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July 2023

The Transport, Fate and Impact of Pharmaceuticals in the Environment in Scotland

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Acknowledgements

Data for this study was provided by Scottish Environment Protection Agency, Scottish Water, NHS Highland, University of Highlands and Islands and Glasgow Caledonian University, which formed part of the CREW project 'Reduction of pharmaceuticals in the water environment – baseline assessment and recommendations (Helwig *et al.,* 2022).'

This study was funded by SEFARI Gateway via their Specialist Advisory Group programme.

Contents

1. Introduction

1.1 Background

Pharmaceuticals (medicines) are a key factor in the improvement of human health and wellbeing. However, there is increasing awareness regarding the prevalence of pharmaceuticals within the natural environment due to the use of medicines. About 30-100% of an orally administered dose of a medicine leaves the body unmetabolized along with other metabolites and enters wastewater streams. This is exacerbated by improper disposal of unused medicines down toilets and sinks. Although wastewater treatment plants can remove some pharmaceuticals, some still enter surface water following treatment (removal efficiency differs depending on treatment plant), where they can be transported downstream to the environment.

A major concern of pharmaceutical pollution is its potential to increase antimicrobial resistance (AMR). Exposure to antibiotics can increase resistance in environmental bacteria. The potential exists to pass resistance to clinically relevant microorganisms that cause disease and so become difficult to treat ('superbugs'). The UK government 5-year strategy to tackling AMR highlights the importance of understanding the role of the environment in AMR dissemination (UK Government, 2019).

In Scotland, a multi-agency alliance was established to tackle the issues of pharmaceutical pollution with a key focus to reduce the concentration of pharmaceuticals in the environment. The One Health Breakthrough Partnership (OHBP) consists of representative members from regulators (Scottish Environment Protection Agency (SEPA)), water services (Scottish Water (SW)), the health service (NHS Highland) and the Environmental Research Institute at the University of the Highlands and Islands, providing leadership in the field and working towards a non-toxic environment, which recognises that the health of humans, animals and the ecosystem is interconnected.

1.2 Aims and Objectives

This project sought to understand the level of risk of commonly prescribed pharmaceuticals detected in the Scottish environment. Veterinary pharmaceuticals were

not considered in this project. This was achieved by undertaking an expert review of the current state of knowledge on the prevalence of pharmaceutical pollutants in the Scottish environment, including potential impacts on AMR, and completing environmental risk assessments for a sub-set of compounds.

The project addressed **five key objectives**:

1. Conduct a literature review on pharmaceutical occurrence in different environmental matrices including waters (coastal, ground), sediments, soils and sewage sludge.
2. Collate unpublished pharmaceutical data in the environment from relevant organisations.
3. Short-list pharmaceutical compounds based on detection frequency, use and ecotoxicology.
4. Conduct a literature review on the potential impact on AMR for the short-listed pharmaceuticals.
5. Conduct an environmental risk assessment for each of the short-listed pharmaceutical compounds using a source-pathway-receptor principle, with a focus on the potential risks to human health.

2. Literature Review (Objective 1)

2.1 Methods

The current extent of pharmaceutical pollution in Scotland was assessed by gathering data from published peer-reviewed journals and grey literature. This was done using Web of Science, but where there were few results, Google Scholar, Science Direct, and Microsoft Academic were also used.

Much of the literature (and associated data covering a period from 2014 to present) on pharmaceutical pollution in surface waters has already been garnered through an existing CREW project (Helwig *et al.,* 2022). A database was created using data from the literature and unpublished data from regulators and research institutes. Hence, the focus of this project was to add to the evidence base with pharmaceutical data from coasts, groundwater, sediment, soil and activated sludge. To capture the breadth of information and data available, no restrictions were place on the literature search other than geographic location (i.e. Scotland). Therefore, the following search terms were used, alone and in combination: coastal, groundwater, sediment, soil, activated sludge, sewage sludge; pharmaceuticals; Scotland. To address the impact of pharmaceuticals on antimicrobial resistance, the following search terms were used, alone and in combination: name of compound; antimicrobial resistance; antibiotic resistance.

We also made further requests for unpublished data from regulators and research institutes. No restrictions were made on the year of data collection.

2.2 Results

2.2.1 Pharmaceutical Prevalence in Water

Over 60 pharmaceuticals have been measured in water compartments in Scotland including rivers or streams, inland waters, estuaries, septic tank effluent, hospital sewage, wastewater treatment plant (WWTP) influent, WWTP effluent, WWTP primary sample and secondary sample, and is reviewed elsewhere (Helwig *et al.,* 2022). No pharmaceuticals were detected in mains drinking water (Helwig *et al.,* 2022). No data

was found on pharmaceutical prevalence in groundwater in Scotland. This is by contrast to the comprehensive survey of pharmaceutical contaminants in groundwater in England and Wales (Manamsa *et al.*, 2016).

We received one response for further unpublished data from SEPA, who supplied an additional dataset for pharmaceuticals from several rivers and inland waters in Scotland. Pharmaceuticals were measured by a combination of gas chromatography-mass spectrometry (GC-MS) and liquid chromatography-mass spectrometry (LC-MS). This addresses **Objective 2** from Section 1.2.

One additional study was found, which focussed on seawater. In the study by Weigel et al., compounds were measured in the North Sea, adjacent to the Firth of Tay and Firth of Forth (Weigel *et al.*, 2002). Measured concentrations of clofibric acid (a herbicide and a metabolite of the pharmaceutical medicine clofibrate), caffeine (a stimulant) and DEET (an insecticide) were determined using a method based on sample collection by solid-phase extraction on a polystyrene-divinylbenzene sorbent with subsequent detection by GC-MS. They were only able to detect caffeine at concentrations of 3.0 ng/L. The low chemical concentrations were attributed to dilution effects from mixing with relatively cleaner North Atlantic water.

2.2.2 Pharmaceutical Prevalence in Sediments

A suite of illicit drugs, pharmaceuticals and bactericides in sewage sludge and the corresponding sediments upstream and downstream from three WWTPs, in undisclosed locations in Western, Central and Eastern Scotland, were measured by Langford *et al.*, 2011. The authors used ultra-high performance liquid chromatography (UHPLC) and mass spectrometry to measure the pharmaceuticals. In the sediment, only the bactericide triclocarban was detected, with overall higher concentrations in the downstream sediments (concentrations ranged from 19.4 to 138.8 ng/g dw) compared to the upstream sediments (concentrations ranged from <2 to 97.0 ng/g dw) for two of the three WWTP sites. Concentrations of other compounds, namely atenolol, carbamazepine, citalopram, ibuprofen, amphetamine, bendroflumethiazide, benzoylecgonine, cocaine,

diclofenac, fluoxetine, salbutamol and triclosan were below the detection limit. The lack of detection of the other compounds in the sediments was attributed to their low partition coefficients.

