased residence time of diazepam in poor quality, nitrate-containing waters. Reactions mediated by ˙OH radicals tend to predominate in waters with high nitrate concentrations (Lam et al., 2003), which generate ˙OH radicals. However, in low nitrate waters, the contributions of other reactive intermediates to the degradation of diazepam, which are unclear in the present study, may become more apparent.

The HC50 parameter contributes 46.0% to the impact variance of the proton-pump inhibitor omeprazole. Moreover, only 1 experimental EC50 value was found in the literature. Very limited data regarding concentrations of omeprazole in WWTP effluents are available in the literature; nevertheless, it is one of the most widely prescribed pharmaceuticals. Omeprazole was detected at a maximum concentration of 0.922 µg/l and an average concentration of 0.322 µg/l in the effluent from a WWTP in Spain (Rosal et al., 2010a). In addition, the uncertainty of K_{OC} estimation represents 42.8% of the variance. Moreover, omeprazole is expected to undergo hydrolysis in the environment due to the presence of functional groups that hydrolyse under environmental conditions, and it may also be susceptible to direct and indirect

photolysis; hence, the residence time in the freshwater compartment is most likely overestimated.

Measurements of the thiazide diuretic bendroflumethiazide in WWTP effluents and in the environment are rare. Kasprzyk-Hordern et al. (2009) reported detection at a median concentration of 0.011 µg/l and a maximum concentration of 0.058 µg/l in the effluent from a WWTP in Wales, UK; conversely, no detection was reported at any other WWTP plant (limit if detection = 0.8 ng/l). In addition, it was not detected in the river into which the former WWTP effluent was discharged (limit of detection = 0.5 ng/l). Bendroflumethiazide is primarily sensitive to the HC50 parameter estimation, with a 52.9% contribution to its impact variance. In addition, ecotoxicological data were estimated for all trophic levels. The agricultural soil pH has a contribution of 28.8%, given that the anionic form of bendroflumethiazide occurs at higher soil pHs (pK_a = 8.50), thus displaying reduced sorption capacity into the solid matrix. No abiotic degradation data are available; however, bendroflumethiazide may be susceptible to indirect and direct photolysis because it contains chromophores that absorb at wavelengths >290 nm.

The non-steroidal anti-inflammatory mefenamic acid is widely used and commonly found in effluents and biosolids (e.g., Tauxe-Wuersch et al. 2005; Barron et al., 2009; Kim et al., 2009a; Radjenovic et al., 2009; Rosal et al., 2010a). Mefenamic acid is essentially in its anionic form at pH 7 (pK_a = 4.20), and thus, poor sorption to particles may be expected in WWTPs; therefore, depending on consumption patterns, mefenamic acid may be present at significant concentrations in WWTP effluents. Concentrations of mefenamic acid in WWTP effluents in the literature vary by 3 orders of magnitude, from 0.005 (Kasprzyk-Hordern et al., 2009) to 3.0 µg/l (Tauxe-Wuersch et al., 2005). At the higher concentrations in the reported range, a significant impact is estimated because the effluent concentration parameter represents 92.0% of the impact variance. However, the comparative impact results of this anti-inflammatory may be overestimated as Werner et al. (2005) suggested that photosensitisation by excited triplet-state DOM may contribute to the environmental degradation of mefenamic acid. The influence of this degradation mechanism on the comparative impact results is yet unknown in the present study.

The lipid regulator gemfibrozil is essentially in its anionic form at environmentally relevant pHs (pK_a = 4.48), thus displaying comparatively higher availability for

transport to the freshwater compartment. This pharmaceutical is commonly found in WWTP effluents (e.g., Ternes, 1998; Andreozzi et al, 2003; Munoz et al., 2009) and is especially sensitive to the effluent concentration parameter, representing 89.4% of its impact variance. The concentrations of gemfibrozil in WWTP effluents reported in the literature range 3 orders of magnitude, from 0.003 (Rosal et al., 2010a) to 5.2 µg/l (Munoz et al., 2009). Indirect photolysis possibly plays a role in the persistence of this compound in the aquatic environment, but no data were available in the literature; therefore, its impact may be overestimated.

The impact results of furosemide are primarily sensitive to the effluent concentration and HC50 parameters, which contribute 57.8 and 23.8% to the variance, respectively. The concentrations of furosemide in WWTP effluents reported in the literature vary by 2 orders of magnitude (Kasprzyk-Hordern et al., 2009), from 0.043 to 1.823 µg/l. Furosemide is not expected to directly photolyse due to the lack of absorption in the environmental UV spectrum (>290 nm), but it is expected to be susceptible to indirect photolysis; therefore, the depletion of furosemide may be underestimated in the aquatic environment.

For sulfapyridine, the HC50 parameter is of relevant concern because it contributes 47.3.1% to the impact variance. Moreover, the ecotoxicological data were estimated for all trophic levels. The concentration of sulfapyridine in effluents contributes 33.0% to its impact variance. Sulfapyridine concentrations in WWTP effluents in the literature vary by 2 orders of magnitude, from 0.040 to 1.112 µg/l (Göbel et al. 2005; Kasprzyk-Hordern et al. 2009). In addition, sulfapyridine contains chromophores that absorb at wavelengths >290 nm, and therefore, it may also be susceptible to direct and indirect photolysis; however, no experimental data were found in the literature.

The antibiotic metronidazole is primarily sensitive to the effluent concentration parameter, which contributes 55.1% to the impact variance. The reported concentrations in WWTP effluents vary from 0.05 µg/l (Rosal et al., 2010a) to 0.56 µg/l (Kasprzyk-Hordern et al., 2009). However, there are very limited concentration data from WWTP effluents. The HC50 parameter contributes 25.8% to the impact, and 3 trophic levels are represented by experimental EC50s of 5 species. In addition, metronidazole may be susceptible to indirect photolysis; however, no experimental data are available.

5.4.2 The biosolids-amended soils pathway

The anti-inflammatory 5-aminosalicylic acid displays the highest median impact result in this contamination pathway (Figure 15). The contribution of each PC to the variance of the total ecotoxicity impact is shown in Figure 16. The contribution of the modelling parameters to the variance of the impact results for the pharmaceuticals of most concern (90% of total ecotoxicity impact) is shown in Figure 17. The anti-inflammatory 5-aminosalicylic acid is essentially in its anionic form at environmentally relevant pHs (pK_a = 5.87); therefore, it displays high availability for transport to the freshwater compartment from the agricultural soil compartment. The most sensitive modelling parameters, HC50 and concentration, contribute 46.8 and 41.2% to the variance, respectively, and the lack of abiotic depletion data were already discussed in the previous section. The anti-inflammatory 5-aminosalicylic acid may be a hydrophilic compound, having an estimated log K_{OW} of 0.98. In addition, its acidity constant is sufficiently low that the molecule is predominantly anionic at pH 7. Both physicochemical properties indicate that poor sorption onto the sewage sludge would be expected because of electrostatic repulsion with the negatively charged groups of the activated sludge. Nevertheless, adsorption of pharmaceuticals onto the sludge can be influenced by intermolecular forces, such as Van der Waals forces. These hydrophobic interactions with the sludge matrix can occur despite the presence of ionic charges and/or the low log K_{OW} of pharmaceuticals (Kulshrestha et al., 2004). However, the biodegradation rate in the WWTP was estimated. Furthermore, the uncertainty inherent in the estimation of this parameter was not included in the Monte Carlo analysis. In summary, in addition to the shortcomings discussed in the previous section, this pharmaceutical warrants further attention regarding its fate in WWTPs.

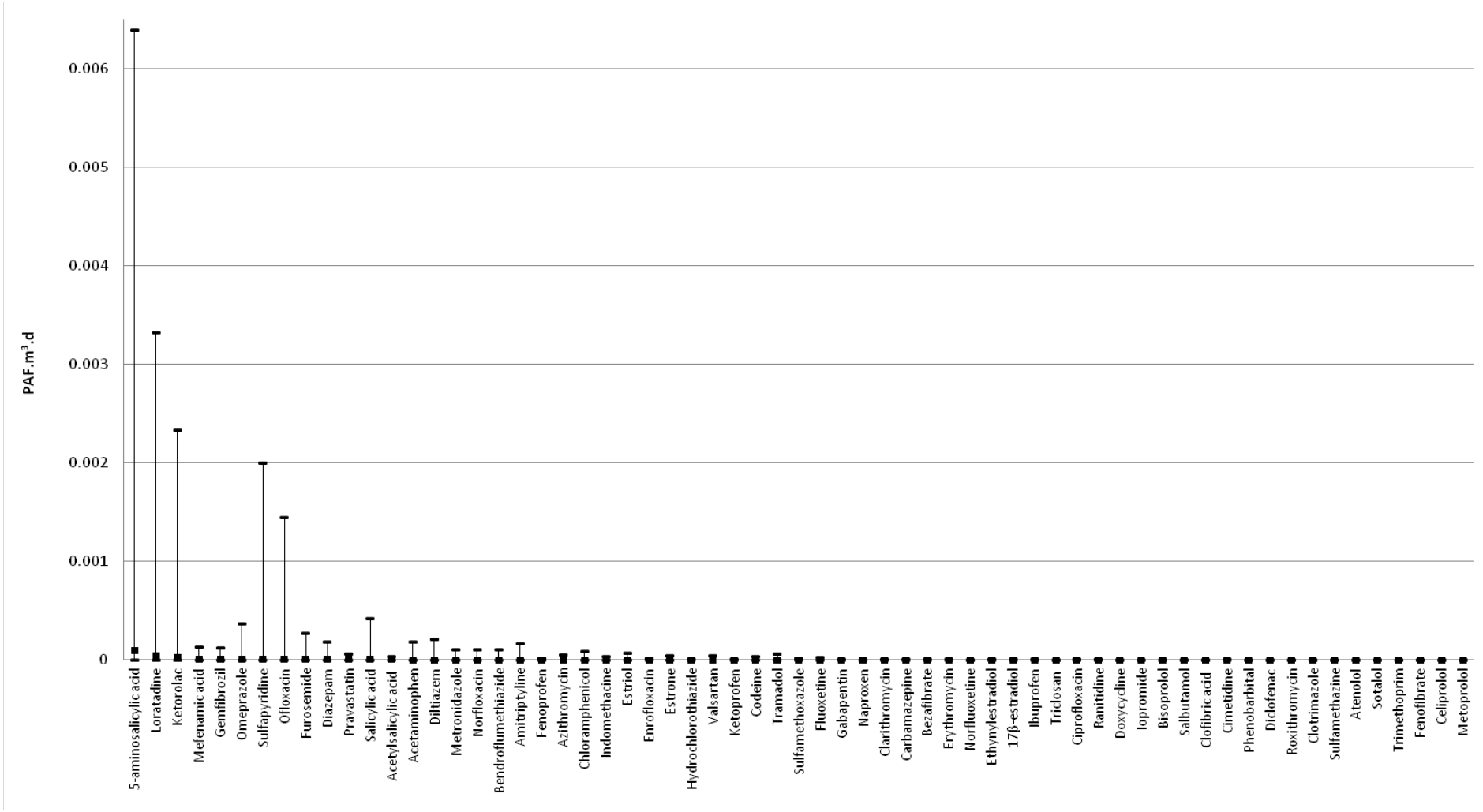

Figure 15: Probability distribution median and 95% confidence interval of ecotoxicity impacts of PC's on freshwater, in PAF m^3 day, per kg of WWTP biosolids (dry matter) as agricultural soil amendment.

The impact results of the receptor antagonist loratadine are primarily sensitive to the uncertainty of the HC50 parameter because it contributes 81.2% of the impact variance. The high hydrophobicity of this pharmaceutical (experimental log K_{OW} = 5.20) indicates a tendency to partition to particles in WWTPs and, therefore, to be present in sewage sludge. Removal in WWTPs through sorption to sludge was shown to be an important pathway in the fate of loratadine in WWTPs (Radjenovic et al., 2009). Nevertheless, such hydrophobicity indicates poor availability for transport to the freshwater compartment in the aqueous phase of the soil matrix. Conversely, its high hydrophobicity also indicates a strong tendency to partition onto biomembranes; therefore, the baseline toxicity of this neutral pharmaceutical may be high. However, EC50 values were estimated for all trophic levels. For this particular contamination route, ecotoxicological tests on loratadine are necessary for more conclusive results. Moreover, the calculated impact of loratadine is based on very limited concentration data for either WWTP effluents or influents. Radjenovic et al. (2009) reported concentrations ranging from 0.015 to 0.043 µg/l in influent to a WWTP in Spain. Loratadine contains chromophores that absorb at wavelengths >290 nm, and therefore, it may also be susceptible to direct and indirect photolysis; however, no experimental data were found in the literature.

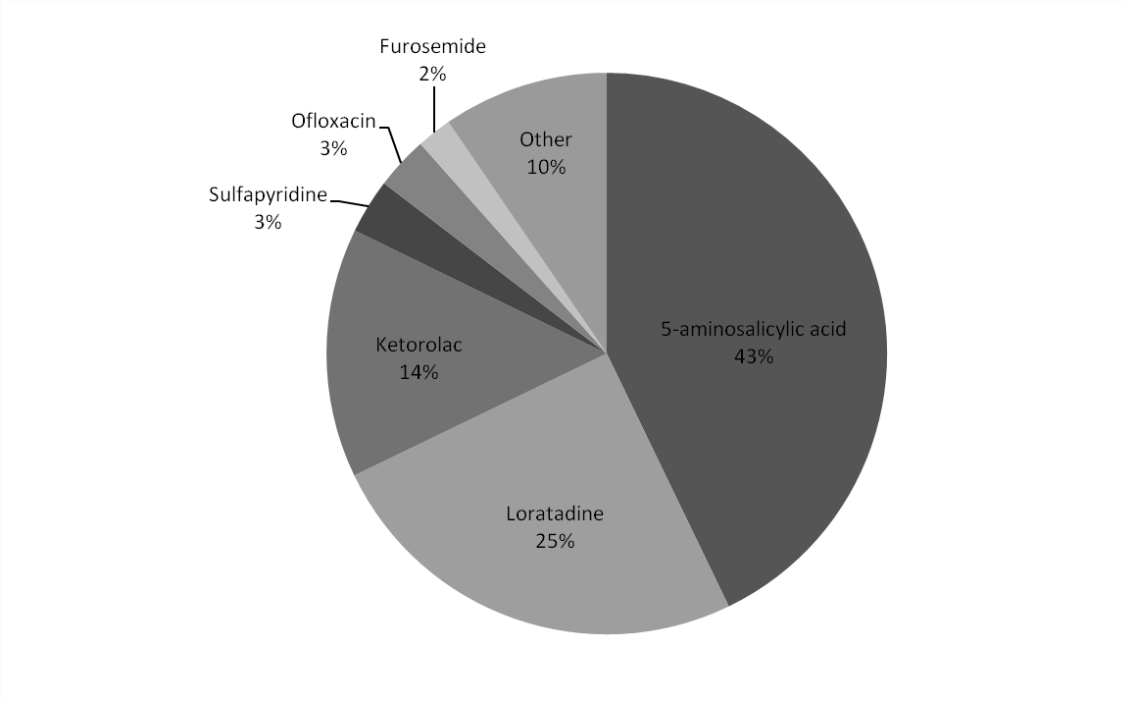

Figure 16: Contribution of PC's to variance of total freshwater ecotoxicity impact for the biosolids pathway

The non-steroidal anti-inflammatory ketorolac is also a pharmaceutical of special concern in this contamination route. The impact results of ketorolac are primarily sensitive to the parameters HC50 and K_{OC}, estimated to contribute 48.0 and 44.0% to the variance, respectively. These parameters were already discussed in the previous sections. The estimation of the ketorolac concentrations in the biosolids was based on very limited data regarding its occurrence in WWTP effluents and influents, where it was detected at a maximum concentration of 2.8 µg/l in Spain (Rosal et al., 2010a). Ketorolac is essentially in its anionic form at pH 7 (pK_a = 3.49), and thus, poor sorption to particles may be expected in WWTPs. However, the STP model estimates that this compound is not readily biodegradable in WWTPs, and the underestimation of the biodegradation rate may have led to the overestimation of the concentration of ketorolac in biosolids. The fate of this anti-inflammatory in WWTPs should be further investigated, and ecotoxicological tests and abiotic degradation studies are necessary, as stated in the previous section.

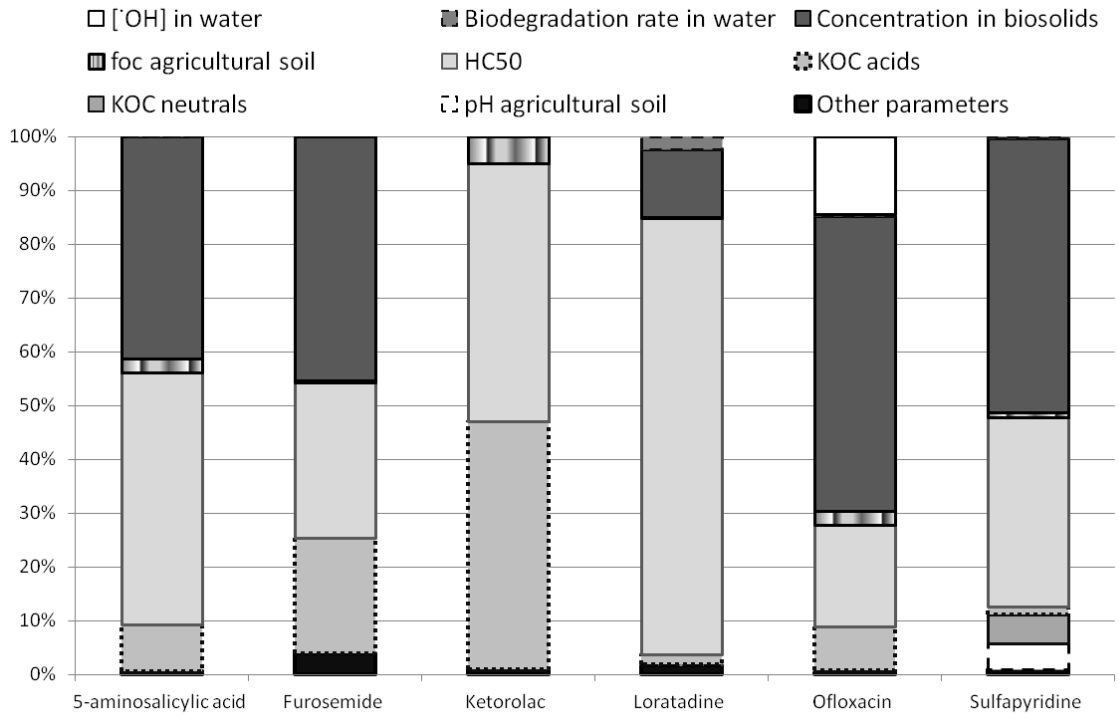

Figure 17: Contribution of model parameters to impact variance of PCs of most concern for the biosolids pathway.

The concentrations reported in the literature of sulfapyridine in WWTP influents range 3 orders of magnitude, from 0.06 to 12.39 µg/l (Göbel et al., 2005; Kasprzyk-Hordern,

et al., 2009). The concentration in biosolids contributes 50.9% to the impact variance of sulfapyridine. The HC50 parameter contributes 35.1% to the impact variance. Moreover, as stated in the previous section, the ecotoxicological data are estimated for this compound, and no experimental abiotic degradation data are available in the literature.

The concentrations of ofloxacin in WWTP effluents reported in the literature range 3 orders of magnitude, from 0.022 to 31.7 µg/l (Radjenovic et al. 2009; Zorita et al., 2009). The propagation of the variability of this parameter onto the estimation of the concentration in biosolids contributes 54.8% to the impact variance. The HC50 parameter contributes 18.9% to the impact variance. Moreover, an estimated EC50 value for algae was applied, and an EC50 value for fish was extrapolated from a no observed effect concentration (NOEC) value. In addition, ofloxacin may also be susceptible to direct photolysis as it contains chromophores that absorb at wavelengths >290 nm; however, no experimental data are available in the literature.

The variability of concentration of the diuretic furosemide in biosolids contributes 42.2% to the statistical spread of the impact result. The concentrations of furosemide in WWTP effluents reported in the literature vary by 2 orders of magnitude (Kasprzyk-Hordern et al., 2009), from 0.043 to 1.823 µg/l. Furosemide is predominantly anionic at pH 7 (pK_a = 3.18); however, its occurrence was reported in sewage sludge in Spain (Rodríguez-Rodríguez et al., 2012) at an average concentration of 23.4 µg/kg dry matter (in the present study, geometric mean = 37.4 µg/kg dry matter and 95% confidence interval = 0.0-942.5 µg/kg dry matter). The HC50 parameter contributes 38.7% to the variance of the output results, and 3 experimental acute EC50 values representing species from 3 trophic levels were applied. As stated in the previous section, the lack of experimental abiotic degradation data may have led to the overestimation of its impact in the present study.

5.4.3 Additional considerations

Table 7 summarises future research topics for the PCs of greatest concern for indirect emission pathways. Anionic compounds that are dissociated at the environmental pH tend to be the most relevant because of their lower potential sorption to solid matrices, and consequently, their higher availability for transport to the freshwater compartment. The transport of basic compounds to freshwater is relevant in SOM-poor soils; however,

among the compounds of most concern, only aminopyrine in the reclaimed water use pathway is of concern. These future research topics can be related to 3 issues: a) the fate of PCs in WWTPs, b) substance-specific modelling parameters, and c) the lack of spatial and time resolution within the model.

The first issue includes compounds with very limited concentration or detection data from the reclaimed water pathway of WWTP effluents, such as ketorolac or 5-aminosalicylic acid, and those of greatest concern for the biosolids pathway because their concentrations of PCs in biosolids were estimated. For more conclusive results, these substances should be the focus of further monitoring in WWTPs, depending on the geographical usage patterns. This category should also include compounds whose impact result would be most sensitive to variations in the emission concentrations. A comparatively well-characterised pharmaceutical from an impact perspective would, ideally, account for the low variance of the output results due to the environmental fate, transport, and impact modelling parameters. The uncertainty of its impact result, from a modelling perspective, would be primarily related to the variability of the concentrations in WWTP effluents, depending on the geographical and seasonal usage patterns, treatment technologies, and operation conditions. For example, variations in the consumption and discharge to effluents of macrolide antibiotics are twice as high in winter because these pharmaceuticals are primarily used to cure infections of the respiratory tract (Alder et al., 2004); membrane bioreactors generally feature higher removal rates than conventional activated sludge systems (Verlicchi et al. 2012), and in terms of operation conditions, several researchers have noted improved removal from WWTPs with increased solid retention time, especially in the case of EDCs (e.g., Göbel et al., 2007; Suarez et al., 2010). These compounds should be subjected to detailed ecological risk assessments, possibly leading to research and development on the operation and design of WWTPs to improve the reduction of effluent concentrations of the compounds. However, the compounds that are most sensitive to the variability in the concentrations in the WWTP emissions, such as diazepam or gemfibrozil, have other research priorities because of either limited occurrence data on their occurrence or incomplete modelling parameters.

Table 7: Research topics for PCs of most concern for the biosolids (‡) and reclaimed water (†) pathways.