2.2.3 Pharmaceutical Prevalence in Sewage Sludge

In the aforementioned study, sewage sludge from three undisclosed WWTPs was shown to contain the pharmaceuticals atenolol, carbamazepine, citalopram, ibuprofen, and the bactericides triclocarban and triclosan (Langford *et al.*, 2011). The study did not disclose the type of sludge material analysed. Ibuprofen was only detected in one of the three sludges at a concentration of 384.8 ng/g dw (dry weight). Atenolol was detected in two of the three sludges, at 84.7 and 112.3 ng/g dw, respectively. Citalopram was also detected in two of the three sludges, at 168.2 and 317.0 ng/g dw, respectively. Carbamazepine was detected in all three sludges, and ranged from 61.8 to 86.4 ng/g dw. The bactericides triclocarban and triclosan were also present in all three sludges; triclocarban ranged from 516 to 2829 ng/g dw, while triclosan ranged from 865 to 5940 ng/g dw (Table 1). The other compounds – amphetamine, bendroflumethiazide, benzoylecgonine, cocaine, diclofenac, fluoxetine and salbutamol were below the detection limit.

In another study, pharmaceutical concentrations were measured in 16 WWTP in the UK (Gardner *et al.*, 2013). Some sites were located in Scotland's central belt (Gardner *et al.*, 2012). The analysed sludges did not undergo further treatment such as anaerobic digestion or thermal treatment. They included primary sludge, combined primary and humus returns and oxidation ditch sludge. Ibuprofen concentrations ranged from 0.01 to 0.67 mg/kg in the sludge. Similarly, propranolol concentrations ranged from 0.1 to 0.38 mg/kg. Oxytetracycline concentrations were much higher ranging from 1.15 to 43 mg/kg, and was attributed to its different binding behaviour (Table 1).

In a follow-up study by Jones *et al.,* additional pharmaceuticals were measured in sewage sludge from WWTPs using LC-MS or GC-MS (Jones *et al.*, 2014). Sludge was collected from the primary settlement tank, along with secondary/biological sludge (e.g. humus sludge)

or mixed sludge (a mixture of primary and secondary biological sludge). Measurements of ibuprofen, propranolol, erythromycin, ofloxacin, oxytetracycline, fluoxetine and triclosan were made in sewage sludges from 28 WWTPs in the UK, while measurements for diclofenac were made from just 6-7 WWTPs. The highest concentrations were observed for oxytetracycline and triclosan, with median concentrations of 4.00 mg/kg and 7.62 mg/kg, respectively. Concentrations of ibuprofen, ofloxacin, propranolol and fluoxetine were a magnitude lower, with median concentrations of ibuprofen being 0.22 mg/kg, ofloxacin being 0.20 mg/kg, propranolol being 0.1 mg/kg and fluoxetine being 0.15 mg/kg. Concentrations of erythromycin and diclofenac were a further order of magnitude lower, with median concentrations of 0.05 mg/kg and 0.07 mg/kg, respectively (Table 1). It should be noted that these concentrations were derived from 28 WWTP across the UK; it was not possible to determine which readings came from the Scottish WWTPs in the paper. Overall, the authors concluded that concentrations of pharmaceuticals in sludges were generally the same across all WWTP regardless of treatment process, influent/effluent concentrations and location of sludge sampling point.

2.2.4 Pharmaceutical Prevalence in Soil

In a study by Zhang et al., estrogenic compounds (including estrone (E1), 17β-estradiol (E2), 17α-ethynylestradiol (EE2) and estriol (E3)) and an estrogen mimicking compound (bisphenol A) were measured in 8 soil samples in NE Scotland (Zhang *et al.*, 2011). These were measured using GC-MS. E1, EE2 and bisphenol A were the most prevalent, with E1 concentrations ranging between 0.6 to 3.2 ng/g, EE2 concentration ranging between 3.3 to 67.3 ng/g and bisphenol A concentrations ranging from 0.9 to 24.7 ng/g. E2 was only detected in one soil at 1.6 ng/g. Similarly, E3 was only detected in one soil at 0.4 ng/g (Table 1).

Furthermore, some preliminary work was done to measure the pharmaceuticals ibuprofen, paracetamol, tramadol, diclofenac, carbamazepine, trimethoprim and the bactericide triclosan in soils in NE Scotland using LC-MS/MS, but the quantification methods are yet to be validated (Z. Zhang, personal communication) (Table 1).

2.3 Summary

Table 1 shows a summary of findings from the literature review. Blank cells indicate that the compound was not measured (i.e. no-one has tested that environmental matrix for the presence of that compound); while n.d. indicates that the compound was measured, but not detected (either because it was below the detection limit of the methods used or was absent). Note that data from the CREW database or unpublished data provided by SEPA is not included in this table.

Some publications included compounds other than pharmaceuticals. Clofibric acid is a herbicide and a metabolite of the pharmaceutical drug clofibrate, while DEET is an insecticide. Although bisphenol A is an oestrogen mimicking compound, it is in fact a plastisicer and so is not considered a pharmaceutical. Benzoylecgonine is a metabolite of cocaine. Therefore, these have been removed from further analysis.

Triclocarban and triclosan are antimicrobials found in personal care products such as soaps. Although caffeine is found in various drinks, it is also added to pain relievers. Amphetamine has been used medically to treat Attention Deficit Hyperactivity Disorder (ADHD) and narcolepsy, has limited use to treat obesity, and is sometimes used to treat depression and cognitive enhancer (Berman *et al.*, 2009). Cocaine has been used medically as an anaesthetic and to decrease bleeding during nasal surgery (Harper and Jones, 2006). Therefore, these compounds have been considered in further analysis (Table 2), though illicit use of these drugs likely accounts for most of the concentrations in the environment.

The greatest diversity of pharmaceuticals as reported in the literature related to the aquatic environment (61 pharmaceuticals) compared to the other environmental matrices. This is followed by sewage sludge (16 pharmaceuticals); sediment (12 pharmaceuticals) and soil (11 pharmaceuticals) (Figure 1). (Note: the numbers in the brackets include values that were below the detection limit /were absent as well as those that were above the detection limit). Of course, there may be other pharmaceuticals

present in these environmental matrices, but to date, no research has been undertaken to measure them.

Figure 1 shows the numbers of studies performed in the different environmental matrices, which includes those from the CREW project (Helwig *et al.,* 2022). The proportions do not reflect the number of tests performed in each matrix as this was difficult to ascertain from the literature. More studies are focussed on aquatic environments, including surface water, sediment and wastewater (12 studies in total). Fewer studies have focussed on terrestrial environments, including soil and sewage sludge (7 studies in total). Therefore, research effort is currently focussed on aquatic environments.

Table 1. Summary of the findings of the literature review, showing pharmaceuticals measured in different environmental matrices. n.d. denotes 'not detected.'