	Effluent characterization [a]	Characterization in biosolids [b]	Sorption to soil matrices [c]	Ecotoxicological effect characterization [d]	Parameter incompleteness	
					Abiotic degradation mechanisms [e]	Derivatives toxicity [f]
5-aminosalicylic acid †‡	↓↓↓	↓↓↓	✔	↓↓↓	↓↓	↓↓
Aminopyrine †	↓		✔	↓↓↓	↓↓	↓↓
Bendroflumethiazide †	↓↓↓			↓↓↓	↓↓	↓↓
Diazepam †	↓			↓		↓↓
Furosemide †‡	↓↓↓	↓↓↓	✔	↓↓	↓↓	↓↓
Gemfibrozil †	↓			↓↓↓	↓	↓↓
Ketorolac †‡	↓↓↓	↓↓↓	✔	↓↓	↓	↓↓
Loratadine ‡	↓↓↓	↓↓↓		↓↓↓	↓↓	↓↓
Mefenamic acid †	↓↓			↓	(↓↓)	↓↓
Metronidazole †	↓↓↓		✔	↓	↓	↓↓
Ofloxacin ‡	↓↓	↓↓↓		↓↓↓	↓	↓↓
Omeprazole †	↓↓↓		✔	↓↓↓	↓↓↓	↓↓↓
Sulfapyridine †‡	↓↓↓	↓↓↓		↓↓↓	↓↓	↓↓

[a] ↓: reported measurements in more than 10 WWTPs; ↓↓: reported measurements in between 5 and 10 WWTPs; ↓↓↓: reported measurements in less than 5 WWTPs.
[b] Compounds of concern for the biosolids pathway; concentration data on biosolids were estimated.
[c] Relevant contribution of K_{OC} estimation to the impact result (>10%).
[d] ↓: more than 3 acute EC50s covering 3 trophic levels; ↓↓: 3 acute EC50s covering 3 trophic levels; ↓↓↓: at least 1 estimated or extrapolated EC50.
[e] number of possible abiotic degradation mechanisms not included in the assessment (hydrolysis, direct and indirect photolysis); (↓↓) denotes a specific degradation pathway with some evidence of occurrence in the literature but with no data available.
[f] number of possible degradation mechanisms generating derivatives (hydrolysis, photolysis and biodegradation).

The second issue, the substance-specific fate and transport modelling parameters and the ecotoxicological effect factor characterisation, includes compounds, such as ketorolac or omeprazole, whose impact results are most sensitive to the uncertainty of substance-specific modelling parameters, such as HC50 and K_{OC}, or whose impact results may be affected by parameter incompleteness, either by the lack of abiotic degradation data or by the lack of inclusion of degradation products. The HC50 parameter is relevant for compounds such as bendroflumethiazide and loratadine. The parametric quantification of HC50 uncertainty is generally based on only 3 data values, which typically would cause wide confidence limits (Larsen and Hauschild, 2007b). These compounds should be subjected to further ecotoxicological tests for more conclusive results. The estimation of the pH-dependent sorption of organic acids is also influential for compounds such as furosemide or ketorolac. The effects of complexation are not addressed in the regressions to estimate the K_{OC} value of dissociating compounds (Franco and Trapp, 2008), which may be especially relevant to the uncertainty of the organic acids regression. The formation of a neutral complex due to the binding of organic anions to metals or other ligands of opposite charge may alter the speciation and sorption equilibria, consequently increasing the lipophilicity of the complexes formed. For these compounds, research should focus on the measurement of an experimental range of K_d values for several soil samples, attending to the variation in the solid matrix characteristics in terms of particle size, pH and organic and clay content, which may be used as inputs into fate and transport models for more conclusive results.

The third issue addresses the variability in the landscape parameters, such as agriculture soil and freshwater pH, and the seasonal variation of the direct photolysis rates. Although the present model does not include the spatial and temporal resolution of the landscape parameters, their variability in the Monte Carlo analysis allows the determination of the sensitivity of PCs to those parameters. However, although the large scale applied in the present study displays a great variety of landscape characteristics, such parameters are generally of minor significance to the impact variance. Nevertheless, the impact of bendroflumethiazide in the reclaimed water use pathway is comparatively relevant for higher soil pH values, and the impact of aminopyrine may be comparatively relevant in SOM-poor soils; in addition, the impact of ofloxacin is estimated to be comparatively relevant in poor quality, nitrate-containing surface waters

because the variability of ˙OH concentration is somewhat significant for the impact of this compound via the biosolids pathway.

However, other sources of uncertainty not included in the Monte Carlo analysis may be important. The uncertainty of ecotoxicological data estimation, the extrapolation of endpoints, the lack of abiotic degradation data for several compounds, and the uncertainty of estimating biodegradation rates in WWTPs were already discussed above. In addition, the effects of the uncertainty of the influence of pH on direct and indirect photolysis rates, the uncertainty of the application of a linear dose-response curve for the calculation of EEFs, and the lack of spatial variation in the background impacts in the AMI method remain unclear, as does the effect of the exclusion of abiotic and biotic derivatives of parent compounds. For example, some researchers have suggested that the photo-transformation products of triclosan, diclofenac and/or hydrochlorothiazide have a higher toxicity potential than that of their parent compounds (Han et al. 2000; Schmitt-Jansen et al., 2007). Of special concern are the photodegradation products of triclosan, which include 2,8-dichlorodibenzo-p-dioxin (2,8-DCDD) and halogenated phenol compounds (Sanchez-Prado et al., 2006). Polychlorinated dibenzo-p-dioxins (PCDDs) containing 4, 5, or 6 chlorine atoms, which originate from the photodegradation of chlorinated triclosan derivatives and form during disinfection with chlorine in WWTPs, are highly toxic, particularly to the early stages of fish, with reported effect concentrations in the ng/l range, and are readily bioaccumulated (Grimwood and Dobbs, 1995). Moreover, the assumption of homogenous compartments for such complex media as soil or water represents a further uncertainty as a chemical entering these compartments is assumed to be immediately and perfectly diluted within the volume.

5.5 Conclusions

Notwithstanding the high uncertainties of the impact results, which range up to 13 orders of magnitude, and the limitations and incompleteness of the model, the outcome of the present study provides guidance towards either further monitoring of PCs or additional research. Thirteen compounds were identified as being of the most concern for the indirect emission pathways to surface waters, 4 of which were for both pathways (5-aminosalicylic acid, ketorolac, furosemide, and sulfapyridine).

The HC50 parameter, the variability of the emissions concentrations, and the K_{OC} estimation of organic acids are generally the model parameters that are most relevant to the uncertainty of the impact results. According to our results, the spatial and temporal variation of the environmental characteristics was found to be of minor significance to the output results.

Most of the identified PCs have rarely been investigated with regard to ecotoxicity, including 5-aminosalicylic acid, ketorolac, aminopyrine, omeprazole, bendroflumethiazide, sulfapyridine, loratadine, and ofloxacin. Moreover, most of these have rarely been investigated with regard to their occurrence in WWTPs, given that PCs such as 5-aminosalicylic acid, ketorolac, omeprazole, bendroflumethiazide, furosemide, and loratadine were only occasionally monitored in WWTPs. In addition, the gaps in knowledge regarding the abiotic degradation of most compounds may have led to the overestimation of their residence times in the freshwater compartment, and consequently to the overestimation of the impact comparatively to well-studied compounds in terms of fate parameters, such as diclofenac or triclosan, that were not identified as of most concern.

5.6 Acknowledgments

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6. General conclusions

In this PhD thesis a new and updated method for comparative risk and life cycle impact assessments adapted for the freshwater ecotoxicity impacts of ionizing organic compounds was outlined and the parameter uncertainty in characterisation factors (CFs) and impact results was addressed. In direct emission scenarios to the freshwater compartment of pharmaceutical compounds negligible differences were estimated between the new method and the conventional USEtox model, in which the former is based. However, in indirect emission scenarios, when the chemical is first emitted to soil compartments, the characterization factors of basic pharmaceutical compounds are overestimated up to 3 orders of magnitude in the conventional model and the 95% confidence intervals are overestimated up to 4 orders and 3 orders of magnitude in the upper and lower endpoint, respectively. In the case of indirect emissions, the underestimation of sorption to solid matrices, when using non-polar conventional regression methods, overestimates the availability for transport in the solution phase and, thus, largely overestimates CFs of basic compounds relatively to the alternative approach. The electrical attraction of basic organic compounds to the negatively charged sorption sites of organic colloids in soil is, therefore, a relevant fate modelling issue when addressing the impacts of indirect emissions of micropollutants to the freshwater compartment.

Considering the freshwater impact assessment regarding the inventory data of pharmaceuticals of a wastewater treatment plant (WWTP) emissions, the conventional model overestimates the impact result by 1 order of magnitude for the contamination pathways of application of biosolids in agricultural soils as soil-amendment and of irrigation of agriculture soils using WWTP effluents, and the 95% confidence interval is overestimated up to a factor of 30 in the upper endpoint and of 3 in the lower endpoint. Nevertheless, LCA applications dealing with the indirect emission of micropollutants to the freshwater compartment are needed in order to conclude about the influence of these uncertainties on the general output of an LCA study.

The new and updated approach represents an improvement towards the modelling of the multimedia fate, exposure, and effects of ionising organic compounds. However, the updated regressions applied in the new approach still have limitations in predicting sorption to solid matrices and need improvement, given that the contribution of the regression uncertainty to the impact variance of compounds with relevant transfer

fractions to the freshwater compartment from the soil compartment, usually anionic organic compounds, are as high as 44%. The regressions to estimate solid-water partition coefficients of organic acids need to be further developed to include the underlying mechanism of complexion, which may alter the speciation and sorption equilibria of these compounds.

The uncertainty of toxic effects is generally of highest significance, given that the contribution of this model parameter to compounds impact variance is as high as 97% for the direct emission and 81% for the indirect emissions scenarios. Moreover, the uncertainty of estimating and extrapolating endpoints was not included in the uncertainty analysis; nevertheless approximately 65% of all compounds addressed in this thesis have at least 1 estimated or extrapolated endpoint in the ecotoxicological effect characterization. The conduction of more experimental tests regarding ecotoxicological effects of pharmaceuticals, and considering specific toxic modes of action, is detrimental for the improvement of multimedia fate, exposure, and effect model results of pharmaceuticals, reducing the typical large statistical spread of impact results when using few ecotoxicity data points.

Noteworthy, the spatial variability of environmental characteristics within the European geographical scale (such as soil pH, rain rate, or the fraction of organic matter in soil) is of secondary relevance regarding its contribution to the impact variance of this class of chemicals. In terms of parameter uncertainty, the toxicity effects and the sorption to solid matrices are the issues of priority in order to improve the model's predictive power, rather than the spatial differentiation, or resolution, within the model.

The model predictions in terms of impact results applied to 85 pharmaceuticals compounds detected in European WWTPs and pertaining to 15 different therapeutic classes, as well as the contribution of parameter uncertainty to impact variance and the incompleteness of model parameters, helped to establish priorities for further research and monitoring in regard to these compounds, for both direct and indirect pathways of contamination.

For the direct emission pathway from WWTPs, 19 compounds of concern were identified. The monitoring in WWTPs is necessary for more conclusive results, whereas 53% of compounds of most concern were reported only in one peer-reviewed publication to have been measured in WWTPs effluents, for example, in such cases as clotrimazole, ketorolac, omeprazole, or aminopyrine. For this pathway of

contamination, the uncertainty of toxicity effects contributes between 24-97% to the impact variance of compounds of most concern. This parameter is in general the most significant one, as stated above, regarding the large statistical spread of impact results, which range up to 12 orders of magnitude. Moreover, 63% of these compounds have at least one estimated or extrapolated endpoint. In addition, the toxicity effect factor calculation of 32% of these compounds relies entirely on estimated data. In terms of gaps of knowledge leading to the incompleteness of model parameters, the lack of experimental abiotic degradation data for several compounds may have a relevant influence on the output results and needs further research. Theoretically, 74% of compounds of most concern may be subject to at least one abiotic degradation mechanism for which no experimental data were available, which is the case of, for example, codeine, omeprazole, or 5-aminosalicylic acid. Usually, pharmaceuticals with high consumption rates are those selected for further investigation (Escher et al., 2011). This may explain the fact that most compounds defined as of priority in the present thesis are poorly monitored in WWTPs or in the environment. The residence times in the freshwater compartment of these compounds may be overestimated due to lack of experimental abiotic degradation data in comparison to well studied compounds, such as diclofenac or ibuprofen. The conduction of experiments on direct and indirect photolysis for compounds theoretically subject to these degradation mechanisms is, therefore, a necessary topic for further research.

Thirteen compounds of concern were identified for the indirect emission pathways. In the scenario of using WWTP effluents as reclaimed water in agricultural soils, the monitoring in WWTPs is also necessary for more conclusive results, given that 61% of compounds of most concern were measured in less than 5 WWTPs, for example, in the cases of metronidazole, sulfapyridine, or furosemide. In the application of biosolids as soil-amendment scenario, the monitoring of compounds of concern in this contamination pathway, such as 5-aminosalicylic acid, oflaxacin, or sulfapyridine, is also necessary given that the concentration of pharmaceutical compounds was estimated. The uncertainty of toxicity effects is also relevant for these contamination pathways, contributing between 8-81% to the impact variance of compounds of most concern and requiring further ecotoxicity tests for compounds such as gemfibrozil, ofloxacin, or bendroflumethiazide. Also, the lack of experimental abiotic degradation data for several compounds may have a relevant influence on the output results and

needs further research, given that, theoretically, 92% of compounds of most concern may be subject to at least one abiotic degradation mechanism for which no experimental data were available, which is the case, for example, of omeprazole, ofloxacin, or loratadine. Moreover, the estimation of the pH-dependent sorption of organic acids is also influential for compounds such as furosemide or ketorolac. For these compounds, further research is needed regarding the measurement of an experimental range of K_d values for several soil samples, attending to the variation in the solid matrix characteristics in terms of particle size, pH and organic and clay content, which may be used as inputs into fate and transport models for more conclusive results.

To establish future research based on the impact results of PCs measured in European WWTPs, as well on parameter uncertainty and incompleteness, was one the objectives of this thesis. However, the model uncertainty not addressed in the present thesis should also serve as recommendations for future work to improve the model's predictive power. Model uncertainty includes all model choices and assumptions, which can be difficult to quantify in comparison to parameter uncertainty. To overcome model uncertainty, information is needed on the most appropriate description of reality and application of the most relevant model (Van Zelm, 2010). The increase of complexity of a multimedia fate, exposure, and effect model, that better simulate reality, leads in general to larger parameter uncertainty; nevertheless it reduces the model uncertainty.

The uncertainty of the following model choices and assumptions was not address in the present thesis:

1. exclusion of abiotic and biotic derivatives of parent compounds,
2. exclusion of the influence of freshwater pH on direct and indirect photolysis rates,
3. application of a linear dose-response curve for the calculation of ecotoxicity effect factors,
4. assessment factor (AF) of 2 to extrapolate average chronic toxicity from acute chronic toxicity.

The influence of degradation derivates on the total compound impact is unclear in the present thesis. Nevertheless, the inclusion of phototransformation products impact is possible by applying the method proposed by van Zelm et al. (2010b). The method calculates the total characterization factor by summing the characterization factors of the parent compounds and its derivates, treating the uncertainties in fractions of

formation as triangular distributions with 0 as minimum and 1 as maximum. The chemical structures of derivates must be identified in order to estimate the necessary fate and effect parameters; however presently these chemical structures are not usually available in the literature for pharmaceuticals compounds. However, for compounds with such data available, the influence of the inclusion of derivates on the total impact should be further addressed.

The speciation of organic compounds affects their photodegradation rates (Boreen et al., 2004; Baeza and Knappe, 2011). A first screening approach to deal with the uncertainty of speciation of an organic compound could be based on a uniformal distribution using the lowest and highest degradation rates among all the species involved in the speciation as the minimum and maximum. Therefore, quantum yields and experimental molar absorption coefficients in function of the UV/VIS wavelength range of all the species involved must be experimentally obtained and applied to models that compute direct photolysis rates and half-lives of pollutants in the aquatic environment. A similar approach can be applied for indirect photolysis by obtaining experimental rate constants between chemical transients and all the chemical species involved in the speciation.

The "average potential affected fraction (PAF) increase" approach based on the $HC50_{EC50}$ applied in the present thesis (consistently with the USEtox model) for calculation of the ecotoxicity effect factors assumes a linear dose-response PAF curve with a slope of 0.5. However, pharmaceuticals-specific PAF curves should computed in order to verify the linearity assumption for this class of compounds, which requires ecotoxicological data for a large number of species, usually not available for pharmaceutical compounds.

An acute-chronic ratio of 2 was applied to extrapolate chronic $HC50_{EC50}$ values from acute $HC50_{EC50}$ values, as applied in the USEtox model. However, best estimate AFs for this extrapolation have not yet been developed and further research is needed in this area, particularly in the context of pharmaceuticals.

Appendix A

A1: Bulk transport rate coefficients and fate matrices

For steady-state conditions, the vector of masses describing the distribution of a contaminant in the environment (mass vector $\overrightarrow{M}$ in kg) is given by

$$\frac{d\vec{M}}{dt} = \vec{S} + \vec{k} \cdot \vec{M} = 0 \Rightarrow \vec{M} = \bar{k}^{-1} \cdot \vec{S} \qquad \text{(A1)}$$

where the emission source (emission flow vector $\vec{S}$ in kg·day^{-1}) is linked to the mass in the environmental compartments by the matrix of bulk transport rate coefficients ($\bar{k}$ in day^{-1}). Table 8 shows $\bar{k}$ for the system under analysis. Off-diagonal elements of Table 8, such as $k_{b,as}$, reflect intermedia or advective transport rates from one compartment to another, while the diagonal elements (in bold), such as $-k_{b,t}$, represent the negative of the total removal rate coefficient for a given compartment, including biotic/abiotic degradation, advective and intermedia removal. For the environmental compartment i the total removal rate coefficient is given by

$$k_{i,\mathrm{t}} = k_{i,\mathrm{deg}} + k_{i,\mathrm{out}} + \sum_{s} k_{i,j} \qquad \text{(A2)}$$

where $k_{i,\mathrm{deg}}$ is the sum of biotic/abiotic degradation rates of a given chemical in compartment; $k_{i,\mathrm{out}}$ is advective transport rate of a given chemical to out of the modelled scale; $k_{i,j}$ is the intermedia transport rate from compartment i to compartment j. . Dividing the off diagonal element by the diagonal element of the respective column, one can readily measure the fraction of removal towards each compartment. Likewise, by dividing a removal process rate, such as degradation or advection, by the diagonal element, one can measure the fraction of that removal process relatively to the overall intermedia transport and removal processes in a given compartment.

The fate matrix $\overline{FF}$ is per definition the negative inverse of the transfer rate coefficient matrix $\bar{k}$ (Table 9). A fate factor, $FF_{\mathrm{i,i}}$ in days^{-1}, represents the mass increase (kg) in a given medium due to an emission flow (kg/day). It is equivalent to the time-integrated concentration × volume over the infinite of a pulse emission (Rosenbaum et al., 2008). Several authors interpreted the physical processes within a fate matrix enabling a

straightforward and transparent analysis of a fate model (Margni et al., 2004; Pennington et al., 2005; Rosenbaum et al., 2007). The diagonal elements $FF_{i,i}$ (in bold), in day^{-1}, describe the effective residence time in the respective compartment *i*. A column describes the mass in the environment resulting from a unit flow in the corresponding compartment. Hence, dividing each element by the sum of the respective columns indicates into which compartment(s) a chemical mainly partitions. A non-diagonal element can also be expressed as the fraction transferred from a source compartment multiplied by the effective residence time in the destination compartment. Hence, by dividing an element in a row by the residence time (the diagonal element), one can measure the transferred fraction from compartment *i* to *j* ($f_{i,j} = FF_{i,j} / FF_{i,i}$), including the sum of all possible transfer pathways through a third media.

Table 8: Bulk transport rate coefficients matrix. Indices *b*, *ag*, *a*, *fw*, *fws*, *sw* and *sws* describe the illustrative compartments biosolids, agricultural soil, air, freshwater, and freshwater sediment.

Receiving compartment \ *Source compartment*	Biosolids	Agricultural Soil	Air	Freshwater	Freshwater sediment
Biosolids	**-**	$k_{ag,\ b}$	$k_{a,\ b}$	*0*	*0*
Agricultural Soil	$k_{b,}$	$\boldsymbol{-k_{as,t}}$	$k_{a,\ ag}$	*0*	*0*
Air	$k_{b,\ a}$	$k_{ag,\ a}$	$\boldsymbol{-k_{a,t}}$	$k_{fw,\ a}$	*0*
Freshwater	*0*	$k_{ag,\ fw}$	$k_{a,\ fw}$	$\boldsymbol{-k_{fw,t}}$	$k_{fws,}$
Freshwater sediment	*0*	*0*	*0*	$k_{fw,\ fws}$	$\boldsymbol{-k_{fws,t}}$

Table 9: Fate factors matrix

	Biosolids	Agricultural Soil	Air	Freshwater	Freshwater sediment
Biosolids	$\boldsymbol{FF_{b,b}}$	$FF_{ag,\,b}$	$FF_{a,\,b}$	$FF_{fw,\,b}$	$FF_{fws,b}$
Agricultural Soil	$FF_{b,\,as}$	$\boldsymbol{FF_{as,as}}$	$FF_{a,\,ag}$	$FF_{fw,\,ag}$	$FF_{fws,\,ag}$
Air	$FF_{b,\,a}$	$FF_{ag,\,a}$	$\boldsymbol{FF_{a,a}}$	$FF_{fw,\,a}$	$FF_{fws,\,a}$
Freshwater	$FF_{b,\,fw}$	$FF_{ag,\,fw}$	$FF_{a,\,fw}$	$\boldsymbol{FF_{fw,fw}}$	$FF_{fws,\,fw}$
Freshwater sediment	$FF_{b,\,fws}$	$FF_{ag,\,fws}$	$FF_{a,\,fws}$	$FF_{fw,\,fws}$	$\boldsymbol{FF_{fws,fws}}$

A2: Intermedia partition coefficients

Under environmental conditions, pharmaceuticals can be neutral, cationic, anionic, or zwitterionic. The extent of dissociation of a pharmaceutical depends on the environmental pH, which therefore influences the octanol–water partition coefficient, K_{OW}. For non-dissociating compounds, experimental log K_{OW} values were obtained from the EPI Suite™ (USEPA, 2008). In the case of dissociating compounds, K_{OW} values published in the literature are often apparent log K_{OW} values (log D_{OW}); that is, they are the sum of the log K_{OW} values of neutral and ionic molecules at the experimental pH. To treat the ionic and neutral fractions separately, experimental log K_{OW} values of the neutral species requires a correction of the pH at which log D_{OW} was determined, often not reported explicitly. Therefore, for dissociating pharmaceuticals at environmental pH values, calculated values are preferred to measured values. The software KOWWIN v1.67a™ from the EPI Suite™ (USEPA, 2008) was used to estimate log K_{OW} values corrected for the neutral species (log $K_{OW,n}$). The base case environmental pH values are 7 for the biosolids, agricultural soil, freshwater and freshwater sediment compartments (Huijbregts, 1999).

Solids-water partitioning

Sorption to solid surfaces is a dominating process driving distribution in soil, surface waters and sediments. Experimental soil-water partitioning coefficients normalized by the organic carbon content, K_{OC} in $L \cdot kg^{-1}$, were preferred for neutral pharmaceuticals and for dissociating pharmaceuticals as long as these remain essentially in one charged state or neutral at a environmental relevant pHs (Table S3). Otherwise experimental K_{OC} values obtained at a given environmental pH would not be suitable for the interval of environmental pHs considered in the model because of the variability of the fractions of neutral and ionic species at different pH. For dissociating compounds at environmental pH the soil-water partitioning coefficients are correlated to K_{OW} and pKa in the present model. The conventional non-polar partitioning models correlated only to K_{OW} do not adequately model the mechanism of sorption to organic matter in the solid state and to inorganic clay minerals for dissociating pharmaceuticals. These models ignore the fact that a dissociated pharmaceutical ingredient can lead to more complex ionic, ion pairing or complexation mechanisms (Cunningham, 2008). A different degree of anion, cation, and neutral molecule sorption can be expected, with cations showing the highest potential for sorption due to electrical attraction to the negative electrical charge of the colloidal fraction at the soil surface, which consists of organic matter and inorganic clay minerals. K_{OC} values for dissociating pharmaceuticals in each environmental compartment were calculated using the Franco and Trapp regression equations (Franco and Trapp, 2008):

$$\log K_{OC,d} = 0.11 \log K_{OW,n} + 1.54, \text{ for the anion} \quad (A3)$$

$$\log K_{OC,d} = pKa^{0.65} \cdot f^{0.14}, \text{ for the cation} \quad (A4)$$

$$\log K_{OC,n} = 0.54 \log K_{OW,n} + 1.11, \text{ for the acid, neutral molecule} \quad (A5)$$

$$\log K_{OC,n} = 0.37 \log K_{OW,n} + 1.70, \text{ for the base, neutral molecule} \quad (A6)$$

$$\log K_{OC,n} = 0.50 \log K_{OW,n} + 1.13, \text{ for the amphoter, neutral molecule} \quad (A7)$$

where pKa is the negative logarithm ($\log_{10}$) of the dissociation constant, and f is $K_{OW,n}/(K_{OW,n}+1)$. The overall K_{OC} of dissociating chemicals results from the sum of the contributions of the neutral ($K_{OC,n}$) and dissociated fractions ($K_{OC,d}$):

$$K_{OC} = f_n \cdot K_{OC,n} + f_d \cdot K_{OC,d} \quad (A8)$$

where f_n is the fraction of neutral molecules in the matrix, and f_d is the fraction of dissociated molecules (1-f_n), according to the *Henderson-Hasselbalch* equation:

$$f_n = \frac{1}{1 + 10^{i(\mathrm{pH}-\mathrm{p}K\mathrm{a})}} \quad \text{(A9)}$$

where i is the valence number, which is +1 for acids and -1 for bases. The above equations are applicable only to monovalent acids and bases; for pharmaceuticals with two cationic or anionic dissociating groups, only the first dissociation was considered. p*K*a values were taken from the EPI Suite™ (USEPA, 2008) or literature reports (main paper, Table 1). For pharmaceuticals without experimentally verified p*K*a values, values were estimated using the SPARC software program (Carreira et al., 2009), in which p*K*a values are given for –OH, -COOH, or the highest NH_x functional group. Ionisation is essentially anionic at environmentally relevant pH values for amphoteric compounds (main paper, Table 1), whereas the cationic form occurs only at low pHs (maximum $pK_{a_{base}}$ = 2.66 for sulfathiazole). For non-dissociating pharmaceuticals at environmental pH, K_{OC} values were estimated with KOCWIN v2.0™ using the first-order Molecular Connectivity Index (MCI) (USEPA, 2009). The adsorption coefficient in solid matrices, K_p, is related to the fraction of organic carbon in the solid matrix according to $K_p = K_{OC} \times f_{OC}$. The fraction of organic carbon was 0.05 for fresh sediment, 0.02 for agricultural soil and 0.30 for biosolids (EC, 2004).

The partitioning coefficient between dissolved organic carbon and organic pollutants in water, K_{DOC} in $L \cdot kg^{-1}$, was estimated using the predictive relationship of $K_{DOC} = 0.08 \times K_{ow}$ for non-ionic compounds (Burkhard, 2000). For dissociating substances at freshwater pH, only the neutral fraction was considered by assuming the K_{ow} of the neutral species in the equation. However, sorption to dissolved organic carbon in the freshwater compartment was not expected to be an important fate process. Obviously, compounds that reach the freshwater compartment through biosolids-amended soils are strongly hydrophilic. Therefore, a limited amount of partitioning to dissolved carbon was expected for these compounds.

Gas-aerosol partitioning

The chemical fraction associated with aerosol particles was estimated on the basis of the chemical's vapour pressure (Huijbregts et al., 2010). Vapour pressure values were estimated with the software MPBPVP v1.43 using the Modified Grain method (USEPA,

2008). For dissociating compounds at environmental pH, the vapour pressure of the total compound was calculated using the vapour pressure of the neutral species and multiplying by the fraction of neutral molecules in a given environmental compartment.

Air-water partitioning

The transfer of a substance from the aqueous phase to the gaseous phase was estimated using the Henry's Law constant. The Henry's law constants of pharmaceuticals were estimated from the ratio of vapour pressure to water solubility. The water solubility of dissociating substances, *S*, was calculated using the *Henderson-Hasselbalch* equation and S_0 values (neutral molecule at 25°C):

$$\log S = \log S_0 + \log (1 + 10^{i\,(\mathrm{pH}-\mathrm{p}Ka)}) \qquad \text{(A10)}$$

Experimental S_0 values were taken from the EPI Suite™ physical properties database. For pharmaceuticals without experimentally verified S_0 values, values were estimated using the software program WSKOW v1.41™ (USEPA, 2008).

A3: Plant uptake

The removal rate by roots is given by

$$k_{\text{roots}} = \frac{K_{\text{av}} \times \text{RCF} \times \rho_{\text{roots}} \times A_s \times f_{\text{ag}}}{K_p' \times V_{\text{ag}}} \qquad \text{(A11)}$$

where k_{roots} is the removal rate from agricultural soils to roots, in day^{-1}; K_{av} is the water absorption rate in agricultural vegetation, set at 0.294 m.year^{-1} (van Zelm et al., 2009); K_p' is the dimensionless agricultural soil-water partition coefficient; A_s is the total area of the system, set at $4.08\times10^{+10}$ m^2 (EC, 2004); f_{as} is the fractional area of agricultural soil, set at 0.594 (EC, 2004); ρ_{roots} is the root density, set at the typical value of 0.7 kg.L^{-1} (EC, 2004); K_p' is the dimensionless agricultural soil-water partition coefficient; and V_{as} is the volume of the agricultural soil compartment, given a soil depth of 0.2 m (EC 2004). For non-dissociating and neutral compounds at agricultural soil pH, RCF is the root concentration factor, in L. kg^{-1}, estimated using a K_{OW}-dependent regression equation (Briggs et al., 1982):

$$\text{RCF} = 0.82 + 0.0303\ K_{\text{OW}}{}^{0.77} \qquad \text{(A12)}$$

For ionisable compounds at agricultural soil pH, the suggestion of the TGD (EC, 2003) for correcting chemical properties by the neutral fraction of the compound, in this case $f_n \times K_{OW}$ ($K_{OW,n}$), was followed. For the particular case of root uptake, such a procedure seems to be reasonable at a screening level because fewer anions than neutral molecules are generally taken up as a result of electric repulsion, which slows transfer across membranes (Trapp, 2009). Moreover, although cations are attracted by the electrical potential of living cells, they have the highest potential of sorption to soil, which reduces their bioavailability and uptake. Plant uptake may be underestimated because the ionic fraction is disregarded. However, the application of Equation A12 to dissociating compounds using the uncorrected K_{OW} overestimates sorption possibly to a greater extent. Nevertheless, as observed by Trapp (2009), the reliability of this procedure for ionisable compounds has never been critically evaluated.

A4: Experimental parameters

Table 10: Experimental logK_{OC} values, biodegradation half-lives in freshwater and soil, direct photolysis quantum yields and biomolecular hydroxyl radical rate constants in water.

Compound	Experimental logK_{OC} ($L \cdot kg^{-1}$)	$t_{b1/2}$ Biodegradation in freshwater (days)	$t_{b1/2}$ Biodegradation in soils (days)	Direct photolysis quantum yield	$k_{OH,\ water}$ [a] $M^{-1}s^{-1}$
Diclofenac			4.8-29.6 (Xu et al. 2009b, Lin and Gan 2011)	9.40×10^{-2} - 1.30×10^{-1} (Werner et al. 2005)	[b]
Ibuprofen	2.01 ± 0.14 [c] (Xu et al. 2009b)	18.7-20 (Yamamoto et al. 2009)	10.4-49.9 (Xu et al. 2009b, Lin and Gan 2011)	1.92×10^{-1} (Yuan, Hu et al. 2009)	7.4×10^{9}-1.0×10^{10} (Huber et al. 2003, Das et al. 2010)
Atenolol		14.2-120.8 (Yamamoto et al. 2009)		[d]	$7.05 \pm 0.27 \times10^{9}$ (Song, et al. 2008)
Carbamazepine	2.95-3.10 (Williams et al. 2006)	125-233.3 (Yamamoto et al. 2009)	Recalcitrant (Monteiro and Boxall 2009)	4.77×10^{-5}- 1.3×10^{-4} (Andreozzi et al. 2003, Lam and Mabury 2005)	3.07×10^{9}- 9.4×10^{9} (Vogna et al. 2004, Lam and Mabury 2005)
Bezafibrate				[e]	$7.4 \pm 1.2 \times10^{9}$ (Huber et al. 2003)
Diazepam	2.40-2.80 (Barron et al. 2009)	Recalcitrant (Suarez et al. 2010)		4.30×10^{-6} (Calisto et al. 2011)	$7.2 \pm 1.0 \times10^{9}$ (Huber et al. 2003)
Fenofibrate				-	$2.56 \pm 0.6 \times10^{9}$ (Kladna et al. 2006)
Mefenamic acid		66.6±13.9 (Araujo et al. 2011)		1.50×10^{-4} (Werner et al. 2005)	[f]
Phenazone	2.36 [g] (Barron et al. 2009)			6.32×10^{-2} (Razavi et al. 2011)	6.28×10^{9} (Yuan et al. 2009)
Atorvastatin	2.70-2.92 (Ottmar et al. 2010)			4.50×10^{-3} (Cermola et al. 2006)	$1.9 \pm 0.5 \times10^{9}$ (Lam and Mabury 2005)
Clarithromycin				5.80×10^{-5} (Vione et al. 2009)	[h]
Sulfamethazine				2.82×10^{-3} (Baeza and Knappe 2011)	[i]
Cimetidine				[j]	$1.5 \pm 0.2 \times10^{10}$ (Latch et al. 2003)
Sulfathiazole				2.00×10^{-2} (Boreen et al. 2004)	[i]
Hydrochlorothiazide				5.10×10^{-2} (Ulvi 1998)	$5.7 \pm 0.3 \times10^{9}$ (Real et al. 2010)

[a] values obtained at pH=7;
[b] direct photolysis is the limiting photodegradation mechanism (Werner et al. 2005);
[c] pH=7.04;
[d] atenolol does not contain chromophores that absorb at wavelengths >290 nm and therefore is not expected to be susceptible to direct photolysis by sunlight.
[e] direct photolysis was not observed (Radke et al. 2010);
[f] photosensitization by hydroxyl radicals is reported to be insignificant (Werner et al. 2005);
[g] pH=6.8;
[h] hydroxyl radicals, singlet oxygen and other photooxidants are reported to have only a very limited impact on the overall degradation (Vione et al. 2009);
[i] photodegradation of sulfa drugs is likely not controlled by reaction with ·OH, although this may not be true in case of high nitrate-containing waters ([·OH]=10^{-15}M) (Boreen et al. 2004);
[j] direct photolysis was not observed (Latch et al. 2003).

A5: Ecotoxicity factor in water

The ecotoxicty factor in water, $EF_{aqua,fw,}$ is calculated according to the AMI method (Payet 2004), which is based on the Hazardous Concentration (HC) of a chemical affecting 50% of the species tested over their chronic EC50 (Effect Concentration affecting 50% of tested individuals), also called $HC50_{EC50}$, according to:

$$EF = \frac{\Delta \mathrm{PAF}}{\Delta \mathrm{C}} = \frac{0.5}{\mathrm{HC50}} \qquad (A13)$$

where C is the exposure concentration, in $kg \cdot m^{-3}$, and PAF is the potentially affected fraction of species due to exposure to the chemical. $HC50_{EC50}$ is given by

$$\log\ \mathrm{HC50} = \frac{1}{\mathrm{ns}} \cdot \sum_{\mathrm{s}} \log \mathrm{EC50} \qquad (A14)$$

where n is the number of species (or trophic levels) for which EC50 values are available. Figure S1 shows the procedure of calculation of the effect factors. The EC50 values must cover at least three different trophic levels (algae, crustacean, and fish) for standard endpoints with standard organisms. For a given chemical, if several EC50 values are available for the same species, the geometric mean of the EC50 is calculated to represent this species. The ability of pharmaceuticals to bioconcentrate and their low concentration but constant introduction and relative persistence in the environment indicate that these compounds are more likely to have chronic rather than acute toxic effects on aquatic biota (Fent et al., 2006; Quinn et al., 2008). Chronic EC50 values are seldom reported in the literature, therefore, according to the AMI method, when chronic data do not cover three different taxa, calculation of chronic $HC50_{EC50}$s must be based on acute data. An acute-to-chronic ratio of 1.9 was applied to extrapolate chronic $HC50_{EC50}$s from acute $HC50_{EC50}$s (Payet, 2004). Experimental acute EC50s were gathered from the ECOTOX database (USEPA, 2007) and literature reports (Table 11).

In Equation A15, $FR_{fw,fw}$ is the environmental exposure factor for freshwater, equivalent to the fraction of chemical dissolved in freshwater (Huijbregts et al., 2010):

$$FR_{\text{ fw, fw}} = \frac{1}{1 + K\mathrm{p} \cdot [\mathrm{SUSP}]_{\mathrm{fw}} + K_{\mathrm{DOC}} \cdot [\mathrm{SUSP}]_{\mathrm{fw}} + \mathrm{BCF}_{\mathrm{fish}} \cdot [\mathrm{SUSP}]_{\mathrm{fw}}} \qquad (A15)$$

where K_p is the partition coefficient between water and suspended matter; the fraction of organic carbon in suspended matter, f_{OC}, necessary to derive K_p from K_{OC}, the partition coefficient normalized by the organic carbon content, is assumed to be 0.10 (EC, 2004); K_{doc} is the partition coefficient between dissolved organic carbon and water; $[SUSP]_{fw}$, $[DOC]_{fw}$, and $[BIOTA]_{fw}$ are the concentrations of suspended matter, dissolved organic carbon and biota in freshwater, set at 15×10^{-6} kg·L^{-1}, 5×10^{-6} kg·L^{-1}, and 1×10^{-6} kg·L^{-1}, respectively, for typical European conditions (Huijbregts et al., 2010); the bioconcentration factor in fish, BCF_{fish} in L·kg^{-1}, is the concentration of a chemical in the fish divided by the dissolved concentration of the chemical in the surrounding water. BCFs in fish for non-dissociating compounds were obtained using K_{OW} regression-based estimates from the BCFBAF v3.00 software program (USEPA, 2008). For dissociating compounds at environmental pH, the regression equations of Fu et al. (2009) were applied:

$$\mathrm{BCF} = f_n \cdot 10^{(0.64 \log K_{OW,n} - 0.12)} + f_d \cdot 10^{(0.37 \log K_{OW,n} + 0.06\, pKa - 0.51)} \text{ for acids} \quad \text{(A16)}$$

$$\mathrm{BCF} = f_n \cdot 10^{(0.62 \log K_{OW,n} - 0.15)} + f_d \cdot 10^{(0.28 \log K_{OW,n} + 0.84 - 0.07\, pKa)} \text{ for bases} \quad \text{(A17)}$$

Fu et al. (2009) showed that these regression equations outperform conventional non-polar regressions using the K_{OW} corrected by the neutral fraction. The equations are valid in the range -0.36 < p*K*a < 10.61. Therefore, the minimum or maximum p*K*a values outside the calibrated range were applied.

Table 11: Acute L(E)C50s values in mg/L for the compounds under study

Compound	Trophic level															
	Algae							Crustacean								
	D. subspicatus	*C. meneghiniana*	*P. subcapitata*	*S. leopoliensis*	*S. Costatum*	*T. chuii*	*C. vulgaris*	*T. platyurus*	*D. Magnia*	*C. dubia*	*M. macrocopa*	*A. salina*	*A. parthenogenetica*	*D. pulex*	*S. proboscideus*	*H. azteca*
Diclofenac	71.9 (Cleuvers 2004)	16 (Grung et al. 2008)	19 (Grung et al. 2008)	14.5 (Grung et al. 2008)				41 (Grung et al. 2008)	49.3*a*	23 (Grung et al. 2008)						
Ibuprofen	342.2 (Cleuvers 2004)				7.1 (Han et al. 2010)				78.7*b*		72.6 (Han, Choi et al. 2010)					
Atenolol	620 (Cleuvers 2005)		313 (Cleuvers 2005)						33.4(Sanderson and Thomsen 2009)							
Carbamazepine	74 (Cleuvers 2003)	85 (Huschek et al. 2004)							76.3 (Kim et al. 2007)							
Bezafibrate								39.7 (Isidori et al. 2007)	54.8*c*	75.8 (Isidori et al. 2007)						
Diazepam						16.5 (Nunes et al. 2005)			14.1 (USEPA 2007)			71.6 (USEPA 2007)	12.2 (Nunes, Carvalho et al. 2005)	11.96 (USEPA 2007)	69.5 (USEPA 2007)	
Fenofibrate									50.1 (Isidori et al. 2007)							
Mefenamic acid	5.4 (Suzuki et al. 2009)							3.85 (Kim et al. 2009b)								
Phenazone																
Atorvastatin		75 (Fass 2011)							200 (Fass 2011)							1.5 (Dussault et al. 2008)
Clarithromycin			0.09 (Huschek et al. 2004)					56.3*d*	25.7 (Isidor et al. 2005)	18.7 (Isidori et al. 2005)						
Sulfamethazine									193.6*e*		110.7 (Park and Choi 2008)					
Cimetidine									271 (Kim et al. 2007)	740(Sanderson and Thomsen 2009)						
Sulfathiazole							163.2 (Baran, Sochacka et al. 2006)		149.3 (Kim et al. 2007)		391.1 (Park and Choi 2008)					
Hydrochlorothiazide		100 (Fass 2011)							100 (Fass 2011)							

a Geometric mean of 68, 80 and 22 (Grung et al. 2008); *b* Geometric mean of 101.2 (Cleuvers 2004), 132.6, 51.44 and 55.6 (Grung et al. 2008); *c* Geometric mean of 30(Hernando et al. 2007) and 100.8 (Isidori et al. 2007); *d* Geometric mean of 33.6(Isidori et al. 2005) and 94.2 (Harada et al. 2008); *e* Geometric mean of 216 (Park and Choi 2008), 202, 185 and 174(De Liguoro et al. 2009).

Table 11 (continued)

Compound	Trophic level																	
	Fish										Other							
	H. azteca	*D. rerio*	*B. rerio*	*O. Latipes*	*G. holbrooki*	*O. mykiss*	*O. kisutch*	*O. tshawytscha*	*P. oregonensis*	*L. Macrochirus*	Frog embryo	*L. minor*	*L. gibba*	*P. carinatus*	*C. tentans*	*H. attenuata*	*B. calyciflorus*	*V. fisheri*
Diclofenac		5.3(van den Brandhof and Montforts 2010)																
Ibuprofen				89 (Yamamoto et al. 2007)						173 (Webb 2004)		9.4 *f*		17.1 (Han et al. 2010)		22.3 (USEPA 2007)		
Atenolol																		
Carbamazepine	9.9 (Dussault et al. 2008)	86.5 (van den Brandhof and Montforts 2010)		35.4 (Kim et al. 2007)								25.5 (Cleuvers 2003)			47.3(Dussault et al. 2008)	29.4 (Quinn et al. 2008)		52.2 (Kim et al. 2007)
Bezafibrate																	60.9 (Isidori et al. 2007)	
Diazepam					12.7 (Nunes, Carvalho et al. 2005)	84 (USEPA 2007)											47.3 (USEPA 2007)	
Fenofibrate																	65 (Isidori et al. 2007)	
Mefenamic acid				8.04 (Kim et al. 2009b)							5.2 (Suzuki et al. 2009)							
Phenazone							10 (USEPA 2007)	10 (USEPA 2007)	10 (USEPA 2007)									
Atorvastatin	1.5 (Dussault et al. 2008)												0.214 (Dussault et al. 2008)		14.3 (Dussault et al. 2008)			
Clarithromycin		280 (Hernando et al. 2007)															35.5 (Isidori et al. 2005)	
Sulfamethazine				500(Park and Choi 2008)		100 (USEPA 2007)												
Cimetidine				1000(Sanderson and Thomsen 2009)														
Sulfathiazole																		
Hydrochlorothiazide			100 (Fass 2011)															

f Geometric mean of 4 (Grung et al. 2008) and 22 (Cleuvers 2004).

A6: Parameter uncertainty and variability included in the Monte Carlo analysis

Table 12: Probability distributions for the 10 regression error parameters (*a1-a10*), experimental K_{OC} values, experimental biodegradation rates ($k_{biodeg, water}$, $k_{biodeg, soil}$), experimental bimolecular ˙OH rate constants in water ($k_{OH, water}$), and environmental parameters (pH and *foc* in agricultural soil, [˙OH] in freshwater, and rain rate) included in the Monte Carlo simulation. The relation of the calibration coefficients to the actual model parameter values is shown in the last column. Parameter abbreviations are explained in the main paper and in the previous sections. S*Dev* denotes standard deviation, *exp* denotes experimental values, *CI* denotes confidence interval, and *DF* denotes degrees of freedom. Asterisks (*) denote base case parameter values

Parameter	Distribution	Mean	Spread	Relation to model parameters
a1	Normal	1.26×10^{-7}	*Sdev*=4.25×10^{-8}	$k_{biodeg, water} = k_{biodeg, water}^{*} \pm a1$
a2	Normal	-3.18×10^{-7}	*Sdev*=2.63×10^{-7}	$k_{biodeg, soil} = k_{biodeg, soil}^{*} \pm a2$
a3	Uniformal	1	[0.5, 1.5]	$k_{biodeg, biosolids} = k_{biodeg, soil} \times a3^{-1}$
a4	Normal	-3.15×10^{-4}	*Sdev*= 4.41×10^{-1}	$logK_{OW} = logK_{OW}^{*} \pm a4$ (KOWWIN v1.67a)
a5	Normal	-9.84×10^{-2}	*Sdev*= 5.48×10^{-1}	$logK_{OC} = logK_{OC}^{*} \pm a5$ (KOCWIN v2.0)
a6	Normal	2.23×10^{-2}	*Sdev*= 5.36×10^{-1}	$logK_{OC} = logK_{OC}^{*} \pm a6$ (acids regression)
a7	Normal	4.45×10^{-2}	*Sdev*= 4.74×10^{-1}	$logK_{OC} = logK_{OC}^{*} \pm a7$ (bases regression)
a8	Normal	1.13×10^{-3}	*Sdev*= 5.11×10^{-1}	$logBCF_{fish} = logBCF_{fish}^{*} \pm a8$ (BCFBAF v3.00)
a9	Normal	5.15×10^{-2}	*Sdev*= 5.41×10^{-1}	$logBCF_{fish} = logBCF_{fish}^{*} \pm a9$ (acids regression)
a10	Normal	2.65×10^{-2}	*Sdev*= 6.61×10^{-1}	$logBCF_{fish} = logBCF_{fish}^{*} \pm a11$ (bases regression)
$k_{photodegradation, water}$	Uniformal		[min, max]	
$logHC50_{EC50}$	Student	$logHC50_{EC50}$	$95\%CI = \pm \frac{1}{\sqrt{n}} \times t_{n-1}^{0.05} \times$ *Sdev*(LogEC50) [a]	
exp K_{OC}	Lognormal		*B*	
exp $k_{biodeg, water}$	Lognormal		*C*	
exp $k_{biodeg, soil}$	Lognormal		*C*	
exp $k_{OH, water}$	Lognormal		*C*	
[˙OH] in water (M)	Uniformal		$[10^{-14}, 10^{-17}]$ (min, max)	
$pH_{agricultural soil}$	Triangular	7	[3.2, 8.5] (min, max) (Reuter et al. 2008)	
$foc_{agricultural soil}$	Triangular	0.02	[0.01, 0.1] (min, max) (Jones et al. 2005)	
Rain rate (mm/year)	Triangular	700	[250, 1500] (min, max)	

[a] $t_{n-1}^{0.05}$ is the *t* value from the student table for a 95% confidence interval with *n-1* degree of freedom, where *n* is the size of sample (or number of species tested, and *Sdev* is the Standard deviation of the LogEC50s.
[b] Minimum and maximum values are shown in Table S3.
[c] Minimum and maximum values are shown as half-lives in Table S3.