Compound	**Classification**	**Coastal water (ng/L)[1]**	**Sediment (mg/kg dw)[2]**	**Sewage Sludge (mg/kg dw)[3]**	**Soil (ng/g dw)[4]**
Caffeine	Stimulant	3.0			
Triclocarban	Bactericide		<0.002 – 0.139	0.516 – 2.829	
Ibuprofen	Anti-inflammatory		n.d.	0.01 – 0.67	Unpublished
Diclofenac	Anti-inflammatory		n.d.	n.d. - 0.07	Unpublished
Carbamazepine	Anti-epileptic		n.d.	0.062 – 0.086	Unpublished
Atenolol	Anti-hypertensive		n.d.	0.085 – 0.112	
Citalopram	Anti-depressant		n.d.	0.1682 – 0.317	
Triclosan	Bactericide		n.d.	0.865 – 7.62	Unpublished
Fluoxetine	Anti-depressant		n.d.	n.d. - 0.15	
Amphetamine	Stimulant		n.d.	n.d.	

Bendroflumethiazide	Diuretic		n.d.	n.d.	
Cocaine	Stimulant		n.d.	n.d.	
Salbutamol	Bronchodilator		n.d.	n.d.	
Propranolol	Anti-hypertensive			0.1 – 0.38	
Oxytetracycline	Antibiotic			1.15 – 43	
Erythromycin	Antibiotic			0.05	
Ofloxacin	Antibiotic			0.20	
Estrone (E1)	Hormone				0.6 – 3.2
17β-estradiol (E2)	Hormone				1.6
17α-ethynylestradiol (EE2)	Hormone				3.3 – 67.3
Estriol (E3)	Hormone				0.4
Paracetamol	Analgesic				Unpublished
Tramadol	Opioid analgesic				Unpublished
Trimethoprim	Antibiotic				Unpublished
No. compounds		**1**	**12**	**16**	**11**

[1] Weigel *et al*., 2002

[2] Langford *et al*., 2011

[3] Langford *et al*., 2011; Gardner *et al*., 2013; Jones *et al*., 2014

[4] Zhang *et al*., 2011; Z. Zhang, personal communication

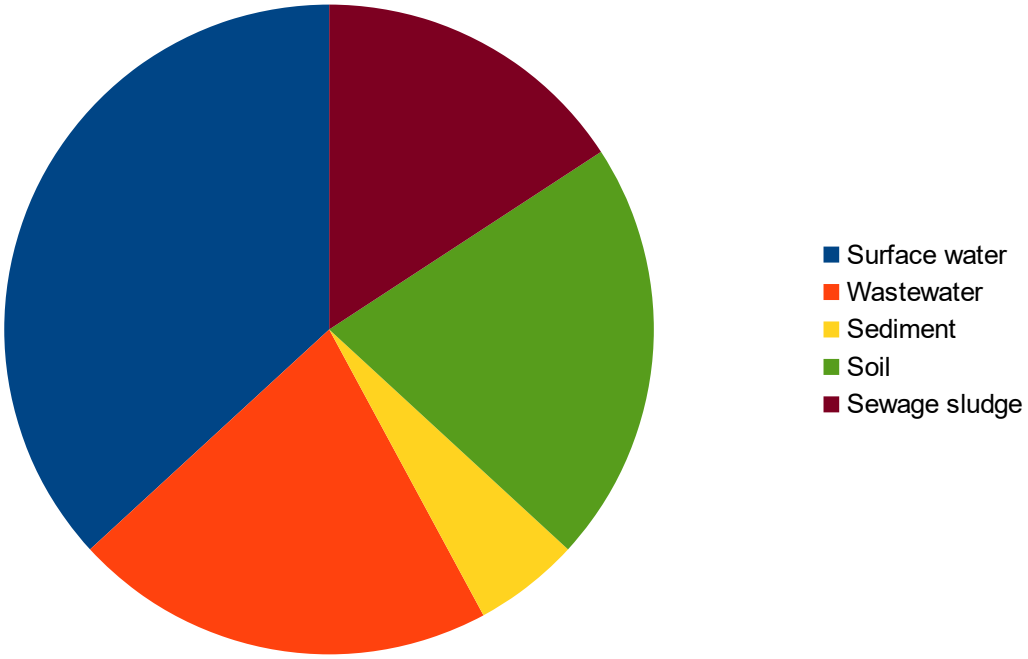

Figure 1. Proportion of studies on pharmaceutical pollution in different environmental matrices.

3. Short-listing Pharmaceutical Compounds for Further Analysis (Objective 3)

3.1 Method

Of the 64 pharmaceuticals detected in the Scottish environment (both aquatic and terrestrial), 20 were short-listed based on the criteria set out below:

1. High use as determined by prescription data taken from (Helwig *et al.*, 2016)
2. High detection frequency. This was calculated as a percentage of the number of times the pharmaceutical was detected within the total number of samples taken. Calculations were made using data from the CREW database (Helwig *et al.,* 2022), the additional SEPA data and data collected from the literature review in this project.
3. High ecotoxicity risk. The potential ecological risks of the contaminants were assessed based on risk quotient (RQ) approach following the Technical Guidance Document on Risk Assessment from the European Commission (Van Leeuwen, 2003; Technical Guidance for Deriving Environmental Quality Standards, 2018). The RQ values of contaminants were calculated by dividing the mean measured environmental concentration (MEC) by the predicted no-effect concentration (PNEC) for each chemical using Eq.: RQ=MEC/PNEC. This calculation could only be performed for pharmaceuticals in the water environment because no PNEC values exist for soils (Jones *et al*., 2014). For the purpose of interpreting the risk calculations, the RQ values were classified into the following four levels: minimal risk (RQ<0.01), low risk (0.01≤RQ<0.1), medium risk (0.1≤RQ<1) and high risk (1≤ RQ).

3.2 Results

It was not possible to ascertain the sample numbers from two of the papers in the literature review, which is required for calculating the detection frequency. In the study by Gardner *et al.,* 2400 samples were taken from 16 WWTPs, but it was not possible to ascertain how many 'detections' versus 'below detection limit' there were in those samples. As mentioned previously, it was also not possible to identify which WWTPs were based in

Scotland (Gardner *et al.*, 2013). A similar issue was encountered for the Jones *et al.* study where 250 sewage sludge samples were taken from 28 WWTPs. Therefore, data from these two studies were omitted from the calculations for the detection frequencies.

Based on the holistic consideration of risk, detection frequency and usage, 20 pharmaceuticals were short-listed (Table 2). Upon further consideration of the level of the potential ecological risks and coverage of different therapeutic groups, this was narrowed down further to five compounds for further analysis:

1. Ibuprofen (anti-inflammatory)
2. Clarithromycin (antibiotic)
3. Erythromycin (antibiotic)
4. Diclofenac (anti-inflammatory)
5. EE2 - 17α-ethinylestradiol (hormone)

Table 2. Short-listed 20 compounds.

Compound	No. Samples[1]	No. Positive Detections[1]	Minimum Risk[1]	Low Risk[1]	Medium Risk[1]	High Risk[1]
Azithromycin	1033	1013	18	17	49	7
Carbamazepine	1350	1202	53	71	11	1
Ciprofloxacin	1078	956	38	41	7	2
Clarithromycin	1258	1141	28	24	64	14
Diclofenac	1408	1234	28	27	63	35
E1	1283	1239	4	14	48	19
E2 - 17β-estradiol	1242	1133	5	1	48	31
EE2 - 17α-ethinylestradiol	1246	1127	21	0	38	28
Erythromycin	1201	1127	28	31	39	18
Fluoxetine	1072	968	19	18	20	2
Ibuprofen	1320	1222	3	0	10	106
Metformin	1021	1021	2	36	49	0
Naproxen	29	29	0	19	5	0
Paracetamol	356	223	73	5	3	3
Propranolol	1123	1070	13	17	65	7
Ranitidine	1091	1041	13	11	54	14
Sertraline	994	994	14	44	8	0
Sulfamethoxazole	145	62	20	38	2	0
Triclosan	1167	1135	0	4	53	39
Trimethoprim	143	77	9	1	6	44

[1] Taken from the CREW database (Helwig *et al.,* 2022) and the SEPA dataset.

4. Potential Impact of Non-Antibiotic Pharmaceuticals on Antimicrobial Resistance (Objective 4)

Bacteria can develop resistance to antibiotics through: i) genetic mutations – this can occur when bacteria are exposed to sub-inhibitory concentrations of antibiotics, ii) horizontal gene transfer (HGT) of specific resistance genes, iii) co-resistance where a resistance gene to one antibiotic is co-inherited with another resistance gene, and iv) cross-resistance where resistance to one antibiotic also confers resistance to a different antibiotic. Exposure to antibiotics in the environment can therefore enhance AMR through any of these mechanisms.

Table 2 shows the 20 pharmaceuticals that were short-listed for further study, and 14 of these are non-antibiotic pharmaceuticals.

Some non-antibiotic pharmaceuticals can enhance AMR. Carbamazepine was recently shown to enhance HGT of AMR genes between lab strains of *E. coli* and *Pseudomonas putida* (Wang *et al.*, 2019). Similarly, triclosan causes co-resistance or cross-resistance in different bacterial genera (Yazdankhah *et al.*, 2006). Propranolol has also been shown to potentially increase cross-resistance in *Pseudomonas putida* (Sayqal *et al*., 2016).

Some non-antibiotic pharmaceuticals do not enhance AMR in the environment but instead have been shown to kill or inhibit the growth of various microorganisms. Such compounds include fluoxetine (Kalaycı *et al.*, 2015), ibuprofen (Obad *et al.*, 2015), metformin (Patil *et al.*, 2018), E2 (Hosoda *et al.*, 2011) and naproxen (Lejal *et al.*, 2013), and have been shown to have antimicrobial effects on a broad range of microorganisms. E2 has been proven to inhibit the growth of *Helicobacter pylori* (Hosoda et al., 2011), and naproxen has been proven to have antiviral properties against influenza A.

Other non-antibiotic pharmaceuticals have been shown to work synergistically with antibiotics, making bacteria more susceptible to the bactericidal effects of antibiotics. Various *in vitro* studies were performed on bacteria grown in the lab to investigate the combined effects of pharmaceuticals with antibiotics. Diclofenac was found to increase

susceptibility to the antibiotics ciprofloxacin, ofloxacin and norfloxacin in *Staphylococcus aureus* (although it also decreased susceptibility to the antibiotics oxacillin and vancomycin, suggesting that effects are compound-specific) (Riordan *et al.*, 2011). Bactericidal activity was improved on *Streptococcus pneumoniae* when the antibiotic cefixime was used in combination with paracetamol (Carsenti-Etesse et al 1998). Ranitidine was found to work synergistically with the antibiotics tetracycline or clarithromycin against resistant strains of *Helicobacter pylori* (Midolo *et al.*, 1999).

Table 3. Impact of non-antibiotic pharmaceuticals on AMR.

Compound	**Classification**	**Enhances AMR**	**Mode of Action**	**Reference**
Carbamazepine	Anti-epileptic	Yes	Enhances HGT of AMR genes	(Wang *et al.*, 2019)
Diclofenac	Anti-inflammatory	No	Increases bacterial susceptibility to antibiotics	(Riordan *et al.*, 2011)
E1	Hormone	No info available	NA	
E2 - 17β-estradiol	Hormone	No	Has antimicrobial properties	(Hosoda *et al.*, 2011)
EE2 - 17α-ethinylestradiol	Hormone	No info available	NA	
Fluoxetine	Anti-depressant	No	Has antimicrobial properties	(Kalaycı *et al.*, 2015)
Ibuprofen	Anti-inflammatory	No	Has antimicrobial properties	(Obad *et al.*, 2015)
Metformin	Diabetes treatment	No	Has antimicrobial properties	(Patil *et al.*, 2018)
Naproxen	Anti-inflammatory	No	Has antiviral properties	(Lejal *et al.*, 2013)
Paracetamol	Analgesic	No	Acts synergistically with antibiotics	(Carsenti-Etesse *et al.*, 1998)
Propranolol	Beta-blocker	Yes	Cross-resistance	(Sayqal *et al.*, 2016)
Ranitidine	Reduces stomach acid	No	Acts synergistically with antibiotics	(Midolo *et al.*, 1999)
Sertraline	Anti-depressant	No	Has antimicrobial properties	(Kalaycı *et al.*, 2015)
Triclosan	Bactericide	Yes	Cross-resistance or co-resistance	(Yazdankhah *et al.*, 2006)

5. Risk assessment of pharmaceutical pollution in the Scottish environment (Objective 5)

5.1 Methods

5.1.1 General principles

The pathway is the means by which the pharmaceutical gets from the source to the receptor (Figure 2). Receptors typically included humans, livestock, wildlife, and/or other sensitive species and microbes and more widely in the environment (soils and water). For risks to be realised, there must be a complete pathway-linkage between the source and the receptor. Various pathways may exist depending on the sources, receptors, and the type of pharmaceutical. Usually, the compound of concern will reach a receptor contained in some carrier medium (e.g. water, food and soil), which will depend on the physico-chemical properties of the compound.