Appendix B

Table 13: Concentration of micropollutants in a conventional WWTP

Substance	Inlet concentration (kg/m^3) (Larsen et al., 2010b)	Outlet concentration (kg/m^3) (Larsen et al., 2010b)	Sludge concentration (kg/kg dry matter of sludge)*
Atenolol	2,52E-06	1,59E-06	1,20E-06
Bezafibrate	7,37E-07	8,23E-08	8,51E-07
Carbamazepine	7,88E-07	7,13E-07	9,78E-08
Clarithromycin	3,69E-07	1,69E-07	2,61E-07
Clindamycin	5,90E-08	3,36E-08	3,31E-08
Clofibric acid	1,30E-07	7,25E-08	7,50E-08
Diatrizoate	2,34E-06	1,85E-06	6,35E-07
Diclofenac	2,00E-06	1,55E-06	5,87E-07
Erythromycin	2,30E-07	9,91E-08	1,71E-07
Ibuprofen	5,68E-06	9,09E-08	7,29E-06
Iohexol	1,79E-06	1,85E-07	2,08E-06
Iopamidol	3,64E-06	1,13E-06	3,25E-06
Iopromide	8,28E-06	1,78E-06	8,42E-06
Metoprolol	5,29E-07	4,13E-07	1,51E-07
Naproxen	4,24E-06	2,33E-07	5,22E-06
Primidone	2,52E-07	1,27E-07	1,63E-07
Propranolol	1,07E-07	9,52E-08	1,54E-08
Roxithromycin	1,05E-07	4,96E-08	7,22E-08
Sotalol	4,76E-07	4,33E-07	5,37E-08
Sulfamethoxazole	8,93E-07	4,97E-07	5,15E-07

* Values estimated by a mass balance. Biodegradation rates were estimated by the software program STP of the EPI Suite™ (USEPA, 2008)

Table 14: Experimental logK_{OC} values, biodegradation half-lives in freshwater and soil, direct photolysis quantum yields and biomolecular hydroxyl radical rate constants in water.

Compound	Experimental logK_{OC} ($L^{\cdot}kg^{-1}$)	$t_{b1/2}$ Biodegradation in freshwater (days)	$t_{b1/2}$ Biodegradation in soils (days)	Direct photolyis quantum yield	$k_{OH,\ water}$ [a] $M^{-1}s^{-1}$
Atenolol		14.2-120.8 (Yamamoto et al. 2009)		-	$7.05 \pm 0.27 \times 10^9$ (Song et al. 2008)
Bezafibrate				*a*	$7.4 \pm 1.2 \times 10^9$ (Huber et al. 2003)
Carbamazepine	2.95-3.10 (Williams et al. 2006)	125-233.3 (Yamamoto et al. 2009)	Recalcitrant (Monteiro and Boxall 2009)	4.77×10^{-5}-1.3×10^{-4} (Andreozzi et al. 2003, Lam and Mabury 2005)	3.07×10^9- 9.4×10^9 (Vogna et al. 2004, Lam and Mabury 2005)
Clarithromycin				5.80×10^{-5} (Vione et al. 2009)	*b*
Clindamycin				*c*	*d*
Clofibric acid				2.0×10^{-3} - 2.22×10^{-3} (Andreozzi et al. 2003, Packer et al. 2003)	4.7×10^9- 6.98×10^9 (Packer et al. 2003, Razavi et al. 2009)
Diatrizoate *(diatrizoic acid)*				*c*	$9.58 \pm 0.23 \times 10^8$ (Jeong et al. 2010)
Diclofenac			4.8-29.6 (Xu et al. 2009b, Lin and Gan 2011)	9.40×10^{-2} -1.30×10^{-1} (Werner et al. 2005)	*E*
Erythromycin				*d*	3.00×10^9 (Abdelmelek et al. 2011)
Ibuprofen	2.01 ± 0.14 (Xu et al. 2009b)	18.7-20 (Yamamoto et al. 2009)	10.4-49.9 (Xu et al. 2009b, Lin and Gan 2011)	1.92×10^{-1} (Yuan et al. 2009)	7.4×10^9-1.0×10^{10} (Huber et al. 2003, Das et al. 2010)
Iohexol				2.95×10^{-2} -4.03×10^{-2} (Pereira et al. 2007)	3.21×10^9 (Abdelmelek et al. 2011)
Iopamidol				*d*	$3.42 \pm 0.28 \times 10^9$ (Jeong et al. 2010)
Iopromide				*d*	$3.34 \pm 0.14 \times 10^9$ (Jeong et al. 2010)
Metopropol		1.45-7.08 (Liu et al. 2009)		*c*	$8.39\pm 0.06 \times 10^9$ (Abdelmelek et al. 2011)
Naproxen				3.6×10^{-2} (Packer et al. 2003)	7.99×10^9- 9.6×10^9 (Packer et al. 2003, Abdelmelek et al. 2011)
Primidone				*d*	*d*
Propanolol		0.25-0.96 (Liu et al. 2009)		2.22×10^{-3} (Andreozzi et al. 2003)	$1.07\pm 0.02 \times 10^{10}$ (Song et al. 2008)
Roxithromycin				*d*	5.00×10^9 (Vione et al. 2009)
Sotalol				*d*	*d*
Sulfamethoxazole				4.29×10^{-3} - 2.97×10^{-2} (Andreozzi et al. 2003, Baeza and Knappe 2011)	3.7×10^9 - 8.5×10^9 (Lam and Mabury 2005, Abdelmelek et al. 2011)
Trimethropim				1.18×10^{-3} (Baeza and Knappe 2011)	8.34×10^9 - 8.92×10^9 (Abdelmelek et al. 2011, Luo et al. 2012)

[a] direct photolysis was not observed (Radke et al. 2010);
[b] hydroxyl radicals, singlet oxygen and other photooxidants are reported to have only a very limited impact on the overall degradation (Vione et al. 2009);
[c] direct photolysis is not expected due to the lack of absorption in the environmental UV spectrum (USNLM, 2011);
[d] data not available;
[e] direct photolysis is the limiting photodegradation mechanism (Werner et al. 2005).

Table 15: Contribution to sensitivity of characterization factor results for each compound for the emission to agricultural soil as reclaimed water scenario. Negative indices indicate that an increase in the parameter is associated with a decrease in the output result. *Exp* denotes experimental values. Values in parenthesis denote USEtox values.

Parameter	Atenolol	Bezafibrate	Carbamazepine	Clarithromycin	Clindamycin	Clofibric acid	Diatrizoate	Diclofenac	Erythromycin	Ibuprofen	Iopamidol	Iopromide	Metoprolol	Naproxen	Primidone	Propranolol	Roxithromycin	Sotalol	Sulfamethoxazole	Trimethoprim
$k_{biodeg,\ water}$	-7.0 (-2.5)	-0.5 (-0.1)	-	-2.3 (-0.3)	-2.7 (-1.8)	-0.3 (-0.1)	-1.2 (-0.7)	-	-2.7 (-0.3)	-	-0.5 (-0.7)	-0.4 (-0.2)	-	0.0 (0.0)	-1.9 (-0.7)	0.0 (0.0)	-1.2 (-0.7)	-0.1 (-0.2)	-0.1 (0.0)	-0.8 (-0.2)
$k_{biodeg,\ soil}$	-0.1 (0.0)	0.0 (0.0)	-	-0.1 (0.0)	0.0 (0.0)	-0.1 (0.0)	-0.2 (0.0)	-10.2 (-3.0)	-0.1 (0.0)	-	0.0 (-0.2)	0.0 (0.0)	-2.0 (-1.4)	-0.4 (-0.1)	-0.1 (-0.2)	-0.2 (0.0)	0.0 (0.0)	-0.1 (0.0)	-0.2 (0.0)	0.0 (0.0)
$k_{direct\ photolysis,\ water}$	-	-	0.0 (0.0)	-12.5 (-12.8)	-	0.0 (0.0)	-	-26.2 (-9.1)	-	0.0 (0.0)	-	-	-	-12.6 (-2.7)	-	-	-	-	0.0 (0.0)	-2.9 (-1.2)
K_{OW} (KOWWIN v1.67a)	-0.4 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (-0.1)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	-0.9 (0.0)	-0.4 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)
K_{OC} neutrals *(*KOCWIN v2.0)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
K_{OC} acids *(*KOCWIN v2.0)	-	(70.2)	-	-	-	(66.1)	(-53.7)	(-82)	(80.3)	-	(-60.5)	(-53.0)	-	(-88.8)	(-60.5)	-	-	(-52.0)	(82.9)	-
K_{OC} bases *(*KOCWIN v2.0)	(-49.0)		-	(35.3)	(-55.6)	-	-	-	-	-	-	-	(-67.3)	-	-	(-70.2)	(-57.5)	-	-	(-85.1)
K_{OC} (acids regression)	-	-20.2	-	-	-	-40.6	-44.2	-41.6	-36.7	-	-26.4	-24.4	-	-53.7	-73.3	-	-	-16.4	-43.8	-
K_{OC} (bases regression)	-34.6	-	-	-31.6	-49.7	-	-	-	-	-	-	-	-30.9	-	-	-21.4	-22.5	-	-	-48.4
K_{DOC} (Burkhard, neutrals regression)	(0.0)	(0.0)	0.0 (0.0)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)
K_{DOC} (dissociating compounds)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	-	0.0	0.0	0.0	0.0	0.0	0.0	0.0
BCF_{fish} neutrals (BCFBAF v3.00)	-	-	0.0 (0.0)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
BCF_{fish} acids (BCFBAF v3.00)	-	(0.0)	-	-	-	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)	-	(0.0)	(0.0)	-	-	(0.0)	(0.0)	-
BCF_{fish} bases (BCFBAF v3.00)	(0.0)	-	-	(0.0)	(0.0)	-	-	-	-	-	-	-	(0.0)	-	-	(0.0)	(0.0)	-	-	(0.0)
BCF_{fish} (acids regression)	-	0.0	-	-	-	0.0	0.0	-0.1	0.0	0.0	0.0	0.0	-	0.0	0.0	-	-	0.0	0.0	-
BCF_{fish} (bases regression)	0.0	-	-	0.0	0.0	-	-	-	-	-	-	-	0.0	-	-	0.0	0.0	-	-	0.0
$HC50_{EC50}$	-23.3 (-21.9)	-4.9 (-1.0)	-5.1 (-6.2)	-46.0 (-49.8)	-35.2 (-39.9)	-12. 4 (-7.2)	-8.8 (-7.5)	-11.5 (-3.5)	-14.5 (-4.6)	-14.3 (-13.7)	-9.9 (-6.4)	-25.9 (-17.2)	-23.5 (-12.7)	-18.1 (-4.6)	-12.5 (-6.4)	-66.7 (-24.1)	-53.3 (-30.4)	-78.7 (-45.7)	-9.9 (-3.0)	-12.6 (-6.4)
exp K_{OC}	-	-	1.3 (-0.7)	-	-	-	-	-	-	0.0	-	-	-	-	-	-	-	-	-	-
exp $k_{biodeg,\ water}$	-	-	-0.1 (0.0)	-	-	-	-	0.0 (0.0)	-	0.0 (-0.8)	-	-	-15.8 (-5.6)	-	-	-	-	-	-	-
exp $k_{biodeg,\ soil}$	-	-	0.0 (0.0)	-	-	-	-	-	-	-32.0 (-31.4)	-	-	-	-	-	-	-	-	-	-
exp $k_{OH,\ water}$	0.0 (0.0)	-0.9 (-0.5)	-9.6 (-13.4)	-	-	-0.8 (-0.6)	0.0 (0.0)	-	0.0 (0.0)	-0.2 (-0.8)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	-	-1.9 (-1.0)	0.0 (0.0)
[˙OH] in water	-26.5 (-24.1)	-68.5 (-25.7)	-60.3 (-60.0)	-	-	-38.2 (-23.3)	-37.9 (-36)	-	-36.7 (-12)	-38.8 (-41.4)	-51.5 (-28.8)	-38. (-27.1)	-20.0 (-10.4)	-4.7 (-1.1)	0.0 (-28.8)	-7.6 (-2.8)	-15.8 (-8.6)	-	-28.1 (-9.5)	-8.6 (-3.9)
$pH_{\ agricultural\ soil}$	0.0	1.0	0.0	0.0	1.7	0.2	0.0	3.0	0.0	0.0	-4.5	-3.7	0.1	0.9	-1.0	0.0	1.3	0.0	6.5	15.6
$pH_{\ freshwater}$	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
$foc_{\ agricultural\ soil}$	-7.1 (1.2)	-3.1 (-1.6)	-22.8 (-22.0)	-6.4 (-0.9)	-9.8 (-1.0)	-6.4 (-1.9)	-6.5 (-0.9)	.-6.4 (-1.7)	.-10.1 (-4.9)	-13.5 (-12-5)	0.0 (-1.0)	-4.3 (-1.6)	-7.2 (-1.5)	-8.2 (-1.9)	-10.9 (-1.0)	-3.3 (-2.2)	-5.8 (-1.8)	-3.48 (-1.2)	.8.7 (-2.7)	-10.6 (-2.3)
Rain rate	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.9 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.1 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)

Table 16: Contribution to sensitivity of characterization factor results for each compound for the direct emission to freshwater scenario.

Parameter	Atenolol	Bezafibrate	Carbamazepine	Clarithromycin	Clindamycin	Clofibric acid	Diatrizoate	Diclofenac	Erythromycin	Ibuprofen	Iopamidol	Iopromide	Metoprolol	Naproxen	Primidone	Propranolol	Roxithromycin	Sotalol	Sulfamethoxazole	Trimethoprim
$k_{biodeg,\ water}$	-0.1 (0.0)	0.0 (0.0)	-	0.0 (-0.1)	-1.9 (-2.7)	0.0 (-0.1)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	-	0.0 (-0.0)	0.0 (0.0)	-	0.0 (0.0)	-5.5 (-5.2)	0.0 (0.0)	0.0 (0.0)	-0.2 (-0.1)	-	0.0 (0.0)
$K_{direct\ photolysis,\ water}$	-	-	-0.0 (0.0)	-21.1 (-21.9)	-	-0.0 (0.0)	-	-68.5 (-68.5)	-	0.0 (0.0)	-	-	-	-35.5 (-36.1)	-	-	-	-	0.0 (0.0)	-10.4 (-11.2)
K_{OW} (KOWWIN v1.67a)	-0.1 (0.0)	-0.0 (0.0)	-	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)
K_{OC} neutrals (KOCWIN v2.0)	(0.0)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
K_{OC} acids (KOCWIN v2.0)	-	(0.0)	-	-	-	(0.0)	(0.0)	(0.0)	(0.0)	-	(0.0)	(0.0)	-	(0.0)	(0.0)	-	-	(-0.1)	(0.0)	-
K_{OC} bases (KOCWIN v2.0)	(0.0)		-	(0.0)	(0.0)	-	-	-	-	-	-	-	(0.0)	-	-	(0.0)	(0.0)	-	-	(0.0)
K_{OC} (acids regression)	-	0.0	-	-	-	0.0	0.0	0.0	0.0	-	0.0	0.0	-	0.0	0.0	-	-	-0.1	0.0	-
K_{OC} (bases regression)	0.0	-	-	-	-0.1	-	-	-	-	-	-	-	0.0	-	-	-	0.0	-	-	-0.0
K_{DOC} (Burkhard, neutrals regression)	(0.0)	(0.0)	(0.0)		(0.0)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)
K_{DOC} (dissociating compounds)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	-	0.0	0.0	0.0	0.0	0.0	0.0	0.0
BCF_{fish} neutrals (BCFBAF v3.00)	-	-	0.0 (0.0)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
BCF_{fish} acids (BCFBAF v3.00)	-	0.0)	-	-	-	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)	-	(0.0)	(0.0)	-	-	(0.0)	(0.0)	-
BCF_{fish} bases (BCFBAF v3.00)	(0.0)	-	-	(0.0)	(0.0)		-	-	-	-	-	-	(0.0)	-	-	(0.0)	(0.0)	-	-	(0.0)
BCF_{fish} (acids regression)	-	0.0	-	0.0	-	0.0	0.0	0.0	0.0	0.0	0.0	0.0	-	0.0	-0.1	-	-	0.0	0.0	-
BCF_{fish} (bases regression)	0.0	-	-	-	0.0	-	-	-	-	-	-	-	0.0	-	-	0.0	0.0	-	-	0.0
$HC50_{EC50}$	-48.4 (-49.5)	-7.0 (-7.0)	-7.8 (-8.2)	-78.3 (-77.1)	-97.3 (-96.0)	25.2 (-26.0)	-20.2 (-21.7)	-30.5 (-30.7)	-30.2 (-29.5)	-28.2 (-30.8)	-18.0 (-18.0)	-41.7 (-16.4)	-54.6 (-54.2)	-51.2 (-51)	-93.2 (-93.9)	-89.9 (-89.3)	-76.2 (-76.2)	-98.5 (-99.1)	-23.8 (-25.5)	-51.4 (-51.2)
exp K_{OC}	-	-	0.0 (0.0)	-	-	-	-	-	-	0.0 (0.0)	-	-	-	-	-	-	-	-		-
exp $k_{biodeg,\ water}$	-	-	0.0 (0.0)	-	-	-	-	-	-	0.0 (0.0)	-	-	0.0 (-0.2)	-	-	-	-	-		-
exp $k_{OH,\ water}$	0.0 (0.0)	-1.4 (-1.6)	-13.8 (-13.4)	0.0 (0.0)	-	2.6 (-2.2)	0.0 (0.0)	-	0.0 (-0.1)	-0.4 (-0.8)	-0.5 (0.0)	-0.1 (0.0)	-0.2 (0.0)	0.0 (0.0)	-	0.0 (0.0)	0.0 (0.0)	-	-7.1 (-6.4)	0.0 (-0.1)
[˙OH] in water	-50.4 (-49.5)	90.6 (-90.3)	-77.4 (-77.4)	0.0 (0.0)	-	71.2 (-70.9)	-78.7 (-77.4)	-	-68.7 (-69.3)	-70.4 (-68.0)	-80.7 (-80.7)	-57.4 (-81.2)	-44.6 (-44.5)	-12.3 (-12.0)	-	-8.9 (-9.7)	-22.9 (-22.7)	-	-68.0 (-67.1)	-37.3 (-36.6)
$pH_{freshwater}$	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.0
Rain rate	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (-0.1)

Appendix C

Table 17: Estimated concentration of PC's in biosolids and reported concentration of PC's on WWTPs effluents and influents (loq=limit of quantification; lod=limit of detection)

PC / Estimated concentration in biosolids (median and 95% confidence interval) (µg /kg dry matter)	WWTP effluent concentration (µg/l)	WWTP influent concentration (µg/l)	WWTP Location	References
Analgesics/anti-inflammatories				
5-aminosalicylic acid	0.63 (<0.172-1.218)	10.691 (3.160–27.490)	Wales, UK	Kasprzyk-Hordern et al. (2009)
199.05 (6.94-2701.08)	21.11 (14.17-30.32)	1.667 (0.841–2.828)	Wales, UK	Kasprzyk-Hordern et al. (2009)
Acetaminophen	0.082-0.145		France	Coetsier et al. (2009)
775.64 (22.63-17522.1)	<loq-4.3	134 (29-243)	Spain	Gómez et al. (2007)
	<20	4.16	England, UK	Roberts and Thomas (2006)
	<0.50-6.0		Germany (49 WWTPs)	Ternes (1998)
	<loq	23.202 (1.571-37.458)	Spain	Rosal et al. (2010a)
		9.90 (7.1–11.4)	Spain	Radjenović et al. (2009)
Acetylsalicylic acid	0.027 (<0.003-0.085)	0.664 (0.485–2.042)	Wales, UK	Kasprzyk-Hordern et al.(2009)
159.6 (0-807.0)	0.170 (<0.002-0.269)	2.490 (1.321–5.448)	Wales, UK	Kasprzyk-Hordern et al.(2009)
	0.22 (<0.10-1.5)		Germany (49 WWTPs)	Ternes (1998)
Aminopyrine	<loq-0.43		France	Andreozzi et al. (2003)
	<loq		4 countries (6 WWTPs)	Andreozzi et al. (2003)
	<0.10-1.0		Germany (16 WWTPs)	Ternes (1998)
Codeine	3.7 (0.9-8.1)	5.2 (2.8–11)	Spain	Gómez et al. (2007)
23.47 (0-1247.06)	2.716 (1.457-4.171)	6.954 (2.496–12.599)	Wales, UK	Kasprzyk-Hordern et al.(2009)
	5.271 (2.940-15.593)	10.321 (1.732–32.295)	Wales, UK	Kasprzyk-Hordern et al.(2009)
	0.160 (<loq-0.319)	0.521 (0.150-2.087)	Spain	Rosal et al. (2010a)
	0.022 (<0.010-0.025)	0.12 (<0.020-0.16)	Germany	Wick et al. (2009)
Dextropropoxyphene	0.1		England, UK	Roberts and Thomas (2006)
Diclofenac	0.41		France	Andreozzi et al. (2003)
10.73 (0-384.92)	0.25		France	Andreozzi et al. (2003)
	0.47		Italy	Andreozzi et al. (2003)
	1.48		Italy	Andreozzi et al. (2003)
	5.45		Italy	Andreozzi et al. (2003)
	0.89		Greece	Andreozzi et al. (2003)
	<loq		Sweden	Andreozzi et al. (2003)
	0.12	0.16	Sweden	Bendz et al. (2005)
	0.78-3.464	0.9-4.1	Austria (5 WWTPs)	Clara et al. (2005 ab)
	1.48-4.09		France	Coetsier et al. (2009)
	0.9 (0.14-2.2)	1.5 (0.2–3.6)	Spain	Gómez et al. (2007)
	0.098 (0.033-0.142)	0.069 (0.026–0.257)	Wales, UK	Kasprzyk-Hordern et al.(2009)
	0.179 (0.006-0.490)	0.260 (0.057–1.161)	Wales, UK	Kasprzyk-Hordern et al.(2009)
	0.35	0.3-0.6	Finland (5 WWTPs)	Lindqvist et al. (2005)
	0.36 (0.0062-1.3)		Spain	Muñoz et al. (2009)
	1.7 (<loq-11.0)		Spain	Muñoz et al. (2009)
	0.14-1.48	0.2-0.7	5 countries	Paxéus (2004)
	1.9		Germany	Quintana et al. (2005)
	7.5	7	Spain	Reif et al. (2008)
	0.34	0.98	England, UK	Roberts and Thomas (2006)
	<loq	<loq	Spain (4 WWTPs)	Santos et al. (2009)
	<loq	<loq	Spain (4 WWTPs)	Santos et al. (2007)
	<0.01	11	Spain	Suárez et al. (2005)
	0.6-2.4	0.3-2.09	Switzerland (3WWTPs)	Tauxe-Wuersch et al. (2005)
	1.3		Germany	Ternes et al. (2003)
	0.81		Germany (49 WWTPs)	Ternes (1998)
	0.40	0.46	Finland	Vieno et al. (2005)
	0.49	0.23	Sweden	Zorita et al. (2009)
	0.160 (<loq-0.319)	0.521 (0.150-2.087)	Spain	Rosal et al. (2010a)
		1.32 (1.0–1.6)	Spain	Radjenović et al. (2009)
Dipyrone	4.9 (2.4-7.5)	14 (4.7–24)	Spain	Gómez et al. (2007)
153.33 (0-3302.05)				
Fenoprofen	<loq		4 countries (7 WWTPs)	Andreozzi et al. (2003)
	<loq	<loq	Sweden	Bendz et al. (2005)
	<0.0055-0.046		France	Coetsier et al. (2009)
	0.20		Germany ((49 WWTPs)	Ternes (1998)
Flurbiprofen	0.21		France	Andreozzi et al. (2003)
	0.34		Italy	Andreozzi et al. (2003)
	<loq		4 countries (5 WWTPs)	Andreozzi et al. (2003)
	<loq	<loq	Sweden	Andreozzi et al. (2003)

PC / Estimated concentration in biosolids (median and 95% confidence interval) (µg /kg dry matter)	WWTP effluent concentration (µg/l)	WWTP influent concentration (µg/l)	WWTP Location	References
				Bendz et al. (2005)
Ibuprofen	1.82		France	Andreozzi et al. (2003)
253.57 (8.40-5313.75)	0.02		France	Andreozzi et al. (2003)
	0.05		Italy	Andreozzi et al. (2003)
	0.18		Italy	Andreozzi et al. (2003)
	0.02		Italy	Andreozzi et al. (2003)
	0.02		Greece	Andreozzi et al. (2003)
	7.11		Sweden	Andreozzi et al. (2003)
	0.15	3.59	Sweden	Bendz et al.(2005)
	0.91-2-10	2.6-5.7	Spain	Carballa et al. (2004)
	0.02-2.40	1.2-3.6	Austria (5 WWTPs)	Clara et al. (2005ab)
	0.023-0.067		France	Coetsier et al.(2009)
	7.1 (0.24-28)	84 (34–168)	Spain	Gómez et al. (2007)
	0.263 (0.131-0.429)	1.681 (0.968–2.986)	Wales, UK	Kasprzyk-Hordern et al.(2009)
	0.143 (0.065.0.491)	2.294 (0.984–6.328)	Wales, UK	Kasprzyk-Hordern et al.(2009)
	13.1	9.8-19.8	Finland (5 WWTPs)	Lindqvist et al. (2005)
	0.54 (<loq-4.6)		Spain	Muñoz et al. (2009)
	4.7 (<loq-32)		Spain	Muñoz et al. (2009)
	0.02-1.9	0.8-11	5 countries	Paxéus (2004)
	0.18	5.7	Germany	Quintana et al. (2005)
	2.9	2.6	England, UK	Roberts and Thomas (2006)
	0.91-2.10	2.8-5.8	Spain	Rodríguez et al. (2009)
	0.135 (<loq-0.653)	2.687 (<loq-4.113)	Spain	Rosal et al. (2010a)
	6.20 (0.8-26.53)	59.14 (12.13–167.23)	Spain	Santos et al. (2007)
	10.89 (0.78-40.17)	94.12 (16.10–231.83)	Spain	Santos et al. (2007)
	12.60 (1.17-40.78)	156.16 (31.43–319.10)	Spain	Santos et al. (2007)
	11.50 (2.30-48.29)	150.73 (53.48–373.11)	Spain	Santos et al. (2007)
	4.13 (<loq-26.5)	69.7 (3.73-353)	Spain	Santos et al. (2009)
	6.69 (<loq-40.2)	84.4 (<lod-294)	Spain	Santos et al. (2009)
	10.16 (<loq-55.9)	105 (<lod-319)	Spain	Santos et al. (2009)
	7.62 (<loq-48.2)	115 (<lod-603)	Spain	Santos et al. (2009)
	1.8	10	Switzerland	Suárez et al. (2005)
	0.1-2.1	1.1-4.6	Germany	Tauxe-Wuersch et al. (2005)
	0.13		Germany	Ternes et al. (2003)
	0.37		Germany (49 WWTPs)	Ternes (1998)
	0.005	23.4	Finland	Vieno et al. (2005)
	0.047	6.9	Sweden	Zorita et al. (2009)
		21.7 (14.6–31.3)	Spain	Radjenović et al. (2009)
Indomethacin	<loq	<loq	Sweden	Bendz et al. (2005)
14.63 (0-133.27)	0.037 (0.02-0.059)	42 (<loq-113)	Spain	Rosal et al. (2010a)
	0.1		Germany	Ternes et al. (2003)
	0.27		Germany (10 WWTPs)	Ternes (1998)
		0.875 (0.66–1.0)	Spain	Radjenović et al. (2009)
Ketoprofen	1.62		France	Andreozzi et al. (2003)
18.05 (0-310.27)	<loq		4 countries (6 WWTPs)	Andreozzi et al. (2003)
	0.33	0.94	Sweden	Bendz et al. (2005)
	0.018 (0.007-0.037)	0.123 (0.031–0.346)	Wales, UK	Kasprzyk-Hordern et al.(2009)
	0.016 (<0.003-0.033)	0.028 (<4–0.119)	Wales, UK	Kasprzyk-Hordern et al.(2009)
	2.0	1.3-3	Finland (5 WWTPs)	Lindqvist et al. (2005)
	0.12	0.5	Germany	Quintana et al. (2005)
	0.392 (0.277-0.539)	0.441 (<loq-0.801)	Spain	Rosal et al. (2010a)
	0.34 (<loq-1.7)	0.54 (<lod–2.25)	Spain	Santos et al. (2007)
	0.21 (<loq-0.55)	0.30 (<lod–2.51)	Spain	Santos et al. (2007)
	0.36 (<loq-1.29)	0.46 (<lod–2.40)	Spain	Santos et al. (2007)
	0.41 (<loq-1.5)	1.36 (<lod–3.59)	Spain	Santos et al. (2007)
	0.86 (<loq-2.7)	1.58 (<lod-5.52)	Spain	Santos et al. (2009)
	0.80 (<loq-1.95)	1.74 (<lod- 6.47)	Spain	Santos et al. (2009)
	0.82 (<loq-3.92)	1.91 (<lod-8.56)	Spain	Santos et al. (2009)
	0.88 (<loq-2.03)	2.07 (<lod-5.70)	Spain	Santos et al. (2009)
	0.1-0.37	0.15-0.41	Switzerland	Tauxe-Wuersch et al. (2005)
	0.2		Germany (49 WWTPs)	Ternes (1998)
	0.23	2.9	Finland	Vieno et al. (2005)
		1.08 (0.70–1.2)	Spain	Radjenović et al. (2009)
Ketorolac	0.228 (<loq-0.539)	0.407 (<loq-2.793)	Spain	Rosal et al. (2010a)
101.57 (0- 301.48)				
Mefenamic acid	0.061 (<0.005-0.222)	0.205 (<20–1.269)	Wales, UK	Kasprzyk-Hordern et al.(2009)
4.43 (0-165.77)	0.039 (<0.005-0.103	0.008 (<0.017–0.032)	Wales, UK	Kasprzyk-Hordern et al.(2009)
	0.96	0.23	England, UK	Roberts and Thomas (2006)

PC / Estimated concentration in biosolids (median and 95% confidence interval) (µg /kg dry matter)	WWTP effluent concentration (µg/l)	WWTP influent concentration (µg/l)	WWTP Location	References
	0.138 (0.087-0.163)	0.141 (0.220-0.101)	Spain	Rosal et al. (2010a)
	0.5-3	0.75-2.9	Switzerland	Tauxe-Wuersch et al. (2005)
		1.07 (0.80–1.2)	Spain	Radjenović et al. (2009)
Naproxen	1.73		France	Andreozzi et al. (2003)
87.76 (0-2259.19)	0.51		France	Andreozzi et al. (2003)
	0.29		Italy	Andreozzi et al. (2003)
	0.41		Italy	Andreozzi et al. (2003)
	5.22		Italy	Andreozzi et al. (2003)
	<loq		Greece	Andreozzi et al. (2003)
	2.15		Sweden	Andreozzi et al. (2003)
	0.25	3.65	Sweden	Bendz et al.(2005)
	0.8-2.6	1.79-4.6	Spain	Carballa et al.(2004)
	0.170 (<0.002-0.269)	1.173 (0.620–3.504)	Wales, UK	Kasprzyk-Hordern et al.(2009)
	0.370 (0.234-0.703)	0.838 (0.400–1.457)	Wales, UK	Kasprzyk-Hordern et al.(2009)
	4.9	3.6-8.2	Finland (5 WWTPs)	Lindqvist et al. (2005)
	0.2-1.51	1.8-3.6	5 countries	Paxéus (2004)
	0.27	1	Germany	Quintana et al. (2005)
	1	6.2	England, UK	Reif et al. (2008)
	1.87-2.1	3.5-4.5	Spain	Rodríguez et al. (2009)
	0.923 (0.359-2.208)	2.363 (1.196-5.228)	Spain	Rosal et al. (2010a)
	2.62 (1.18-4.04)	4.04 (2.02–7.23)	Spain	Santos et al. (2007)
	1.18 (0.22-2.29)	11.14 (2.05–26.64)	Spain	Santos et al. (2007)
	1.83 (0.83-3.12)	5.18 (1.60–27.40)	Spain	Santos et al. (2007)
	1.96 (0.29-4.28)	5.07 (1.10–9.10)	Spain	Santos et al. (2007)
	2.74 (0.54-5.09)	4.83 (2.02-8.50)	Spain	Santos et al. (2009)
	1.64 (0.22-3.52)	8.07 (2.03-52.9)	Spain	Santos et al. (2009)
	2.18 (0.83-3.64)	4.69 (1.63-27.4)	Spain	Santos et al. (2009)
	1.67 (0.29-4.28)	4.28 (1.14-9.10)	Spain	Santos et al. (2009)
	3.2	10	Switzerland	Suárez et al. (2005)
	0.3		Germany (10 WWTPs)	Ternes (1998)
	0.1		Germany	Ternes et al. (2003)
	0.42	8.6	Finland	Vieno et al. (2005);
	0.34	4.9	Sweden	Zorita et al. (2009)
		0.463 (0.13–0.67)	Spain	Radjenović et al. (2009)
Phenazone	0.37		Italy	Andreozzi et al. (2003)
	<loq		4 countries (6 WWTPs)	Andreozzi et al. (2003)
	0.027(<loq-0.058)		Spain	Rosal et al. (2010a)
	0.16		Germany (30 WWTPs)	Ternes (1998)
Propyphenazone		0.065 (0.046-0.097)	Spain	Radjenović et al. (2009)
0.14 (0-239.54)				
Salicylic acid	0.164 (<0.001-0.497)	5.866 (1.479-18.479)	Wales, UK	Kasprzyk-Hordern et al.(2009)
591.82 (46.82-2480.78)	0.075(<0.001-0.391)	12.647 (5.644-32.082)	Wales, UK	Kasprzyk-Hordern et al.(2009)
	<0.05-0.14		Germany (36 WWTP)	Ternes (1998)
Tramadol	28.15 (12.78-56.18)	48.4882 (3.037–85.843)	Wales, UK	Kasprzyk-Hordern et al.(2009)
11.42 (0-51668.44)	43.81 (24.13-97.62)	5.866 (1.479–18.479)	Wales, UK	Kasprzyk-Hordern et al.(2009)
	0.23 (0.02-0.37)	0.23-0.47	Germany	Wick et al. (2009)
Antibiotics				
Azithromycin	0.160 (0.04-0.40)	0.170 (0.090-0.380)	Switzerland (2 WWTP)	Göbel et al. (2005)
7.25 (0-91.27)				
Chloramphenicol	<0.006	0.014 (<0.004–0.319)	Wales, UK	Kasprzyk-Hordern et al.(2009)
28.66 (0-388.23)	0.021 (<0.006-0.069)	0.248 (0.150–0.452)	Wales, UK	Kasprzyk-Hordern et al.(2009
Ciprofloxacin	0.06		France	Andreozzi et al. (2003)
5.69 (0-191.39)	0.06		France	Andreozzi et al. (2003)
	0.07		Italy	Andreozzi et al. (2003)
	0.06		Italy	Andreozzi et al. (2003)
	0.04		Italy	Andreozzi et al. (2003)
	0.07		Greece	Andreozzi et al. (2003)
	0.03		Sweden	Andreozzi et al. (2003)
	0.061-0.087	0.315-0.570	Switzerland	Golet et al.(2003)
	2.0 (<loq-5.7)		Spain	Muñoz et al. (2009)
	0.71 (0.310-1.5)		Spain	Muñoz et al. (2009)
	2.38 (<loq-5.69)	5.524 (0.160-13.625)	Spain	Rosal et al. (2010a)
	0.094	0.32	Sweden	Zorita et al. (2009)
Clarithromycin	0.24 (0.11-0.38)	0.380 (0.330-0.600)	Switzerland (2 WWTP)	Göbel et al. (2005)
30.15 (0-304.68)	0.21		Germany	Ternes et al. (2003)
Enoxacin	0.03		France	Andreozzi et al. (2003)
	0.01		France	Andreozzi et al. (2003)
	0.03		Italy	Andreozzi et al. (2003)
	0.03		Italy	Andreozzi et al. (2003)

PC / Estimated concentration in biosolids (median and 95% confidence interval) (µg /kg dry matter)	WWTP effluent concentration (µg/l)	WWTP influent concentration (µg/l)	WWTP Location	References
	0.01		Italy	Andreozzi et al. (2003)
	0.03		Greece	Andreozzi et al. (2003)
	0.01		Sweden	Andreozzi et al. (2003)
Erythromycin	0.07 (0.06-0.11)	0.70 (0.60-0.190)	Switzerland (2 WWTP)	Göbel et al. (2005)
17.57 (0-518.49)	0.696 (0.023-2.772)	2.530 (0.144–10.025)	Wales, UK	Kasprzyk-Hordern et al.(2009)
	1.385 (0.292-2.841)	1.609 (0.242–6.755)	Wales, UK	Kasprzyk-Hordern et al.(2009)
	0.89 (<loq-6.3)		Spain	Muñoz et al. (2009)
	0.57 (<loq-1.7)		Spain	Muñoz et al. (2009)
	0.9	10	England, UK	Reif et al. (2008)
	0.2	0.11	England, UK	Roberts and Thomas (2006)
	0.331 (<loq-0.760)	0.346 (<loq-2.310)	Spain	Rosal et al. (2010a)
	0.62		Germany	Ternes et al. (2003)
Lomefloxacin	0.18		France	Andreozzi et al. (2003)
	0.19		France	Andreozzi et al. (2003)
	0.32		Italy	Andreozzi et al. (2003)
	0.18		Italy	Andreozzi et al. (2003)
	0.22		Italy	Andreozzi et al. (2003)
	0.29		Greece	Andreozzi et al. (2003)
	0.13		Sweden	Andreozzi et al. (2003)
Metronidazole	0.265 (0.06-0.421)	0.643 (0.158–1.583)	Wales, UK	Kasprzyk-Hordern et al.(2009)
0.29 (0-90.16)	0.353 (0.129-0.561)	0.569 (0.347–962)	Wales, UK	Kasprzyk-Hordern et al.(2009)
	0.055 (<loq-127)	90 (0.044-0.165)	Spain	Rosal et al. (2010a)
Norfloxacin	0.05		France	Andreozzi et al. (2003)
3.26 (0-45.02)	0.08		France	Andreozzi et al. (2003)
	0.07		Italy	Andreozzi et al. (2003)
	0.06		Italy	Andreozzi et al. (2003)
	0.06		Italy	Andreozzi et al. (2003)
	0.07		Greece	Andreozzi et al. (2003)
	0.03		Sweden	Andreozzi et al. (2003)
	<0.0052-0.247		France	Coetsier et al. (2009)
	0.039-0.064	0.343-0.520	Switzerland	Golet et al. (2003)
	0.019	0.018	Sweden	Zorita et al. (2009)
Ofloxacin	0.33		France	Andreozzi et al. (2003)
20.23 (0-4590.13)	0.51		France	Andreozzi et al. (2003)
	0.58		Italy	Andreozzi et al. (2003)
	0.29		Italy	Andreozzi et al. (2003)
	0.31		Italy	Andreozzi et al. (2003)
	0.46		Greece	Andreozzi et al. (2003)
	0.12		Sweden	Andreozzi et al. (2003)
	0.0641 (<loq-0.816)	2.275 (0.848-5.286)	Spain	Rosal et al. (2010a)
	0.019	0.022	Sweden	Zorita et al. (2009)
		10.5 (0.89-31.7)		Radjenović et al. (2009)
Roxithromycin	<0.020-0.057	0.025-0.078	Austria (5 WWTPs)	Clara et al. (2005ab)
0.14 (0-214.39)	0.01 (0.01-0.03)	0.20 (0.10-0.40)	Switzerland (2 WWTP)	Göbel et al. (2005)
	5	17	England, UK	Reif et al. (2008)
	0.05	0.08	France (6 WWTPs)	Ruel et al. (2010)
	0.54		Germany	Ternes et al. (2003)
Sulfamethoxazole	0.09		France	Andreozzi et al. (2003)
7.75 (0-394.35)	0.07		France	Andreozzi et al. (2003)
	0.01		Italy	Andreozzi et al. (2003)
	<lod		Italy	Andreozzi et al. (2003)
	0.03		Italy	Andreozzi et al. (2003)
	0.09		Greece	Andreozzi et al. (2003)
	0.02		Sweden	Andreozzi et al. (2003)
	0.07		Sweden	Bendz et al. (2005)
	0.25	<loq-0.58	Spain	Carballa et al. (2004)
	<lod-0.09	0.02-0.075	Austria (5 WWTPs)	Clara et al. (2005ab)
	0.29 (0.13-0.86)	1.700 (0.940-1.900)	Switzerland (2 WWTP)	Göbel et al. (2005)
	0.010 (<3-0.023)	0.029 (<0.003-0.150)	Wales, UK	Kasprzyk-Hordern et al. (2009)
	0.019 (0.004-0.044)	0.115 (0.020-0.274)	Wales, UK	Kasprzyk-Hordern et al. (2009)
	0.18		Spain	Muñoz et al. (2009)
	5	10	England, UK	Reif et al. (2008)
	0.104 (0.0173-0.231)	0.279 (0.162-0.530)	Spain	Rosal et al. (2010a)
	0.3	0.53	France (6 WWTPs)	Ruel et al. (2010)
	0.62		Germany	Ternes et al. (2003)
		0.093 (0.25-1.3)	Spain	Radjenović et al. (2009)
Sulfapyridine	0.090 (0.040-0.350)	0.090 (0.060-0.150)	Switzerland (2 WWTP)	Göbel et al. (2005)
9.94 (0-3039.16)	0.455 (0.094-1.112)	4.971 (2.164-12.397)	Wales, UK	Kasprzyk-Hordern et al. (2009)
	0.277 (0.127-0.378)	0.914 (0.026-5.763)	Wales, UK	Kasprzyk-Hordern et al. (2009)

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Sulfasalazine	0.0003 (0.0005-0.0015)	0.116 (<0.080-0.447)	Wales, UK	Kasprzyk-Hordern et al. (2009)
2.71 (0-250.68)	0.484 (0.100-2.185)	0.0002 (0.0005–0.004)	Wales, UK	Kasprzyk-Hordern et al. (2009)
Trimethoprim	0.04		France	Andreozzi et al. (2003)
3.59 (0-212.01)	0.02		France	Andreozzi et al. (2003)
	0.04		Italy	Andreozzi et al. (2003)
	0.03		Italy	Andreozzi et al. (2003)
	0.13		Italy	Andreozzi et al. (2003)
	0.08		Greece	Andreozzi et al. (2003)
	0.05		Sweden	Andreozzi et al. (2003)
	0.04	0.08	Sweden	Bendz et al. (2005)
	0.70 (0.20-0.31)	0.290 (0.210-0.440)	Switzerland (2 WWTP)	Göbel et al. (2005)
	1.152 (0.625-3.052)	2.192 (0.464-6.796)	Wales, UK	Kasprzyk-Hordern et al. (2009)
	0.876 (0.385-1.218)	2.925 (1.514-4.673)	Wales, UK	Kasprzyk-Hordern et al. (2009)
	0.02-0.24	0.1-0.3	5 countries	Paxéus, (2004)
	6.7	10.5	England, UK	Reif et al. (2008)
	0.4	0.25	England, UK	Roberts and Thomas (2006)
	0.0051 (<loq-0.099)	0.104 0.078-(0.197)	Spain	Rosal et al. (2006)
	0.34		Germany	Ternes et al. (2003)
		0.204 (0.15-0.43)	Spain	Radjenović et al. (2009)
Antifungals				
Clotrimazole	0.014-0.027	0.029	England, UK	Roberts and Thomas, 2006
0.42 (0-6.28)	<lod-0.006		Switzerland (10WWTP)	Kahle et al. (2008)
Antihypertensives				
Diltiazem	0.267 (0.095-0.642)	0.770 (0.228-3.207)	Wales, UK	Kasprzyk-Hordern et al. (2009)
38.74 (0-2251.01)	0.357 (0.108-1-156)	1.559 (0.405-5.258)	Wales, UK	Kasprzyk-Hordern et al. (2009)
Hydrochlorothiazide	1.8 (<loq-11)		Spain	Muñoz et al. (2009)
0.066 (0-894.28)	3(<loq-15)		Spain	Muñoz et al. (2009)
	0.135 (<loq-0.653)	2.514 (0.617-10.018)	Spain	Rosal et al. (2010a)
		2.74 (2.3-4.8)	Spain	Radjenović et al. (2009)
β-blockers				
Acebutolol	0.13		France	Andreozzi et al. (2003)
	0.08		France	Andreozzi et al. (2003)
	0.04		Italy	Andreozzi et al. (2003)
	0.02		Italy	Andreozzi et al. (2003)
	0.11		Italy	Andreozzi et al. (2003)
	0.01		Greece	Andreozzi et al. (2003)
	<0.01		Sweden	Andreozzi et al. (2003)
Atenolol	0.31-1.33	2.29	Switzerland (3 WWTP)	Alder et al. 2010)
15.62 (0-1520.45)	0.16	0.03	Sweden	Bendz et al. (2005)
	2.123 (1.292-3.168)	14.223 (8.102-25.146)	Wales, UK	Kasprzyk-Hordern et al. (2009)
	2.870 (1.260-7.602)	12.913 (3.090-33.106)	Wales, UK	Kasprzyk-Hordern et al. (2009)
	0.404-0.678	1.69-2.54	Switzerland (2 WWTP)	Maurer et al. (2007)
	4.8 (0.14-73)		Spain	Muñoz et al. (2009)
	15 (0.30-130)		Spain	Muñoz et al. (2009)
	0.01-0.73		5 countries	Paxéus (2004)
	1.025 (0.517-2.438)	1.197 (0.660-2.432)	Spain	Rosal et al. (2010)
	0.36		Germany	Ternes et al. (2003)
	0.30	0.72	Germany	Wick et al. (2009)
		2.0 (0.84-2.8)	Spain	Radjenović et al. (2009)
Betaxolol	<loq		4 countries (7 WWTPs)	Andreozzi et al. (2003)
	0.057		Germany (29 WWTPs)	Ternes (1998)
	<loq	0.006-0.009	Germany	Wick et al. (2009)
Bisoprolol	0. 057		Germany (29 WWTPs)	Ternes (1998)
0.31 (0-17.99)	0.21	0.21-0.38	Germany	Wick et al., 2009
Carazolol	<lod-0.12		Germany (29 WWTPs)	Ternes (1998)
Celiprolol	0.28		Germany	Ternes et al (2003)
1.72 (0.060-7.16)	0.12	0.10-0.16	Germany	Wick et al. (2009)