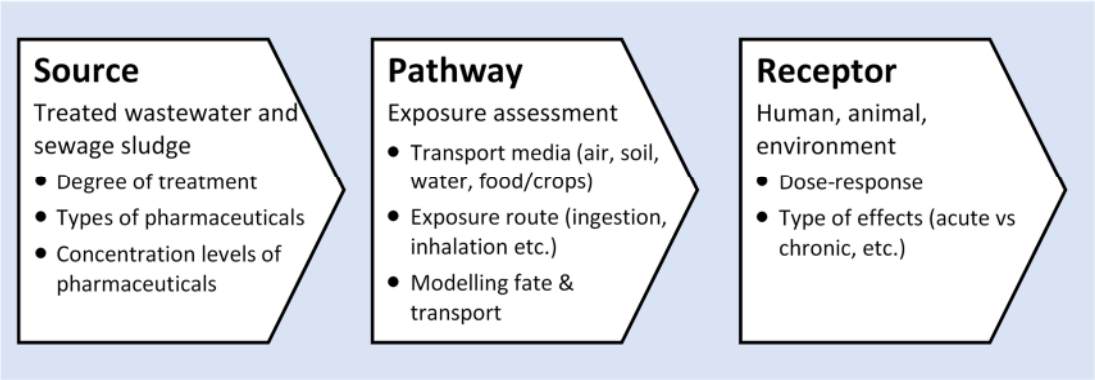

Figure 2. Theoretical source-pathway-receptor concept for the risk assessments.

Figure 3 shows a conceptual model for quantifying the risks to human health and the environment from pharmaceuticals in wastewater effluent and sewage sludge. It is assumed that the main pathway for pharmaceuticals present in wastewater effluent to reach receptors are through direct discharge into surface waters. The resulting concentrations of pharmaceuticals in surface water can subsequently have a direct impact on aquatic organisms and/or on human health (through ingestion if the surface water is used for drinking water – as is the case for some private water supplies in

Scotland – or through direct skin contact if surface water is used for recreational activities such as wild swimming, fishing, etc.). Pharmaceuticals present in sewage sludge are assumed to reach receptors through application of sludge to land. The sludge and resulting pharmaceutical concentrations in soil can lead to direct exposure of soil organisms and terrestrial wildlife but can also enter the food chain through uptake into crops or enter the aquatic environment by leaching to groundwater or run-off to surface waters.

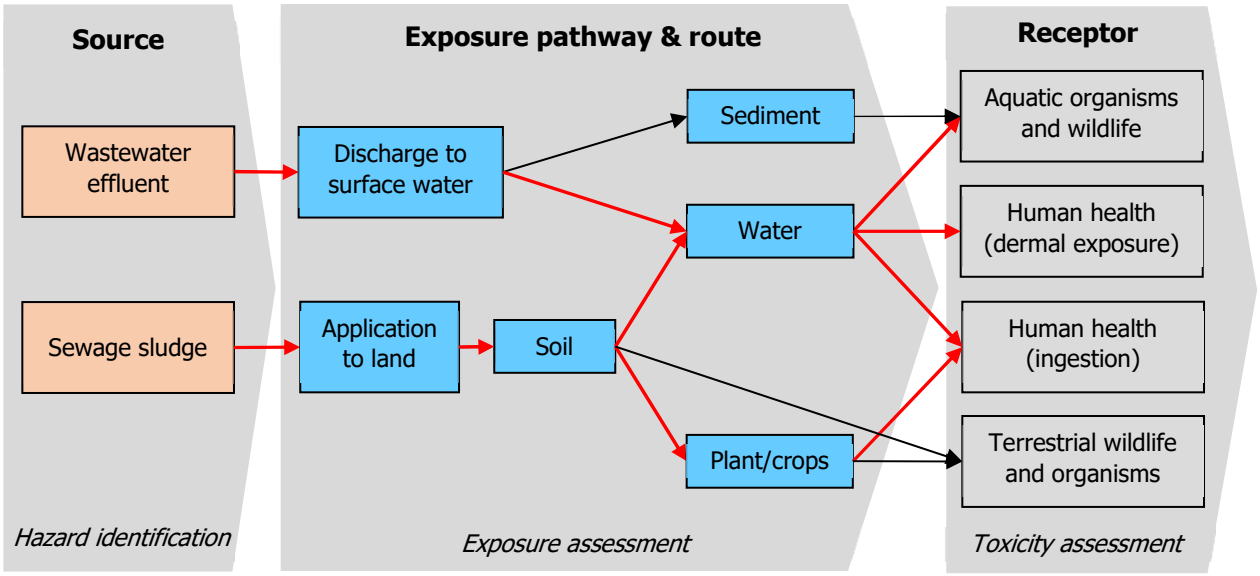

Figure 3. Conceptual source-pathway-receptor models for assessing the risks to human health and the environment associated with pharmaceuticals in wastewater effluent and sewage sludge. The pathways considered in the QRA are marked with red arrows.

5.1.2 Exposure assessment

Depending on the specific source-pathway scenario and the type of pharmaceuticals, a given receptor may be exposed to pharmaceuticals. Exposure assessment is the process of estimating the magnitude, frequency and duration of exposure that may occur due to contact with the contaminated carrier media. The aim of the exposure assessment is to determine the expected chemical concentration in the environment (often referred to as

the **Predicted Environmental Concentration (PEC)** or the **Measured Environmental Concentration (MEC)** if based on measurements) or, as is the case for most human health risk assessment, the dose (often expressed as the **Average Daily Dose (ADD)** in mg kg^{-1} d^{-1}) of a specific agent that a given receptor is being exposed to. The calculation of ADD depends on the specific exposure pathway and route, but can usually be expressed in the form:

$$ADD = \frac{C_m R_i}{BW} F_i \qquad (1.1)$$

where C_m (mg kg^{-1}) is the concentration of the specific agent in the carried medium (e.g. soil, water, and/or crops), R_i is the ingestion or intake rate of the carried media (kg day^{-1}), BW is the body weight (kg) of the receptor, and F_i is the fractional time of exposure. The main challenge for Eq. 1.1 is to estimate the concentration of the specific agent in the carrier media (i.e. the PEC/MEC) and the amount of contaminated media taken in by the receptor over time for each of the considered exposure pathways.

A way of attaining the PEC values is directly through measured data in the given media. A review of measured pharmaceutical concentrations in a range of environmental media in Scotland (soil, surface water, sediments, coastal waters etc.) was presented in Section 2. This review showed that there is only limited data and information on pharmaceuticals in the Scottish environment, and MECs can therefore only be derived for a limited number of environmental media. In order to estimate PEC values and the magnitude of the exposure for a given pathway, contaminant fate and transport modelling is typically required. Such environmental transport and fate modelling are commonly based on so-called multimedia models (Mackay, 2001), which are based on mass balance and fugacity principles. In multimedia models the environment is separated into "compartments" such as air, water, soil and sediment, and the partitioning of a given substance between the different compartments are then calculated based on the substance's physico-chemical properties and the amount emitted to the environment. Key physico-chemical properties that may affect the behaviour and fate of a pharmaceutical once it enters the environment are listed in Table 4 and described further in Section 5.2

Fugacity modelling can be carried out at different levels. Level I fugacity modelling evaluates the steady-state equilibrium distribution of a fixed quantity of chemical between the compartments within the ‘‘unit world’’ environment and does not account for advective flows or degradation. A Level I calculation indicates how the chemical is likely to partition in the different environmental compartments and provides estimates of equilibrium concentrations and masses of the chemical in each compartment of the model environment. Level II is similar to Level I but accounts for steady inflows of the chemical as well as advective flows and degradation in each compartment. Level II calculations can therefore also provide an estimate of the overall residence times and/or persistence in the different compartments. For the work here, a Level III fugacity calculation is carried out, which has proved to be the most useful and realistic. Level III is still a steady-state simulation with a constant inflow of chemical but unlike Levels I and II, equilibrium is not assumed between environmental compartments and inter-compartmental transport processes are also accounted for. The chemical inflow rates can also be specified into each compartment to reflect the use patterns of the substance.