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Metoprolol	0.160-0.240	0.24	Switzerland (3 WWTP)	Alder et al. (2010)
0.039 (0-63.49)	0.08		France	Andreozzi et al. (2003)
	0.08		France	Andreozzi et al. (2003)
	0.01		Italy	Andreozzi et al. (2003)
	0.01		Italy	Andreozzi et al. (2003)
	0.01		Italy	Andreozzi et al. (2003)
	0.1		Greece	Andreozzi et al. (2003)
	0.39		Sweden	Andreozzi et al. (2003)
	0.041 (0.034-0.057)	0.094 (0.056-0.146)	Wales, UK	Kasprzyk-Hordern et al. (2009)
	0.069 (0.035-0.130)	0.075 (0.039-0.117)	Wales, UK	Kasprzyk-Hordern et al. (2009)
	0.103-0.161		Switzerland (2 WWTP)	Maurer et al. (2007)
	<0.01-0.39	0.3	5 countries	Paxéus (2004)
	0.069 (<loq-0.038)	0.020 (<loq-0.052)	Spain	Rosal et al. (2010a)
	0.73		Germany (29 WWTP)	Ternes (1998)
	1.7		Germany	Ternes et al (2003)
	0.64	1.2	Germany	Wick et al. (2009)
		0.039 (0.026-0.063)	Spain	Radjenović et al. (2009)
Nadolol	0.025		Germany (29 WWTPs)	Ternes (1998)
Oxprenolol	0.05		France	Andreozzi et al. (2003)
	0.02		France	Andreozzi et al. (2003)
	0.01		Italy	Andreozzi et al. (2003)
	0.03		Italy	Andreozzi et al. (2003)
	<0.01		Italy	Andreozzi et al. (2003)
	0.01		Greece	Andreozzi et al. (2003)
	<lod		Sweden	Andreozzi et al. (2003)
Propranolol	0.160-0.240	0.05	Switzerland (3 WWTP)	Alder et al. (2010)
0.13 (0-77.84)	0.01		France	Andreozzi et al. (2003)
	0.04		France	Andreozzi et al. (2003)
	0.01		Italy	Andreozzi et al. (2003)
	0.01		Italy	Andreozzi et al. (2003)
	0.01		Italy	Andreozzi et al. (2003)
	0.01		Greece	Andreozzi et al. (2003)
	0.09		Sweden	Andreozzi et al. (2003)
	0.03	0.05	Sweden	Bendz et al. (2005)
	0.160-0.560		France	Coetsier et al. (2009)
	0.265 (0.160-0.405)	0.557 (0.125-1.962	Wales, UK	Kasprzyk-Hordern et al. (2009)
	0.264 (0.130-0.523)	0.638 (0.110-1.946)	Wales, UK	Kasprzyk-Hordern et al. (2009)
	0.032-0.123		Switzerland (2 WWTP)	Maurer et al. (2007)
	0.39	0.08	England, UK	Roberts and Thomas (2006)
	0.036 (<loq-0.057)	0.036 (0.061-0.012)	Spain	Rosal et al. (2010a)
	0.17		Germany	Ternes (1998)
	0.18		Germany	Ternes et al. (2003)
	0.40	0.073	Germany	Wick et al. (2009)
		0.292 (0.108–1.13)	Spain	Radjenović et al. (2009)
Sotalol	0.210-0.330	0.29	Switzerland (3 WWTP)	Alder et al. (2010)
0.98 (0-57.80)	0.249-0.251	0.3	Switzerland (2 WWTP)	Maurer et al. (2007)
	1.32		Germany	Ternes et al. (2003)
	0.71	1.1	Germany	Wick et al. (2009)
		0.509 (0.17–0.85)	Spain	Radjenović et al. (2009)
Timolol	<loq-0.07		Germany (29 WWTPs)	Ternes (1998)
Diuretics				
Bendroflumethiazide	<0.008	0.044 (<0.008-0.101)	Wales, UK	Kasprzyk-Hordern et al. (2009)
0.62 (0.028-1.91)	0.011 (<0.008-0.058)	0.017 (<0.008-0.066)	Wales, UK	Kasprzyk-Hordern et al. (2009)
Furosemide	0.629 (<0.043-1.823)	2.789 (1.580-6.022)	Wales, UK	Kasprzyk-Hordern et al. (2009)
37.45 (0-942.53)	1.161 (0.583-1.956)	1.476 (0.036–5.111)	Wales, UK	Kasprzyk-Hordern et al. (2009)
	0.116 (<loq-0.666)	0.413 (<loq-1.051)	Spain	Rosal et al. (2010a)
Lipid regulators				
Bezafibrate	1.07		France	Andreozzi et al. (2003)
20.44 (0-1494.53)	0.91		Italy	Andreozzi et al. (2003)
	<lod		4 Countries (5 WWTPs)	Andreozzi et al. (2003)
	<lod-0.715	1.55-7.6	Austria (5 WWTPs)	Clara et al. (2005ab)
	0.177 (<0.094-0.393)	0.600(0.135-1.285)	Wales, UK	Kasprzyk-Hordern et al. (2009)
	0.231 (<0.085-0.667)	0.420 (0.209-1.391)	Wales, UK	Kasprzyk-Hordern et al. (2009)
	0.091 (0.033-0.393)	0.141 (0.048-0.361)	Spain	Rosal et al. (2010a)
	2.2		Germany (49 WWTPs)	Ternes (1998)
	0.14	2.2	Finland	Vieno et al. (2005)
		14.9 (1.9–29.8)	Spain	Radjenović et al. (2009)
Clofibrate	<loq		4 countries (6 WWTPs)	Andreozzi et al. (2003)
	0.8		Greece	Andreozzi et al. (2003)

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	<0.10		Germany (20 WWTPs)	Ternes (1998)
Clofibric acid	0.68		Italy	Andreozzi et al. (2003)
2.69 (0-84.07)	0.23		Italy	Andreozzi et al. (2003)
	0.46		Sweden	Andreozzi et al. (2003)
	<lod		3 Countries (4 WWTPs)	Andreozzi et al. (2003)
	<loq		Sweden	Bendz et al. (2005)
	0.006(<0.001-0.048)	0.001 (<0.001–0.012)	Wales, UK	Kasprzyk-Hordern et al. (2009)
	0.015 (<0.001-0.075)	0.019 (<0.001–0.057)	Wales, UK	Kasprzyk-Hordern et al. (2009)
	0.078	0.49	England, UK	Roberts and Thomas (2006)
	0.012 (<loq-0.0542)	0.026 (<loq-0.127)	Spain	Rosal et al. (2010a)
	0.15-0.27	0.17-0.37	Switzerland	Tauxe-Wuersch et al. (2005)
	0.36		Germany	Ternes (1998)
	0.12	0.05	Germany	Ternes et al. (2003)
	0.024		Sweden	Zorita et al. (2009)
Fenofibrate	0.12		France	Andreozzi et al. (2003)
0.66 (0-3.54)	0.02		France	Andreozzi et al. (2003)
	0.16		Italy	Andreozzi et al. (2003)
	0.1		Italy	Andreozzi et al. (2003)
	0.16		Italy	Andreozzi et al. (2003)
	0.16		Greece	Andreozzi et al. (2003)
	<lod		Sweden	Andreozzi et al. (2003)
	<loq-0.03		Germany	Ternes (1998)
Fenofibric acid	4.7(<loq-80)		Spain	Muñoz et al. (2009)
	17(<loq-200)		Spain	Muñoz et al. (2009)
	0.0013 (<loq-0.078)	0.079 (<loq-0.12)	Spain	Rosal et al. (2010a)
	0.38		Germany	Ternes (1998)
	0.13		Germany	Ternes et al. (2003)
Gemfibrozil	1.34		France	Andreozzi et al. (2003)
31.68 (0-546.56)	0.06		France	Andreozzi et al. (2003)
	0.81		Italy	Andreozzi et al. (2003)
	0.84		Italy	Andreozzi et al. (2003)
	4.76		Italy	Andreozzi et al. (2003)
	0.71		Greece	Andreozzi et al. (2003)
	2.07		Sweden	Andreozzi et al. (2003)
	0.18	0.71	Sweden	Bendz et al. (2005)
	1 (0.0029-5.2)		Spain	Muñoz et al. (2009)
	6.8 (0.089-36)		Spain	Muñoz et al. (2009)
	0.06-0.84	0.6-1.1	5 countries	Paxéus (2004)
	0.845 (0.003-5.233)	3.525 (0.415-17.055)	Spain	Rosal et al., 2010;
	0.4		Germany	Ternes (1998)
		3.08 (2.0-5.9)	Spain	Radjenović et al. (2009)
Pravastatin	<0.006	<0.006	Wales, UK	Kasprzyk-Hordern et al. (2009)
35.73 (3.11-194.95)	<0.006	<0.006	Wales, UK	Kasprzyk-Hordern et al. (2009)
Proton-pump inhibitors				
Omeprazole	0.334 (<loq-0.922)	0.365 (0.057-2.134)	Spain	Rosal et al. (2010a)
55.02 (0-135.21)				
Psychiatric drugs				
Amitriptyline	0.197 (<0.002-0.357)	1.249 (0.341-5.143)	Wales, UK	Kasprzyk-Hordern et al. (2009)
67.02 (0-2963.06)	0.085 (<0.002-0.335)	2.092 (0.504-6.711)	Wales, UK	Kasprzyk-Hordern et al. (2009)
Carbamazepine	0.98		France	Andreozzi et al. (2003)
2.95 (0-528.22)	1.2		France	Andreozzi et al. (2003)
	0.30		Italy	Andreozzi et al. (2003)
	0.34		Italy	Andreozzi et al. (2003)
	0.50		Italy	Andreozzi et al. (2003)
	1.03		Greece	Andreozzi et al. (2003)
	0.87		Sweden	Andreozzi et al. (2003)
	1.18	1.68	Sweden	Bendz et al. (2005)
	0.465-1.594	0.32-0.7	Austria (5 WWTPs)	Clara et al. (2005ab)
	0.326-1.518		France	Coetsier et al. (2009)
	0.13 (0.11-0.23)	0.35 (0.3-0.5)	Spain	Gómez et al. (2007)
	0.826 (0.152-2.3249	0.950 (0.104-3.110)	Wales, UK	Kasprzyk-Hordern et al. (2009)
	2.499 (0.644-4.596)	1.694 (0.709-2.930)	Wales, UK	Kasprzyk-Hordern et al. (2009)
	0.110 (0.140-0.260)		Spain	Muñoz et al. (2009)
	0.210 (<loq-1.600)		Spain	Muñoz et al. (2009)
	0.1-1.2	1.3-2	5 countries	Paxéus (2004)
	17.8	19.5	England, UK	Reif et al. (2008)
	0.069 (0.117-0.173)	0.129 (0.106-0.173)	Spain	Rosal et al., 2010;
	0.29 (<lod-0.55)	0.28 (0.12-0.94)	Spain	Santos et al. (2007)
	0.50 (0.12-1.29)	0.30 (<lod-1.38)	Spain	Santos et al. (2007)

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	0.37 (0.15-0.47)	0.29 (<lod–1.31)	Spain	Santos et al. (2007)
	0.32 (<lod-0.70)	0.36(<lod-2.15)	Spain	Santos et al. (2007)
	0.58 (<lod-1.18)	0.53 (<lod-3.78)	Spain	Santos et al. (2009)
	0.61 (0.15-1.29)	0.47 (<lod-2.10)	Spain	Santos et al. (2009)
	0.49 (<lod-0.84)	0.41 (<lod-1.31)	Spain	Santos et al. (2009)
	0.56 (0.15-1.55)	0.49 (<lod-2.15)	Spain	Santos et al. (2009)
	2.1		Germany (30 WWTPs)	Ternes (1998)
	2.1		Germany	Ternes et al. (2003)
	0.74	1	Germany	Wick et al. (2009)
		0.156 (0.054-0.22)	Spain	Radjenović et al. (2009)
Diazepam	<loq	23	Austria (5 WWTPs)	Clara et al. (2005ab)
882.86 (0-1114.91)	17		England, UK	Reif et al. (2008)
	19.3	21	Spain	Suárez et al. (2005)
	<0.03-0.04		Germany (20 WWTPs)	Ternes (1998)
	<0.010		Germany	Wick et al. (2009)
Fluoxetine	0.270 (0.016-2.000)		Spain	Muñoz et al. (2009)
0.45 (0-796.93)	0.077 (<loq-0.920)		Spain	Muñoz et al. (2009)
	0.223 (0.034-0.929)	0.585 (<loq-1.827)	Spain	Rosal et al. (2010a)
	<loq	0.011	Sweden	Zorita et al. (2009)
		0.573 (0.12–2.3)	Spain	Radjenović et al. (2009)
Gabapentin	2.952 (1.786-3.514)	17.925 (10.674–25.079)	Wales, UK	Kasprzyk-Hordern et al. (2009)
444.62 (18.52-1761.97)	15.747 (3.001-42.611)	15.034 (2.059-37.426)	Wales, UK	Kasprzyk-Hordern et al. (2009)
Lorazepam	0.031-0196		France	Coetsier et al. (2009)
Norfluoxetine	0.006	0.011	Sweden	Zorita et al. (2009)
0.23				
Oxcarbazepine		0.011-0.046	Italy	Conti et al. (2011)
0.98 (0.14-7.18)				
Receptor antagonists				
Cimetidine	2.605 (0.828-0.938)	3.452 (0.733-13.057)	Wales, UK	Kasprzyk-Hordern et al. (2009)
6.37 (0-12631.16)	0.462 (0.253-0.781)	2.219 (0.680-6.509)	Wales, UK	Kasprzyk-Hordern et al. (2009)
Loratadine		0.028 (0.015-0.043)	Spain	Radjenović et al. (2009)
1.18 (0.27-5.04)				
Ranitidine	0.224 (<0.09-0.455)	1.733 (<10–11.664)	Wales, UK	Kasprzyk-Hordern et al. (2009)
11.51 (0-1182.52)	0.462 (0.253-0.781)	5.060 (2.005-11.153)	Wales, UK	Kasprzyk-Hordern et al. (2009)
	0.360-0.942	0.524 (<loq-1.466)	Spain	Rosal et al. (2010a)
		0.347 (0.072–0.54)	Spain	Radjenović et al. (2009)
Valsartan	0.275 (0.006-0.711)	1.734 (0.354-5.388)	Wales, UK	Kasprzyk-Hordern et al. (2009)
38.74 (0-2657.70)	0.192 (<0.005-0.710)	0.342 (0.132-1.660)	Wales, UK	Kasprzyk-Hordern et al. (2009)
Hormones				
Estradiol	<0.001	0.012-0.02	Germany	Andersen et al. (2003)
0.73 (0-40.22)	0.00035-0.0035	0.008-0.016	Italy (6WWTPs)	Baronti et al. (2000)
	<0.001		Spain	Carballa et al. (2004)
	<lod-0.018	0.035-0.067	Austria (5 WWTPs)	Clara et al. (2005a)
	0.0025	0.003	Sweden	Zorita et al. (2009)
Estriol	0.00044-0.0084	0.05-0.12	Italy (6WWTPs)	Baronti et al. (2000)
4.37 (0-36.73)	<lod-0.275	0.023-0.326	Austria (5 WWTPs)	Clara et al. (2005a)
Estrone	0.0005	0.05-0.07	Germany	Andersen et al. (2003)
1.14 (0-27.65)	0.0025-0.0821	0.03-0.07	Italy (6 WWTPs)	Baronti et al. (2000)
	<0.0001-0.0044	0.002	Spain	Carballa et al. (2004)
	<lod-0.071	0.034-0.071	Austria (5 WWTPs)	Clara et al. (2005a)
	0.07	0.014	Sweden	Zorita et al. (2009)
E**thinylestradiol**	<0.0003-0.0017	0.002-0.004	Italy (6WWTPs)	Baronti et al. (2000)
0.26 (0-6.88)	<lod-0.106	0.004-0.02	Austria (5 WWTPs)	Clara et al. (2005a)
	<loq	<loq	Sweden	Zorita et al., 2009
Beta-antagonists				
Clenbuterol	<0.05-0.08		Germany (29 WWTPs)	Ternes (1998)
Fenoterol	<0.05-0.06		Germany (29 WWTPs)	Ternes (1998)
Salbutamol	0.001 (<0.001-0.022)	0.089 (0.050-0.150)	Wales, UK	Kasprzyk-Hordern et al. (2009)
1.99 (0-13.77)	0.063 (<0.001-0.234)	0.1 (<0.002-0.321)	Wales, UK	Kasprzyk-Hordern et al. (2009)
			Germany (29 WWTPs)	Ternes (1998)
Terbutaline	<0.05-0.12		Germany (29 WWTPs)	Ternes (1998)
Antineoplastics				
Cyclophosphamide	<0.010-0.02		Germany (16 WWTPs)	Ternes (1998)
Ifosfamide	<0.0038		France	Coetsier et al. (2009)
	<0.010-2.9		Germany (16 WWTPs)	Ternes (1998)
Tamoxifen	<0.0058-0.102		France	Coetsier et al. (2009)
	0.6		England, UK	Roberts and Thomas (2006)

PC / Estimated concentration in biosolids (median and 95% confidence interval) (µg /kg dry matter)	WWTP effluent concentration (µg/l)	WWTP influent concentration (µg/l)	WWTP Location	References
Antiseptic				
Triclosan 22.40 (0-234.78)	0.2 (0.08-0.40) 0.340 (0.052-2.500) 0.310 (0.024-1.100) 0.09-0.58 0.219 (<loq-0.512) <loq	1.8 (0.39-4.2) 0.4-2.2 0.860 (<loq-2.417)	Spain Spain Spain 5 countries Spain France (6 WWTPs)	Gómez et al. (2007) Muñoz et al. (2009) Muñoz et al. (2009) Paxéus (2004) Rosal et al. (2010a) Ruel et al. (2010)
Contrast agent				
Iopromide 77.95 (0-307.57)	<loq-9.3 <loq-5.06	6.6 0.3-3.84	Spain Austria (5 WWTPs)	Carballa et al. (2009) Clara et al. (2005b)

Table 18: Experimental log K_{OC} values, biodegradation half-lives in freshwater and soil, hydrolysis half-lives in freshwater, direct photolysis quantum yields and biomolecular hydroxyl radical rate constants in water.