Based on the amount and type of chemical released into a “unit world” environment, the resulting chemical concentrations and masses in air (including aerosols), water (including fish and suspended particles), soil and sediment can be estimated using standard multimedia fugacity-based modelling (Mackay, 2001). For the risk assessment here, the resulting concentrations in crops and plants are also needed. These can again be estimated using fugacity-type modelling as described in Appendix A.

5.1.3 Toxicity assessment

The aim of the toxicity assessment is to determine a hazard-specific Predicted No Effect Concentration (PNEC) or the acceptable dose (i.e. the maximum daily uptake level of a hazard that is likely not to result in any adverse effects and hence is considered ‘safe’). For many chemicals, the safe dose is expressed as a so-called reference dose (RfD). PNECs are used in ecotoxicological/environmental risk assessments, whereas RfDs are mainly used in human health risk assessments.

Both PNECs and RfDs are usually estimated based on dose-response-relationships, which describe what the adverse effects are at different exposure levels, when no effects are observed and when responses start to appear. PNECs are usually calculated based on acute or chronic toxicological dose descriptors such as LC50/EC50 (i.e. the concentrations at which 50% mortality or inhibition of a function like reproduction are observed), NOEC (the highest tested No Observed Effect Concentration) or LOEC (Lowest Observed Effect Concentration). Depending on the type of toxicological data used for deriving the PNEC, an assessment factor is used to account for the confidence of the toxicity data being extrapolated to an entire ecosystem. Similarly, many methodological approaches exist for deriving RfDs from dose-response data. Often RfDs are estimated by extrapolating dose-response data, but this can be associated with significant uncertainty. Mathematical curve-fitting models may be applied to dose-response data to estimate a no observed adverse effect level (NOAEL) or to calculate the dose at which a specific proportion of the receptors are expected to show a response (expected dose, ED). An alternative is to use the lowest observed adverse effects level (LOAEL). This is an experimentally derived value and therefore reduces reliance on model fitting.

The toxicity assessment depends on the specific contaminant/hazard and the exposure route (whether the contaminant enters the receptor through e.g. inhalation, ingestion or dermal contact), but also on the type of response and whether chronic or acute effects are considered. For non-cancer endpoints, it is standard practice to assume that a threshold of effect exists, while no threshold is usually assumed with carcinogenic endpoints.

For non-carcinogenic agents for which it is not possible to find RfDs in the literature, the RfDs can be determined based on the lower 95% confidence interval of the reported NOAEL ($NOAEL_5$) or LOAEL following the method of US EPA (Equation 2.6; USEPA, 1996). The RfD is usually determined by applying Uncertainty Factors (UF) to the $NOAEL_5$ to account for: (i) uncertainties associated with extrapolating from the experimental population to the study population at risk (UF_L) (e.g. extrapolating from an experimental rat population to a human): and/or (ii) the variability within receptor populations (UF_H),

(e.g. differences in the amount of contaminated media consumed, differences in the inherent susceptibility of different members of the population) (Barnes *et al.*, 1988).

$$RfD = \frac{NOAEL_5}{UF_L UF_H} \qquad (1.2)$$

For carcinogenic agents, it is often assumed that a threshold of effect does not exist. Instead, a cancer slope factor is derived from the NOAEL/LOAEL. This is derived as the slope of the linear extrapolation to the origin drawn from the 95% lower confidence interval on dose at the lowest prescribed risk level supported by the data (Subramaniam *et al.*, 2006).

5.1.4 Risk characterisation

The final stage is risk characterisation. For environmental risk assessment this involves calculating the Risk Quotient (RQ), which is the ratio of the predicted or measured environmental concentration (PEC/MEC) to the predicted no effect concentration (PNEC), i.e.:

$$RQ = \frac{PEC}{PNEC} \qquad (1.3)$$

For human health risk assessment, the Hazard Quotient (HQ) is calculated, which is the ratio of the Average Daily Dose (ADD) to the reference dose (RfD):

$$HQ = \frac{ADD}{RfD} \qquad (1.4)$$

If the ADD exceeds the RfD or if PEC exceed PNEC, HQ (Hazard Quotient) or the RQ (Risk Quotient) will be greater than 1 and we might expect to see deleterious effects. Due to the uncertainties associated with estimating risks, an HQ or RQ greater than 1.0 indicates an issue that may require further investigation. HQ less than or equal to 1.0 may be regarded as 'safe' (or negligible risk).

5.2 Pharmaceuticals selected for QRA

Table 4 shows key physico-chemical and ecotoxicological properties for pharmaceuticals selected for the QRA. The properties in Table 4 have been gathered from a range of chemical databases (ChemIDplus, ChemEurope.com, ChemSpider, US EPA's Aggregated Computational Toxicology Online Resource, PubChem, ECHA, EPI Suite) and consist of a mix of experimentally derived and estimated values. Because of limited data availability, many of the physico-chemical properties were estimated using EPI Suite developed by US EPA. EPI Suite is a collection of programs that can be used to estimate physical/chemical properties and environmental fate based on the structure of a chemical. It should be noted that many of the physico-chemical data are associated with large uncertainty. This is particularly the case for the organic carbon-water partitioning coefficient (K_{oc}) and the half-life of the substance in the different carrier media, two properties that have a critical influence on the behaviour and fate of the substance in the environment.

K_{oc} describes how strongly the substance will adsorb to soil and sediments (as well as to sludge in sewage treatment). K_{oc} can be determined experimentally but is often estimated based on the substance's $\log K_{ow}$ and a range of published regression models exist for this purpose. The EPI Suite programme provide estimate of K_{oc} based on both $\log K_{ow}$ and the molecular connectivity index (MCI). K_{oc} values can quite easily vary by orders of magnitude depending on the regression used for the estimation.

The half-lives determine how long the substance will persist in the environment. Data on degradability of the selected pharmaceuticals were very limited. Because of this, it was decided to supplement the limited available data with half-life estimates using BIOWIN, which is one of the programs included in EPI Suite. BIOWIN contains seven different models for estimating biodegradation, some of which are based on expert survey and some on regressions models. BIOWIN rates the time it takes to achieve ultimate and primary degradation of a compound in a 'typical' aquatic environment and groups these ratings into the 8 classes, which subsequently is assigned a half-life value as follows: Hours (0.17 days); Hours to days (1.25 days); Days (2.33 days); Days to weeks (8.67 days); Weeks (15 days); Weeks to months (37.5 days); Months (60 days); Recalcitrant

(180 days). In EPI Suite, it is furthermore assumed that the decay in soil and sediment is 2 and 9 times slower than in water. The half-life data and estimates are deemed to be associated with considerable uncertainty. In general, the more conservative estimates of the half-lives (Table 4) have therefore been chosen for the later risk assessment (see next section).

As shown in Table 4, all of the selected pharmaceuticals can dissociate in solution (their pKa values range between 4 and 10), meaning they have the potential to form ions in water. The ionization of a pharmaceutical can alter its physical behaviour and properties such as solubility and lipophilicity ($logK_{ow}$), e.g. ionization will increase the solubility in water, but decrease the lipophilicity. Understanding the ionic state of a pharmaceutical therefore provides important information on its potential mobility and persistence in the environment. However, the fugacity models applied as part of this project do not account for dissociation, which introduces further uncertainty into the calculation of the partitioning and the subsequent risks. It is beyond the scope of this project to fully account for ionization effects but is something that could be explored in future projects. Future work could also involve a critical review of the values used in Table 4 and whether these are representative under environmental conditions.

The ecotoxicological data are also scarce and associated with large uncertainty. While published PNEC values exist for all 5 pharmaceuticals (UKWIR, 2018; Loos *et al.*, 2018; SCHER, 2011), it has not been possible to find published reference dose (RfD) estimates for acute or chronic exposure for the selected pharmaceuticals. The RfDs have here been estimated based on reported NOAEL (USEPA, 2020; ECHA, 2020) and assuming a composite uncertainty factor of 10,000. It was not possible to find NOAEL or LOAEL values for clarithromycin; instead the RfD value for clarithromycin was assumed to be similar but slightly lower than the RfD for erythromycin based on a comparison of other ecotoxicological data (e.g. LD50 and EC50) for the these two pharmaceuticals.

Based on the physico-chemical properties in Table 4, it is already possible to suggest how these chemicals might behave once entering the environment. For example, all the substances have relatively high $logK_{ow}$ values (> 3) and K_{oc} values, which suggest that

they are likely to adsorb to organic matter in soil and sediments. They also all have very low vapour pressures and Henry's Law constants, which suggest that they are not volatile. The substances also generally have long half-lives in different media, which suggest that they are persistent or very persistent in the environment.

Table 4. Selected pharmaceuticals for the risk assessment with key physico-chemical properties and inputs. Sources: EPI Suite, ChemIDplus, PubChem, ChemEurope.com, ChemSpider, ACToR, ECHA.

Property	**Clarithromycin**	**Diclofenac**	**EE2**	**Erythromycin**	**Ibuprofen**
CAS number	81103-11-9	15307-86-5	57-63-6	114-07-8	15687-27-1
Molar weight [g/mol]	747.97	296.15	296.41	733.95	206.29
Solubility [mg/l]	1.69	2.37	11.3	4.24	21
log(K_{ow}) (1)	3.16	4.51	3.67	3.06	3.97
K_{oc} [m^3/kg] (2)	149.4	458	1917	567	422
Melting point [°C]	220	175	183	191	76
Acid dissociation (pKa)	8.99	4.15	10	8.88	4.91
Vapour pressure [mm Hg]	2.32E-25	6.14E-08	1.95E-09	2.12E-25	4.74E-5
K_H [atm-m^3/mol] (3)	1.73E-29	1.55E-10	7.94E-12	5.42E-29	1.5E-7
Half-life (decay) [days] (4)	0.03 (air) 180 (water) 360 (soil) 1620 (sediment) 0.04-0.3 (biota)	0.07 (air) 37.5 (water) 75 (soil) 337.5 (sediment) 6.1 (biota)	0.09 (air) 60 (water) 120 (soil) 540 (sediment) 0.03-1.5 (biota)	0.027 (air) 180 (water) 360 (soil) 1620 (sediment) 0.02-0.06 (biota)	0.9 (air) 15 (water) 30 (soil) 135 (sediment) 0.1-1.87 (biota)
PNEC [µg/l]	0.12	0.05	0.000035	0.2	0.01
RfD [mg kg_{bw}^{-1} day^{-1}]	1.0E-3	2.0E-4	5.0E-7	1.5E-3	4.0E-3

(1) Octanol-water partition coefficient

(2) Organic carbon and water distribution coefficient

(3) Henry's law constant

(4) Half-lives have in most case been estimated using BIOWIN.

5.3 Results: Risk assessment of selected pharmaceuticals

5.3.1 Estimating pharmaceutical concentrations in the environment

In order to carry out a risk assessment, the concentrations of the chemicals need to be determined in the different relevant carrier media (cf. Section 5.1.2). Table 5 shows a summary of the measured concentration levels of the five selected pharmaceuticals in surface waters, and influents and effluents of WWTPs in Scotland based on monitoring data from SEPA and a comprehensive literature review of pharmaceutical concentrations in the Scottish environment (Helwig *et al.,* 2022). While it was possible to find limited pharmaceutical concentration data in Scottish surface water, it was much harder to find data on the selected pharmaceuticals in sewage sludge, soil and sediment for Scotland (Section 2).

Multimedia fugacity modelling (Mackay, 2001) allows for estimating the concentrations of the substances in different environmental compartments based on their physico-chemical properties and total emissions to the environment. In this context, the emissions to the environment are assumed to originate from wastewater and sewage sludge. The total pharmaceutical emissions to the environment are estimated from the reported wastewater influent concentrations and the fact that about 996,000 m^3 of wastewater is treated every day in Scotland (Scottish Water, 2018).

It is assumed that the emissions to the water environment originate solely from discharges of wastewater effluents and therefore can be estimated from the reported effluent concentrations in Table 5. The emissions to the soil environment are assumed to originate from application of sewage sludge to land. It is assumed that the mass of pharmaceuticals in the sludge can be estimated from the difference in the measured influent and effluent concentrations and the amount of wastewater treated, i.e. that there is no degradation during wastewater treatment. The resulting concentration in dry sewage sludge (DS) can be estimated by assuming that 136,000 tonnes of dry sewage sludge is produced in Scotland annually (68 g DS day^{-1} $capita^{-1}$; (Evans, 2016)). It should be noted that the estimation of the emissions does not account for any reductions in pharmaceutical concentrations during the wastewater and sewage treatment process

and hence is likely to overestimate the emissions to the environment. This is therefore a conservative estimate which ensures that the risks to the environment will not be underestimated.