PC	Exp log K_{OC} ($L^{-1}kg$)	$t_{b1/2}$ freshwater (days)	$t_{b1/2}$ soils (days)	$t_{h1/2}$ freshwater (days)	Φ	Molar absorption coefficients (UV/VIS)	$k_{OH,\ water}$ $M^{-1}s^{-1}$
Analgesics/anti-inflammatories							
Acetylsalicylic acid				6.3 (pH=7.4) (OECD 1981)			
Diclofenac			4.8; 29.6 (Xu et al. 2009b; Lin and Gan 2011)		9.40×10^{-2}; 1.30×10^{-1} (Werner et al. 2005)	Werne et al. (2005)	
Ibuprofen	2.01 ± 0.14 (Xu et al. 2009b)	18.7; 20 (Yamamoto et al. 2009)	10.4; 49.9 (Xu et al. 2009b; Lin and Gan 2011)		1.92×10^{-1} (Yuan et al. 2009)	Yuan et al. (2009)	7.4×10^{-9}; 1.0×10^{10} (Huber et al. 2003; Das et al. 2010)
Mefenamic acid					1.5×10^{-4} Werner et al (2005)	Werner et al (2005)	
Naproxen					3.6×10^{-2} (Packer et al. 2003)	Packer et al. (2003)	7.99×10^{9}; 9.6×10^{9} (Packer et al. 2003; Abdelmelek et al. 2011)
Phenazone	2.36 (Barron et al. 2009)				6.32×10^{-2} Yuan et al. (2009)	Yuan et al. (2009)	6.28×10^{9} (Yuan et al. 2009)
Tramadol		4.56×10^{-3} (Rua-Gomez and Puttmann 2013)					$t_{1/2\ indirect\ photolysis}$ = 5h (Rua-Gomez and Puttman, 2013)
Antibiotics					Antibiotics		
Clarithromycin					5.80×10^{-5} (Vione et al. 2009)	Vione et al. (2009)	
Ofloxacin							7.66×10^{9} (Abdelmelek et al. 2011)
Sulfamethoxazole					4.29×10^{-3} ; 2.97×10^{-2} (Andreozzi et al. 2003; Baeza and Knappe 2011)	Baeza and Knappe (2011)	3.7×10^{9}; 8.5×10^{9} (Lam and Mabury 2005; Abdelmelek et al. 2011)

PC	Exp log K_{OC} ($L \cdot kg^{-1}$)	$t_{b1/2}$ freshwater (days)	$t_{b1/2}$ soils (days)	$t_{h1/2}$ freshwater (days)	Φ	Molar absorption coefficients (UV/VIS)	$k_{OH, water}$ $M^{-1}s^{-1}$
Sulfapyridine							3.7×10^{9} (Boreen et al. 2004)
Trimethoprim					1.18×10^{-3} (Baeza and Knappe 2011)	Luo et al. (2012)	8.34×10^{9}; 8.92×10^{9} (Abdelmelek et al. 2011, Luo et al. 2012)
Antifungals							
Clotrimazole				200 OSPAR (2005)		$t_{1/2\ \text{direct photolysis}}$ = 3 - 310 (OSPAR (2005)	
Antihypertensives							
Hydrochlorothiazide					5.10×10-2 (Ulvi 1998)	Ulvi (1998)	$5.7 \pm 0.3 \times10^{9}$ (Real et al. 2010)
β-blockers							
Acebutolol							4.6×10^{9} (Benne et al. 2008)
Atenolol		14.2; 120.8 (Yamamoto et al. 2009)			-		$7.05 \pm 0.27 \times 10^{9}$ (Song et al. 2008)
Metoprolol		1.45; 7.08 (Liu et al. 2009)					$8.39\pm 0.06 \times10^{9}$ (Abdelmelek et al. 2011)
Propranolol		0.25; 0.96 (Liu et al. 2009)			2.22×10^{-3} (Andreozzi et al. 2003)	Liu and Williams (2007)	$1.07\pm 0.02 \times10^{10}$ (Song et al. 2008)
Diuretics							
Bezafibrate							$7.4 \pm 1.2 \times10^{9}$ (Huber et al. 2003)
Lipid regulators							
Clofibric acid					2.0×10^{-3}; 2.22×10^{-3} (Andreozzi et al. 2003; Packer et al. 2003)	Packer et al. (2003)	4.7×10^{9}; 6.98×10^{9} (Packer et al. 2003; Razavi et al. 2009)
Fenofibrate							$2.56 \pm 0.6 \times10^{9}$ (Kladna et al. 2006)
Gemfibrozil							1.0×10^{10} Abdemelek et al. (2011)
Psychiatric drugs							
Carbamazepine	2.95; 3.10 (Williams et al. 2006)	125; 233.3 (Yamamoto et al. 2009)	Recalcitrant (Monteiro and Boxall 2009)		4.77×10^{-5}; 1.3×10^{-4} (Andreozzi et al. 2003; Lam and Mabury 2005)	Doll and Frimmel (2003)	3.07×10^{9}; 9.4×10^{9} (Vogna et al. 2004; Lam and Mabury 2005)
Diazepam	2.40; 2.80 (Barron et al. 2009)	Recalcitrant (Suarez et al. 2010)			4.30×10^{-6} (Calisto et al. 2011)	Calisto et al. (2011)	$7.2 \pm 1.0 \times10^{9}$ (Huber et al. 2003)

PC	Exp log K_{OC} ($L \cdot kg^{-1}$)	$t_{b1/2}$ freshwater (days)	$t_{b1/2}$ soils (days)	$t_{h1/2}$ freshwater (days)	Φ	Molar absorption coefficients (UV/VIS)	$k_{OH, water}$ $M^{-1}s^{-1}$
Fluoxetine							8.89×10^{9}; 9.6×10^{9} (Lam et al. 2004)
Lorazepam					7.80×10^{-5} Calisto et al. (2011)	Calisto et al. (2011)	
Receptor antagonists							
Cimetidine							$1.5 \pm 0.2 \times10^{10}$ (Latch et al. 2003)
Hormones							
Estradiol							1.41×10^{10} (Rosenfeldt and Linden 2004)
Estriol						Lin and Reinhard (2005)	
Estrone							2.6×10^{10} Nakonechny et al. 2008)
Ethinylestradiol							9.8×10^{9} (Huber et al. 2003)
Antineoplastics							
Tamoxifen						DellaGreca et al. (2007)	
Antiseptic					Antiseptic		
Triclosan					0.31 (Tixier et al. 2002)	Tixier et al. (2002)	5.4×10^{9} (Latch et al. 2005)
Contrast agent							
Iopromide							$3.34 \pm 0.14 \times10^{9}$ (Jeong et al. 2010)

Table 19: Ecotoxicity data for PCs under study

PC	Species / endpoint	Toxicity (mg/L)	References
Analgesics/anti-inflammatories			
5-aminosalicylic acid	Algae / acute EC50 ECOSAR	63.75	Nabholz and Mayo-Bean (2009)
	Invertebrate/ acute EC50 ECOSAR	12.88	Nabholz and Mayo-Bean (2009)
	Fish: *P. oregonensis* / acute LC50 *O. kisutch* / acute LC50 *O. tshawytscha* / acute LC50	 10 10 10	 (USEPA 2007) USEPA (2007) USEPA (2007)
Acetaminophen	Algae *P. subcapitata* / acute EC50 (growth inhibition)	 134	 Henschel et al. (1997)
	Invertebrate *D. magna* / acute EC50 (immobilization) *D. magna* / acute EC50 (immobilization)	 9.2 50	 USEPA (2007) Henschel et al. (1997)
	Fish *P. promelas* / acute LC50 *S. proboscideu* / acute LC50 *B. rerio* / acute LC50	 814 29.6 378	 USEPA (2007) Stuer-Lauridsen et al. (2000) Henschel et al. (1997)
Acetylsalicylic acid	Algae *D. subspicatus* / acute EC50 (growth inhibition)	 106.7	 Cleuvers (2004)
	Invertebrate *D. magna* / acute EC50 (immobilization)	 88.1	 Cleuvers (2004)
	Fish / acute LC50 ECOSAR	771	Nabholz and Mayo-Bean (2009)

PC	Species / endpoint	Toxicity (mg/L)	References
Aminopyrine	Algae / chronic EC50 ECOSAR	1.3	Nabholz and Mayo-Bean (2009)
	Crustacean / chronic EC50 ECOSAR	8.3	(Nabholz and Mayo-Bean 2009)
	Fish / chronic LC50 ECOSAR	3.7	Nabholz and Mayo-Bean (2009)
Codeine	Algae / chronic EC50 ECOSAR	23	Nabholz and Mayo-Bean (2009)
	Crustacean / chronic EC50 ECOSAR	16	Nabholz and Mayo-Bean (2009)
	Fish / chronic LC50 ECOSAR	238	Nabholz and Mayo-Bean (2009)
Dextropropoxyphene	Algae / chronic EC50 ECOSAR	1	Nabholz and Mayo-Bean (2009)
	Crustacean / chronic EC50 ECOSAR	24	Nabholz and Mayo-Bean (2009)
	Fish / chronic LC50 ECOSAR	13	Nabholz and Mayo-Bean (2009)
Diclofenac	Algae		
	P. subcapitata / acute EC50 (growth inhibition)	16	Cleuvers (2004)
	D. subspicatus / acute EC50 (growth inhibition)	71.9	Ferrari et al. (2004)
	C. meneghiniana / acute EC50 (growth inhibition)	19	Ferrari et al. (2004)
	S. leopoliensis / acute EC50 (growth inhibition)	14.5	Ferrari et al. (2004)
	Invertebrate		
	D. magna / acute EC50 (immobilization)	80	Cleuvers (2004)
	D. magna / acute EC50 (immobilization)	68	Han et al. (2006)
	D. magna / acute EC50 (immobilization)	22	Ferrari et al. (2004)
	C. dubia / acute EC50 (immobilization)	23	Ferrari et al. (2004)
	T. platyurus/ acute EC50 (immobilization)	41	Nalecz-Jawecki and Persoone (2006)
	Fish		
	D. rerio / acute LC50 (fish embryo)	2	van den Brandhof and Montforts (2010)
Dipyrone	Algae / chronic EC50 ECOSAR	139	Nabholz and Mayo-Bean (2009)
	Crustacean / chronic EC50 ECOSAR	34330	Nabholz and Mayo-Bean (2009)
	Fish / chronic LC50 ECOSAR	3261	Nabholz and Mayo-Bean (2009)
Fenoprofen	Algae / chronic EC50 ECOSAR	16.8	Nabholz and Mayo-Bean (2009)
	Crustacean / chronic EC50 ECOSAR	4.6	Nabholz and Mayo-Bean (2009)
	Fish / chronic LC50 ECOSAR	4.7	Nabholz and Mayo-Bean (2009)
Ibuprofen	Algae		
	S. subspicatus / acute EC50 (growth inhibition)	342.2	Cleuvers (2004)
	S. Costatum / acute EC50 (growth inhibition)	7.1	Han et al. (2010)
	L. minor / acute EC50 (growth inhibition)	4	Grung et al. (2008)
	L. minor / acute EC50 (growth inhibition)	22	Cleuvers (2004)
	Invertebrate		
	D. magna / acute EC50 (immobilization)	132.6	Han et al. (2006)
	D. magna / acute EC50 (immobilization)	51.44	Han et al. (2010)
	D. magna / acute EC50 (immobilization)	55.6	Han et al. (2010)
	M. macropora / acute EC50 (immobilization)	72.6	Han et al. (2010)
	P. carinatus / acute LC50	17.08	Han et al. (2010)
	H. attenuata / acute LC50	22.3	USEPA (2007)
	Fish		
	O. latipes / acute LC50	89	Yamamoto et al. (2007)
	L. macrochirus / acute LC50	173	Webb (2004)
Indomethacin	Algae / chronic EC50 ECOSAR	18	Nabholz and Mayo-Bean (2009)
	Crustacean / chronic EC50 ECOSAR	26	Nabholz and Mayo-Bean (2009)
	Fish / chronic LC50 ECOSAR	23.9	Nabholz and Mayo-Bean (2009)
Ketoprofen	Algae / chronic EC50 ECOSAR	164	Nabholz and Mayo-Bean (2009)
	Crustacean / chronic EC50 ECOSAR	168.9	Nabholz and Mayo-Bean (2009)
	Fish / chronic LC50 ECOSAR	258.3	Nabholz and Mayo-Bean (2009)
Ketorolac	Algae / chronic EC50 ECOSAR	12.000	Nabholz and Mayo-Bean (2009)
	Crustacean / chronic EC50 ECOSAR	1.561	Nabholz and Mayo-Bean (2009)
	Fish / chronic LC50 ECOSAR	1.345	Nabholz and Mayo-Bean (2009)
Mefenamic acid	Algae		
	D. subspicatus / acute EC50 (growth inhibition)	5.4	Suzuki et al. (2009)
	Crustaceans		
	T. platyurus/ acute EC50 (immobilization)	3.85	Kim et al. (2009b)
	Fish		
	O. Latipes / acute LC50	8.04	Kim et al. (2009b)
	Frog embryo / acute LC50	5.2	Suzuki et al.(2009)
Naproxen	Algae		
	D. subspicatus / acute EC50 (growth inhibition)	625.4	Cleuvers (2004)
	Invertebrate		
	D. magna / acute EC50 (immobilization)	166.3	Cleuvers (2004)
	Fish / acute LC50 ECOSAR	195.5	Nabholz and Mayo-Bean (2009)
Phenazone	Algae / acute EC50 (growth inhibition)	>1000	MEJ (2011)
	Invertebrate		
	D. magna / acute EC50 (immobilization)	>1000	MEJ (2011)
	Fish		
	O. kisutch / acute LC50	10	USEPA (2007)
	O. tshawytscha / acute LC50	10	USEPA (2007)

PC	Species / endpoint	Toxicity (mg/L)	References
	P. oregonensis / acute LC50	10	USEPA (2007)
Propyphenazone	Algae / chronic EC50 ECOSAR	1	Nabholz and Mayo-Bean (2009)
	Crustacean / chronic EC50 ECOSAR	3.5	Nabholz and Mayo-Bean (2009)
	Fish / chronic LC50 ECOSAR	0.8	Nabholz and Mayo-Bean (2009)
Salicylic acid	Algae		
	P. subcapitata / acute EC50 (growth inhibition)	1060	USEPA (2007)
	P. subcapitata / acute EC50 (growth inhibition)	870	USEPA (2007)
	Invertebrate		
	D. magna / acute LC50	111	USEPA (2007)
	Fish		
	L. idus / acute LC50	90	USEPA (2007)
Tramadol	Algae		
	L. variegates / chronic NOEC (growth inhibition)	0.8	Jagodzinski et al. (2009)
	Invertebrate		
	D. magna / acute EC50 (immobilization)	73	Montforts (2005)
	Fish / acute LC50	130	Montforts (2005)
Antibiotics			
Azithromycin	Algae / chronic EC50 ECOSAR	0.554	Nabholz and Mayo-Bean (2009)
	Crustacean / chronic EC50 ECOSAR	0.064	Nabholz and Mayo-Bean (2009)
	Fish / chronic LC50 ECOSAR	0.450	Nabholz and Mayo-Bean (2009)
Chloramphenicol	Algae		
	S. intermedius / acute EC50 (growth inhibition)	100	USEPA (2007)
	Invertebrate		
	D. magna / acute EC50 (immobilization)	1085	USEPA (2007)
	Fish		
	A. japonica / acute LC50	1828	USEPA (2007)
Ciprofloxacin	Algae		
	P. subcapitata / acute EC50 (growth inhibition)	2.97	Grung et al. (2008)
	P. subcapitata / acute EC50 (growth inhibition)	18.7	Grung et al. (2008)
	M. aeruginosa / acute EC50 (growth inhibition)	0.005	Grung et al. (2008)
	M. aeruginosa / acute EC50 (growth inhibition)	0.017	Grung et al. (2008)
	L. minor / acute EC50 (growth inhibition)	0.203	Grung et al. (2008)
	Invertebrate/ acute EC50 ECOSAR	620.7	Nabholz and Mayo-Bean (2009)
	Fish / acute LC50 ECOSAR	9303.9	Nabholz and Mayo-Bean (2009)
Clarithromycin	Algae		
	P. subcapitata / acute EC50 (growth inhibition)	0.09	Huschek et al. (2004)
	Invertebrate		
	D. magna / acute EC50 (immobilization)	25.7	Isidori et al. (2005)
	C. dubia / acute EC50 (immobilization)	18.7	Isidori et al. (2005)
	Fish		
	D. rerio / acute LC50	280	Hernando et al. (2007)
Enoxacin	Algae / chronic EC50 ECOSAR	114.6	Nabholz and Mayo-Bean (2009)
	Crustacean / chronic EC50 ECOSAR	80.5	Nabholz and Mayo-Bean (2009)
	Fish / chronic LC50 ECOSAR	171.8	Nabholz and Mayo-Bean (2009)
Erythromycin	Algae		
	C. vulgaris / acute LC50	12.0	USEPA (2007)
	Invertebrate		
	D. magna / acute EC50 (immobilization)	22.45	USEPA (2007)
	T. platyurus / acute LC50	17.68	USEPA (2007)
	V. vannamei / acute LC50	30.8	USEPA (2007)
	C. dubia / acute EC50 (immobilization)	10.23	USEPA (2007)
	B. calyciflorus / acute LC50	27.53	USEPA (2007)
	Fish		
	M. saxatilis / acute LC50	349	
Lomefloxacin	Algae / acute EC50 ECOSAR	63.3	Nabholz and Mayo-Bean (2009)
	Invertebrate		
	D. magna / acute EC50 (immobilization)	130	Montforts (2005)
	Fish / acute LC50 ECOSAR	96.0	Nabholz and Mayo-Bean (2009)
Metronidazole	Algae		
	P. subcapitata / acute EC50 (growth inhibition)	39.1	USEPA (2007)
	P. subcapitata / acute EC50 (growth inhibition)	40.4	USEPA (2007)
	C. spirulina / acute EC50 (growth inhibition)	12.5	USEPA (2007)
	C. spirulina / acute EC50 (growth inhibition)	38.8	USEPA (2007)
	C. spirulina / acute EC50 (growth inhibition)	40.4	USEPA (2007)
	Invertebrate		
	A. bahia / acute EC50 (immobilization)	182	USEPA (2007)
	Fish		
	C. variagatus / acute LC50	>1060	USEPA (2007)
Norfloxacin	Algae / chronic EC50 ECOSAR	112.7	Nabholz and Mayo-Bean (2009)
	Crustacean / chronic EC50 ECOSAR	0.636	Nabholz and Mayo-Bean (2009)
	Fish / chronic LC50 ECOSAR	193.9	Nabholz and Mayo-Bean (2009)

PC	Species / endpoint	Toxicity (mg/L)	References
Ofloxacin	Algae / acute EC50 ECOSAR	1.44	Nabholz and Mayo-Bean (2009)
	Invertebrate		
	D. magna / acute EC50 (immobilization)	31.75	Isidori et al. (2005)
	C. dubia / acute EC50 (immobilization)	14.4	USEPA (2007)
	Fish		
	P. promelas / acute NOEC	10	USEPA (2007)
Roxithromycin	Algae / acute EC50 ECOSAR	42.4	Nabholz and Mayo-Bean (2009)
	Invertebrate		
	D. magna / acute EC50 (immobilization)	7.1	Choi et al. (2008)
	M. macropora / acute EC50 (immobilization)	39.3	Choi et al. (2008)
	Fish		
	O. Latipes / acute LC50	288	Choi et al. (2008)
Sulfamethoxazole	Algae		
	P. subcapitata / acute EC50 (growth inhibition)	0.57	Isidori et al. (2005)
	P. subcapitata / acute EC50 (growth inhibition)	0.146	Ferrari et al. (2004)
	S. leopoliensis / acute EC50 (growth inhibition)	0.027	Ferrari et al. (2004)
	C. meneghiniana/ acute EC50 (growth inhibition)	2.4	Ferrari et al. (2004)
	Invertebrate		
	D. magna / acute EC50 (immobilization)	25	Isidori et al. (2005)
	D. magna / acute EC50 (immobilization)	123.1	USEPA (2007)
	C. dubia / acute EC50 (immobilization)	15.5	Isidori et al. (2005)
	B. calyciflorus / acute LC50	26	Isidori et al. (2005)
	T. platyurus / acute EC50 (immobilization)	35.4	USEPA (2007)
	S. capricornutum / acute EC50 (immobilization)	110	Langdon et al. (2010)
	M. macropora / acute EC50 (immobilization)	70.4	Park and Choi (2008)
	Fish		
	O. Latipes / acute LC50	562.5	USEPA (2007)
	D. rerio / acute LC50	1000	USEPA (2007)
Sulfapyridine	Algae / acute EC50 ECOSAR	114.6	Nabholz and Mayo-Bean (2009)
	Invertebrate		
	H. attenuata / acute LC50	100	USEPA (2007)
	Fish / acute LC50 ECOSAR	171.8	Nabholz and Mayo-Bean (2009)
Sulfasalazine	Algae / acute EC50 ECOSAR	10.25	Nabholz and Mayo-Bean (2009)
	Invertebrate		
	D. magna / acute EC50 (immobilization)	212	USEPA (2007)
	Algae / acute EC50 ECOSAR	5.12	Nabholz and Mayo-Bean (2009)
Trimethoprim	Algae		
	P. subcapitata / acute EC50 (growth inhibition)	110	Grung et al. (2008)
	M. aeruginosa / acute EC50 (growth inhibition)	112	Grung et al. (2008)
	R. salina / acute EC50 (growth inhibition)	16	Grung et al. (2008)
	Invertebrate		
	D. magna / acute EC50 (immobilization)	120.1	USEPA (2007)
	D. magna / acute EC50 (immobilization)	92	USEPA (2007)
	D. magna / acute EC50 (immobilization)	167.4	USEPA (2007)
	D. magna / acute EC50 (immobilization)	155.6	USEPA (2007)
	M. macropora / acute EC50 (immobilization)	144.8	USEPA (2007)
	M. macropora / acute EC50 (immobilization)	54	USEPA (2007)
	M. macropora / acute EC50 (immobilization)	8	USEPA (2007)
	Fish / acute LC50 ECOSAR	635	Nabholz and Mayo-Bean (2009)
Antifungals			
Clotrimazole	Algae		
	P. subcapitata / acute EC50 (growth inhibition)	0.098	OSPAR (2005)
	Invertebrate		
	D. magna / acute EC50 (immobilization)	0.02	OSPAR (2005)
	Fish		
	B. rerio / acute LC50	0.29	OSPAR (2005)
Antihypertensives			
Diltiazem	Algae / acute EC50 ECOSAR	1.2	Nabholz and Mayo-Bean (2009)
	Invertebrate		
	D. magna / acute EC50 (immobilization)	8.2	Kim et al. (2007)
	Fish / acute LC50 ECOSAR	23	Nabholz and Mayo-Bean (2009)
Hydrochlorothiazide	Algae		
	C. meneghiniana / acute EC50 (growth inhibition)	100	Fass (2011)
	Invertebrate		
	D. magna / acute EC50 (immobilization)	100	Fass (2011)
	Fish		
	B. rerio / acute LC50	100	Fass (2011)
β-blockers			
Acebutolol	Algae / chronic EC50 ECOSAR	0.562	Nabholz and Mayo-Bean (2009)
	Crustacean / chronic EC50 ECOSAR	0.048	Nabholz and Mayo-Bean (2009)
	Fish / chronic LC50 ECOSAR	1	Nabholz and Mayo-Bean (2009)

PC	Species / endpoint	Toxicity (mg/L)	References
Atenolol	Algae		
	P. subcapitata / acute EC50 (growth inhibition)	620	Cleuvers (2005)
	Invertebrate		
	D. magna / acute EC50 (immobilization)	313	Cleuvers (2005)
	Fish		
	O. latipes / acute LC50	>100	USEPA (2007)
Betaxolol	Algae / acute EC50 ECOSAR	0.99	Nabholz and Mayo-Bean (2009)
	Invertebrate		
	D. magna / acute EC50 (immobilization)	300	Hernando et al. (2004)
	Fish / acute LC50 ECOSAR	13.86	Nabholz and Mayo-Bean (2009)
Bisoprolol	Algae		
	D. subspicatus / acute EC50 (growth inhibition)	11.5	Fass (2011)
	Invertebrate		
	D. magna / acute EC50 (immobilization)	100	Fass (2011)
	Fish		
	D. rerio / acute LC50	100	Fass (2011)
Carazolol	Algae / chronic EC50 ECOSAR	6	Nabholz and Mayo-Bean (2009)
	Crustacean / chronic EC50 ECOSAR	2.5	Nabholz and Mayo-Bean (2009)
	Fish / chronic LC50 ECOSAR	31	Nabholz and Mayo-Bean (2009)
Celiprolol	Algae / chronic EC50 ECOSAR	0.265	Nabholz and Mayo-Bean (2009)
	Crustacean / chronic EC50 ECOSAR	0.780	Nabholz and Mayo-Bean (2009)
	Fish / chronic LC50 ECOSAR	2.490	Nabholz and Mayo-Bean (2009)
Metoprolol	Algae		
	D. subspicatus / acute EC50 (growth inhibition)	7.9	Cleuvers (2005)
	Lemna / acute EC50 (growth inhibition)	320	Cleuvers (2005)
	Invertebrate		
	D. magna / acute EC50 (immobilization)	63.9	Grung et al. (2008)
	D. magna / acute EC50 (immobilization)	64	Grung et al. (2008)
	C. dubia / acute EC50 (immobilization)	77.5	Grung et al. (2008)
	T. platyurus / acute EC50 (immobilization)	8.8	Grung et al. (2008)
	Fish		
	D. rerio / acute LC50 (fish embryo)	31	van den Brandhof and Montforts (2010)
Nadolol	Algae / chronic EC50 ECOSAR	2.19	Nabholz and Mayo-Bean (2009)
	Crustacean / chronic EC50 ECOSAR	0.044	Nabholz and Mayo-Bean (2009)
	Fish / chronic LC50 ECOSAR	2.70	Nabholz and Mayo-Bean (2009)
Oxprenolol	Algae / chronic EC50 ECOSAR	0.913	Nabholz and Mayo-Bean (2009)
	Crustacean / chronic EC50 ECOSAR	0.033	Nabholz and Mayo-Bean (2009)
	Fish / chronic LC50 ECOSAR	1	Nabholz and Mayo-Bean (2009)
Propranolol	Algae		
	D. subspicatus / acute EC50 (growth inhibition)	0.7	Cleuvers (2005)
	Invertebrate		
	D. magna / acute EC50 (immobilization)	7.7	Cleuvers (2005)
	S. proboscideus / acute LC50	1.87	USEPA (2007)
	A. salina / acute LC50	407	USEPA (2007)
	B. calyciflorus / acute LC50	2.59	USEPA (2007)
	Fish		
	O. latipes / acute LC50	11.4	USEPA (2007)
Sotalol	Algae / chronic EC50 ECOSAR	21502	Nabholz and Mayo-Bean (2009)
	Crustacean / chronic EC50 ECOSAR	94024	Nabholz and Mayo-Bean (2009)
	Fish / chronic LC50 ECOSAR	779000	Nabholz and Mayo-Bean (2009)
Timolol	Algae / chronic EC50 ECOSAR	15.5	Nabholz and Mayo-Bean (2009)
	Crustacean / chronic EC50 ECOSAR	54	Nabholz and Mayo-Bean (2009)
	Fish / chronic LC50 ECOSAR	126	Nabholz and Mayo-Bean (2009)
Diuretics			
Bendroflumethiazide	Algae / chronic EC50 ECOSAR	0.704	Nabholz and Mayo-Bean (2009)
	Crustacean / chronic EC50 ECOSAR	23.17	Nabholz and Mayo-Bean (2009)
	Fish / chronic LC50 ECOSAR	0.443	Nabholz and Mayo-Bean (2009)
Furosemide	Algae		
	D. subspicatus / acute EC50 (growth inhibition)	45	Fass (2011)
	Invertebrate		
	D. magna / acute EC50 (immobilization)	100	Fass (2011)
	Fish		
	L. idus melanotus / acute LC50	500	Fass (2011)
Lipid regulators			
Bezafibrate	Algae / acute LC50 ECOSAR	1.87	Nabholz and Mayo-Bean (2009)
	Invertebrate		
	D. magna / acute EC50 (immobilization)	100.8	Isidori et al. (2007)
	D. magna / acute EC50 (immobilization)	30	Hernando et al. (2007)
	T. platyurus / acute EC50 (immobilization	39.7	Isidori et al. (2007)
	C. dubia / acute EC50 (immobilization)	75.8	Isidori et al. (2007)

PC	Species / endpoint	Toxicity (mg/L)	References
	B. calyciflorus / acute EC50 (immobilization)	60.9	Isidori et al. (2007)
	Fish / acute LC50 ECOSAR	7.69	Nabholz and Mayo-Bean (2009)
Clofibrate	Algae		
	S. subspicatus / acute EC50 (growth inhibition)	12.0	USEPA (2007)
	Invertebrate		
	D. magna / acute EC50 (immobilization)	28.2	USEPA (2007)
	A. parthenogenetica / acute LC50	36.6	USEPA (2007)
	Fish		
	G.holbrooki / acute LC50	7.7	USEPA (2007)
Clofibric acid	Algae		
	S. subspicatus / acute EC50 (growth inhibition)	89	Hernando et al. (2007)
	T. chuii / acute EC50 (growth inhibition)	318.2	USEPA (2007)
	Invertebrate		
	D. magna / acute EC50 (immobilization)	141	Hernando et al. (2007)
	A. parthenogenetica / acute LC50	87.2	USEPA (2007)
	Fish		
	G. holbrooki / acute LC50	526.5	USEPA (2007)
Fenofibrate	Algae		
	P. subcapitata / chronic EC50 (growth inhibition)	19.84	Isidori et al. (2007)
	Invertebrate		
	C. dubia / chronic EC50 (immobilization)	0.76	Isidori et al. (2007)
	B. calyciflorus / chronic EC50 (immobilization)	1.44	Isidori et al. (2007)
	Fish / chronic LC50 ECOSAR	0.031	Nabholz and Mayo-Bean (2009)
Fenofibric acid	Algae / acute EC50 ECOSAR	36.7	Nabholz and Mayo-Bean (2009)
	Invertebrate		
	D. magna / acute EC50 (immobilization)	4.9	Rosal et al. (2010b)
	Fish / acute LC50 ECOSAR	42.8	Nabholz and Mayo-Bean (2009)
Gemfibrozil	Algae		
	C. vulgaris / acute LC50	60	USEPA (2007)
	Invertebrate		
	D. magna / acute LC50	10.4	USEPA (2007)
	Fish		
	D. rerio / chronic NOEC	0.00038	USEPA (2007)
Pravastatin	Algae / chronic EC50 ECOSAR	31.316	Nabholz and Mayo-Bean (2009)
	Crustacean / chronic EC50 ECOSAR	119	Nabholz and Mayo-Bean (2009)
	Fish / chronic LC50 ECOSAR	7.226	Nabholz and Mayo-Bean (2009)
Proton-pump inhibitors			
Omeprazole	Algae / chronic EC50 ECOSAR	9.14	Nabholz and Mayo-Bean (2009)
	Invertebrate		
	D. magna / acute EC50 (immobilization)	88	Montforts (2005)
	Fish / chronic LC50 ECOSAR	5.033	Nabholz and Mayo-Bean (2009)
Psychiatric drugs			
Amitriptyline	Algae / chronic EC50 ECOSAR	0.021	Nabholz and Mayo-Bean (2009)
	Invertebrate		
	C. dubia / chronic EC50 (immobilization)	1	Fass (2011)
	M. bahia / chronic EC50 (immobilization)	3.2	Fass (2011)
	Fish		
	P. promelas / chronic LC50	0.32	Fass (2011)
	C. variegatus / chronic LC50	0.31	Fass (2011)
Carbamazepine	Algae		
	D. subspicatus / acute EC50 (growth inhibition)	74	Cleuvers (2003)
	C. meneghiniana / acute EC50 (growth inhibition)	85	Huschek et al. (2004)
	L. minor / acute EC50 (growth inhibition)	25.5	Cleuvers (2003)
	Invertebrate		
	D. magna / acute EC50 (immobilization)	76.3	Kim et al. (2007)
	H. azteca / acute EC50 (immobilization)	9.9	Dussault et al. (2008)
	H. attenuata / acute LC50	29.4	Quinn et al. (2008)
	Fish		
	O. latipes / acute LC50	35.4	Kim et al. (2007)
	D. rerio / acute LC50	86.5	Brandhof and Montforts (2010)
	Other		
	C. tentans / acute LC50	47.3	Dussault et al. (2008)
Diazepam	Algae		
	T. chuii acute EC50 (growth inhibition)	16.5	Nunes et al. (2005)
	Invertebrate		
	D. magna / acute EC50 (immobilization)	14.1	USEPA (2007)
	A. salina / acute LC50	71.6	USEPA (2007)
	A. parthenogenetica / acute EC50 (immob.)	12.2	Nunes et al. (2005)
	D. pulex / acute EC50 (immobilization)	11.96	USEPA (2007)
	S. proboscideu / acute LC50	69.5	USEPA (2007)
	B. calyciflorus / acute LC50	47.3	USEPA (2007)

PC	Species / endpoint	Toxicity (mg/L)	References
	Fish		
	O. mykiss / acute LC50	84	USEPA (2007)
	G. holbrooki / acute LC50	12.7	Nunes et al. (2005)
Fluoxetine	Algae / acute EC50	0.024	Sanderson and Thomsen (2009)
	Invertebrate		
	D. magna / acute EC50 (immobilization)	0.820	Brooks et al. (2003)
	Fish		
	P. promelas / chronic LC50	0.705	Brooks et al. (2003)
Gabapentin	Algae / chronic EC50 ECOSAR	1944	Nabholz and Mayo-Bean (2009)
	Crustacean / chronic EC50 ECOSAR	243	Nabholz and Mayo-Bean (2009)
	Fish / chronic LC50 ECOSAR	10121	Nabholz and Mayo-Bean (2009)
Lorazepam	Algae / chronic EC50 ECOSAR	0.54	Nabholz and Mayo-Bean (2009)
	Crustacean / chronic EC50 ECOSAR	6.72	Nabholz and Mayo-Bean (2009)
	Fish / chronic LC50 ECOSAR	0.12	Nabholz and Mayo-Bean (2009)
Norfluoxetine	Algae / acute EC50 ECOSAR	0.338	Nabholz and Mayo-Bean (2009)
	Crustacean / acute EC50 ECOSAR	0.36	Nabholz and Mayo-Bean (2009)
	Fish		
	O. latipes / acute LC50	5.5	Nakamura et al. (2008)
Oxcarbazepine	Algae / chronic EC50 ECOSAR	0.421	Nabholz and Mayo-Bean (2009)
	Crustacean / chronic EC50 ECOSAR	49.63	Nabholz and Mayo-Bean (2009)
	Fish / chronic LC50 ECOSAR	0.98	Nabholz and Mayo-Bean (2009)
Receptor antagonists			
Cimetidine	Algae / acute EC50 ECOSAR	306	Nabholz and Mayo-Bean (2009)
	Invertebrate		
	D. magna / acute EC50 (immobilization)	740	Sanderson and Thomsen (2009)
	Fish / acute LC50	>1000	Sanderson and Thomsen (2009)
Loratadine	Algae / chronic EC50 ECOSAR	0.29	Nabholz and Mayo-Bean (2009)
	Crustacean / chronic EC50 ECOSAR	0.006	Nabholz and Mayo-Bean (2009)
	Fish / chronic LC50 ECOSAR	0.007	Nabholz and Mayo-Bean (2009)
Ranitidine	Algae / chronic EC50 ECOSAR	66	Nabholz and Mayo-Bean (2009)
	Crustacean / chronic EC50 ECOSAR	63	Nabholz and Mayo-Bean (2009)
	Fish / chronic LC50 ECOSAR	1076	Nabholz and Mayo-Bean (2009)
Valsartan	Algae / acute EC50	90	FDA (2009)
	Invertebrate		
	D. magna / acute EC50 (immobilization)	580	FDA (2009)
	Fish		
	S. sairdeneri / acute LC50	>100	FDA (2009)
Hormones			
Estradiol	Algae / chronic EC50 ECOSAR	1.97	Nabholz and Mayo-Bean (2009)
	Invertebrate		
	D. magna / chronic LC50	0.648	USEPA (2007)
	T. battagliai / chronic LC50	1.6	USEPA (2007)
	Fish		
	L. cephalus / chronic EC50 (sex ratio)	10.3	USEPA (2007)
	D. rerio / chronic LOEC (sex ratio)	0.0000537	USEPA (2007)
	O. latipes / chronic LOEC (sex ratio)	0.0000279	USEPA (2007)
Estriol	Algae / chronic EC50 ECOSAR	7	Nabholz and Mayo-Bean (2009)
	Crustacean / chronic EC50 ECOSAR	0.995	Nabholz and Mayo-Bean (2009)
	Fish		
	D. rerio / chronic LOEC (sex ratio)	0.0217	USEPA (2007)
Estrone	Algae		
	P. subcapitata / chronic NOEC	0.452	USEPA (2007)
	Invertebrate		
	T. battagliai / chronic LC50	0.1	USEPA (2007)
	Fish		
	D. rerio / chronic LOEC (sex ratio)	0.0000355	USEPA (2007)
	O. javanicus / chronic LOEC (sex ratio)	0.003701	USEPA (2007)
Ethinylestradiol	Algae		
	S. subspicatus / chronic EC50 (growth inhibition)	0.84	USEPA (2007)
	Invertebrate		
	G. pulex / chronic LC50	0.8	USEPA (2007)
	Fish		
	D. rerio / chronic LOEC (sex ratio)	0.000116	USEPA (2007)
	P. promelas / chronic LOEC (sex ratio)	0.01	USEPA (2007)
Beta-antagonists			
Clenbuterol	Algae / chronic EC50 ECOSAR	10	Nabholz and Mayo-Bean (2009)
	Crustacean / chronic EC50 ECOSAR	2	Nabholz and Mayo-Bean (2009)
	Fish / chronic LC50 ECOSAR	30	Nabholz and Mayo-Bean (2009)
Fenoterol	Algae / chronic EC50 ECOSAR	25	Nabholz and Mayo-Bean (2009)
	Crustacean / chronic EC50 ECOSAR	17.5	Nabholz and Mayo-Bean (2009)

PC	Species / endpoint	Toxicity (mg/L)	References
	Fish / chronic LC50 ECOSAR	20	Nabholz and Mayo-Bean (2009)
Salbutamol	Algae / chronic EC50 ECOSAR	2.04	Nabholz and Mayo-Bean (2009)
	Crustacean / chronic EC50 ECOSAR	1.78	Nabholz and Mayo-Bean (2009)
	Fish / chronic LC50 ECOSAR	2.39	Nabholz and Mayo-Bean (2009)
Terbutaline	Algae / chronic EC50 ECOSAR	32	Nabholz and Mayo-Bean (2009)
	Crustacean / chronic EC50 ECOSAR	27	Nabholz and Mayo-Bean (2009)
	Fish / chronic LC50 ECOSAR	1.05	Nabholz and Mayo-Bean (2009)
Antineoplastics			
Cyclophosphamide	Algae / chronic EC50 ECOSAR	11	Nabholz and Mayo-Bean (2009)
	Crustacean / chronic EC50 ECOSAR	1795	Nabholz and Mayo-Bean (2009)
	Fish / chronic LC50 ECOSAR	70	Nabholz and Mayo-Bean (2009)
Ifosfamide	Algae / chronic EC50 ECOSAR	11	Nabholz and Mayo-Bean (2009)
	Crustacean / chronic EC50 ECOSAR	1795	Nabholz and Mayo-Bean (2009)
	Fish / chronic LC50 ECOSAR	140	Nabholz and Mayo-Bean (2009)
Tamoxifen	Algae / acute EC50 ECOSAR	0.006	Nabholz and Mayo-Bean (2009)
	Invertebrate *D. magna* / acute NOEC	 0.043	 Fass (2011)
	Fish *O. mykiss* / acute LC50 *L. macrochirus* / acute LC50	 0.32 0.23	 Fass (2011) Fass (2011)
Antiseptic			
Triclosan	Algae *A. flosaquae* / acute EC50 (growth inhibition)	 0.00097	 USEPA (2007)
	Invertebrate *C. dubia* / acute LC50 *D. magna* / acute LC50 *P. subcapitata* / acute LC50	 0.13 0.39 0.0007	 USEPA (2007) USEPA (2007) USEPA (2007)
	Fish *O. mykiss* / acute LC50 *L. macrochirus* / acute LC50 *O. latipes* / acute LC50 *P. promelas* / acute LC50	 0.288 0.370 0.352 0.250	 USEPA (2007) USEPA (2007) USEPA (2007) USEPA (2007)
Contrast agent			
Iopromide	Algae *D. subspicatus* / acute EC50 (growth inhibition)	 10000	 USEPA (2007)
	Invertebrate *D. magna* / acute EC50 (immobilization)	 1000	 USEPA (2007)
	Fish *L. idus* / acute LC50	 10000	 USEPA (2007)

Table 20: Probability distributions for the 10 regression error parameters (*a1-a10*), photodegradation rates, experimental K_{OC} values, experimental biodegradation rates in water and soil ($k_{biodeg,\ water}$ and $k_{biodeg,\ water}$), experimental bimolecular ˙OH rate constants in water ($k_{OH,\ water}$), and environmental parameters (rain rate, fraction of organic matter in agricultural soil, pH in freshwater and agricultural soil, and concentrations of dissolved organic carbon (DOC), suspended matter (SM), and ˙OH in freshwater) included in the Monte Carlo simulation. The relation of the calibration coefficients to the actual model parameter values is shown in the last column. S*Dev* denotes standard deviation, *exp* denotes experimental values, *CI* denotes confidence interval, and *DF* denotes degrees of freedom. Asterisks (*) denote base case parameter values

Parameter	Distribution	Mean	Spread	Relation to model parameters
a1	Uniformal	1	[0.5, 1.5]	$k_{biodeg,\ biosolids} = k_{biodeg,\ soil} \times a1^{-1}$
a2	Normal	-3.18×10^{-7}	*Sdev*=2.63×10^{-7}	$k_{biodeg,\ soil} = k_{biodeg,\ soil}^{*} \pm a2$
a3	Normal	1.26×10^{-7}	*Sdev*=4.25×10^{-8}	$k_{biodeg,\ water} = k_{biodeg,\ water}^{*} \pm a3$
a4	Normal	-3.15×10^{-4}	*Sdev*= 4.41×10^{-1}	$logK_{OW} = logK_{OW}^{*} \pm a4$ (KOWWIN v1.67a)
a5	Normal	-9.84×10^{-2}	*Sdev*= 5.48×10^{-1}	$logK_{OC} = logK_{OC}^{*} \pm a5$ (KOCWIN v2.0, neutrals)
a6	Normal	2.23×10^{-2}	*Sdev*= 5.36×10^{-1}	$logK_{OC} = logK_{OC}^{*} \pm a6$ (acids regression)
a7	Normal	4.45×10^{-2}	*Sdev*= 4.74×10^{-1}	$logK_{OC} = logK_{OC}^{*} \pm a7$ (bases regression)
a8	Normal	1.13×10^{-3}	*Sdev*= 5.11×10^{-1}	$logBCF_{fish} = logBCF_{fish}^{*} \pm a8$ (BCFBAF v3.00, neutrals)
a9	Normal	5.15×10^{-2}	*Sdev*= 5.41×10^{-1}	$logBCF_{fish} = logBCF_{fish}^{*} \pm a9$ (acids regression)
a10	Normal	2.65×10^{-2}	*Sdev*= 6.61×10^{-1}	$logBCF_{fish} = logBCF_{fish}^{*} \pm a10$ (bases regression)
$k_{photodegradation,\ water}$	Uniformal		[min, max]	
$logHC50_{EC50}$	Student	$logHC50_{EC50}$	95%*CI* = $\pm \frac{1}{\sqrt{n}} \times t_{n-1}^{0.05} \times$ *Sdev*(LogEC50) [a]	
exp K_{OC}	Lognormal		*b*	
exp $k_{biodeg,\ water}$	Lognormal		*b*	
exp $k_{biodeg,\ soil}$	Lognormal		*b*	
exp $k_{OH,\ water}$	Lognormal		*b*	
Concentration $_{effluent}$	Lognormal	Geometric mean [c]	Geometric *Sdev*	
[˙OH] in water (M)	Uniformal		[10^{-14}, 10^{-17}] (min, max) (Lam, Tantuco et al. 2003)	
$[SM]_{freshwater}$ (kg/m^3)	Triangular	15	[3, 50] (min, max) (Meybeck 1982)	
$[DOC]_{freshwater}$ (kg/m^3)	Triangular	5	[1, 20] (min, max) (Meybeck 1982)	
$pH_{\ agricultural\ soil}$	Tringular	7	[3.2, 8.5] (min, max) (Reuter et al. 2008)	
$pH_{\ freshwater}$	Tringular	7	[3.2, 8.5] (min, max) (Reuter et al. 2008)	
$foc_{\ agricultural\ soil}$	Tringular	0.02	[0.01, 0.1] (min, max) (Jones et al. 2005)	
Rain rate (mm/year)	Tringular	700	[250, 1500] (min, max)	

[a] $t_{n-1}^{0.05}$ is the *t* value from the student table for a 95% confidence interval with *n-1* degree of freedom, where *n* is the size of sample (or number of species tested), and *Sdev* is the Standard deviation of the LogEC50s.
[b] Experimental values are shown in Table 18.
[c] values obtained from Table 17.

C5: Further discussion of results

Measurements of the thiazide diuretic bendroflumethiazide in WWTP effluents and in the environment are scarce. Kasprzyk-Hordern et al. (2009) reported detection at a median concentration of 0.011 µg/l and a maximum concentration of 0.058 µg/l in a WWTP effluent in Wales, UK; conversely, no detection was reported in other WWTP plant (limit if detection = 0.8 ng/l). In addition, it was not detected in the river to which the former WWTP effluent was discharged (limit of detection = 0.5 ng/l). The HC50 parameter contributes 95.2% to the impact result variance. Moreover, ecotoxicological data were estimated for all trophic levels. No abiotic degradation data is available however bendroflumethiazide may be susceptible to indirect photolysis, as well as, containing chromophores that absorb at wavelengths >290 nm, it may also be susceptible to direct photolysis.

The anti-inflammatory 5-aminosalicylic acid, or mesalazine, impact result is mainly sensitive the HC50 parameter, which contributes 85.5% to the variance of output results. Moreover, this parameter warrants further investigation given that only 1 experimental EC50 value was available in the literature; for other trophic levels EC50s were estimated. Very limited data on measurements of 5-aminosalicylic in WWTP effluents are also available in the literature. It was detected in 2 WWTP effluents from activated sludge treatments at median concentrations of 0.63 and 30.32 µg/l in South Wales, UK (Kasprzyk-Hordern et al., 2009). In addition, 5-aminosalicylic does contains chromophores that absorb at wavelengths >290 nm and therefore may be susceptible to direct photolysis by sunlight, as well as it may be susceptible to photosensitization.

The HC50 parameter contributes 97.7% to the impact result variance of the non-steroidal anti-inflammatory ketorolac impact result. In addition, further uncertainty related to HC50 parameter was not quantified given that EC50 values were estimated. In several European countries ketorolac marketing was withdraw or the dose and treatment duration were restricted due to several side effects (U.N., 2003). Generally, pharmaceuticals with high consumption are those selected for further investigation (Escher et al. 2011); hence very limited data on measurements of ketorolac in WWTP effluents are available in the literature. It was detected at a maximum concentration of 0.539 µg/l in a WWTP effluent in Spain (Rosal et al., 2010). Ketorolac is expected to be susceptible to indirect photolysis and it does contains chromophores that absorb at wavelengths >290 nm; hence it may be also susceptible to direct photolysis.

The confidence limits of the unpolar lipid regulator clofibrate impact result are comparatively narrow, having an insignificant contribution to total impact variance (<0.05%). Therefore, clofibrate does not figure among compounds of greatest concern (Figure 2); however, the median impact result is comparatively high. In general clofibrate is not detectable in WWTP effluents, as well as fenofibrate and etofibrate. The complete hydrolysis of these drugs to fenofibric acid and clofibric acid occurs in the human body immediately after intake; therefore, the occurrence of these metabolites are quite common in WWTP effluents (Ternes, 1998). Moreover, this neutral lipid regulator has an estimated log K_{OW} of 3.62 (USEPA, 2008), hence significant removal in WWTPs may be expected due to partitioning to particles, given that, for hydrophobic interactions, compounds exhibiting log K_{OW} values greater than 3 would undergo significant removal (i.e., >50% associated with particles in equilibrium) (Sedlak, 2000). In fact, the parent compound clofibrate was not detected in 20 WWTP and in 20 rivers in Germany (Ternes, 1998), and in 5 WWTPs in Italy, France and Sweden (Andreozzi et al., 2003). However, its detection in 1 WWTP effluent in Greece (Andreozzi et al., 2003), but not clofibric acid, is rather unusual and the authors do not have any explanation. The impact result of clofibrate is based on the reported concentration of 0.8 μg/l in the Greek WWTP. Nevertheless, considering the discussion above, this compoud may be comparatively of minor significance. Moreover, no data on indirect photolysis was found in the literature therefore the residence time of clofibrate on the aquatic environment may be overestimated in the present study.

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