Table 5 shows the estimated annual emissions. These estimates are obviously very approximate but do agree reasonably well with the reported consumption data (Table 4). The main outlier is clarithromycin for which the emissions are estimated ~2250 kg/yr but the consumption is only reported to 98 kg. For the other compounds, the emissions are lower than the consumption data, which seems reasonable if it is assumed that not all of the consumed pharmaceutical will end up in the waste streams (e.g. due to breakdown in the human body). It is not clear why the estimated clarithromycin emissions are higher than the consumption data, but it could be due to the uncertainty associated with both the emission estimates and the consumption data, e.g. detailed data for over-the-counter sales of medicines are not readily available for the UK (Helwig *et al*., 2016).

Based on the estimated emissions (Table 5) and the physico-chemical properties (Table 4) it is now possible to calculate the concentrations in air, water, soil, sediment, fish and suspended solids for an assumed 'unit world' representing Scotland (Table 6) using multimedia fugacity-based modelling (Mackay, 2001). Most of the inputs for the modelling are based on the Equilibrium Criterion (EQC) model default values. For this application, the water area in the model is assumed to be the area of Scotland covered by water, while the soil area in the model is assumed to be the area of arable land in Scotland.

Table 5 shows the calculated concentrations in water, soil, sediment and fish using both Level I and Level III fugacity modelling. The Level I calculated concentrations in water are generally about 5-25 times higher than the corresponding Level III ones (however, note these concentrations cannot be directly compared as Level I is based on a one-time input of pollutant, whereas Level III is based on a continuous rate). A comparison of the modelled and the measured concentrations in water shows that there is a reasonably good agreement with the level III calculated concentrations generally being at the lower end of the measured ones. This gives some confidence that the predicted concentrations in the other environmental compartments are reasonable. It should be stressed that the

predicted concentrations are very uncertain and will depend on, for example, the assumed size and properties of the "unit world", and the input values in Table 4. Also, as previously noted, the effect of dissociation is not accounted for, which might mean that the propensity for partitioning into the solid and soluble phases are over- and underestimated, respectively. Thus, the calculations can therefore mainly be used to give an indication of where and to what extent a given pharmaceutical will partition in the environment.

The application of sewage sludge to land, whether directly on to the soil surface or through incorporation into the topsoil (e.g. through ploughing), will potentially directly expose the soil and any associated crops to pharmaceuticals. The migration of pharmaceuticals, in particular from soil to plants, could facilitate a potential entry pathway into the human food chain and subsequent human exposure (Colon and Toor, 2016). In order to quantify this exposure, the concentrations in crops resulting from plant uptake need to be estimated. This is done here using the standard plant uptake model developed by Trapp and Legind (2011) (see Appendix A) and using the estimated soil concentrations from the multimedia modelling as input. As an additional worst-case scenario, it was assumed that sewage sludge with pharmaceutical concentration levels as estimated in Table 5 were applied to land at a rate of 25 tonnes/ha and mixed in with the upper 0.2 m of soil. The resulting pharmaceutical concentrations in soil are also given in Table 5 and were used to calculate worst-case concentrations in crops. The resulting concentrations in crops are also shown in Table 5.

Table 5. Measured mean and modelled concentrations of the selected pharmaceuticals in different media (µg/l). The measured concentration values are from a database collated as part of the CREW project (Helwig *et al.*, 2022), where average concentration values were reported for different environmental media (e.g. surface waters and wastewaters) across different locations in Scotland. In the table below, measured concentrations are presented as the average of those means across all locations; the range in mean values is given in brackets.

	Clarithromycin	**Diclofenac**	**EE2**	**Erythromycin**	**Ibuprofen**
Measured concentrations					
WWTP influent,	0.82 (0.01 –6.7)	0.49 (0.04 - 2.0)	4.3e-4	0.7 (0.02 –2.6)	9.9 (0.47 – 39.6)

measured mean [µg/l]			(1.4e-4 – 1.6e-3)		
WWTP effluent, measured mean [µg/l]	0.51 (0.02 – 1.32)	0.26 (0.04 – 0.72)	3.5e-4 (3.4e-5 – 1.1e-3)	1.0 (5e-3 – 17)	0.6 (6e-3 – 4.4)
Surface water, measured mean [µg/l]	0.05 (2e-5 – 0.48)	0.10 (8e-4 – 0.56)	4.0e-5 (1.5e-5 – 1.8e-4)	0.27 (2.5e-3 – 11.1)	0.14 (1.0e-3 – 0.94)
Surface water, measured max [µg/l]	1.25	2.2	1.7	14	6.6
% surface water samples above PNEC	11.5%	23.5%	30.8%	15.5%	90.6%
Consumption and estimated emissions to the environment					
Total Consumption [kg/yr] (1)	98	3177	1	2086	16289
Total emissions [kg/yr] (2)	2250	730	0.58	1100	12700
Emissions to water [kg/yr] (3)	500	230	0.39	1000	1200
Emission to soil [kg/yr]	1750	500	0.19	100	11500
Estimated concentration in sewage sludge (mg/kg DS) (4)	12.85	3.67	0.00136	0.73	84.46
Modelled concentrations					
Water concentration, Level III (Level I) [µg/l]	0.0023 (0.0356)	3.0E-4 (0.008)	6.3E-07 (2.4E-06)	0.002 (0.010)	0.001 (0.140)
Soil concentration, Level III (Level I) [µg/kg]	0.86 (0.26)	0.08 (0.17)	4.6E-05 (2.0E-4)	0.07 (0.28)	0.71 (2.83)
Soil concentration, realistic worst -case [µg/kg] (5)	107.1	30.6	0.01	6.12	703.8

Sediment concentration, Level III (Level I) [µg/kg]	0.008 (0.40)	0.003 (0.27)	3.8E-05 (3.4E-4)	0.03 (0.44)	0.007 (4.42)
Concentration in fish, Level III (Level I) [µg/kg]	0.17 (2.57)	0.54 (12.47)	1.5E-4 (5.6E-4)	0.12 (0.60)	0.53 (65.1)
Concentration in root crops, Level III (realistic worst-case) [µg/kg]	0.88 (109.5)	0.05 (19.9)	5.7E-06 (1.4E-3)	0.02 (1.6)	0.44 (430.8)
Concentration in leafy crops, Level III (realistic worst-case) [µg/kg]	2.59 (322.6)	0.01 (5.0)	6.5E-06 (1.6E-3)	0.06 (5.4)	0.21 (203.8)

(1) Consumption data are from PCA and HMUD (Helwig *et al.*, 2016)

(2) Estimated by multiplying the WWTP influent concentration with 996,000 m^3/day of treated wastewater.

(3) Estimated by multiplying the WWTP effluent concentration with 996,000 m^3/day of treated wastewater.

(4) Estimated by dividing the emissions to soils by a sewage sludge production of 136,000 tonnes/yr.

(5) Estimated by using the estimated pharmaceutical concentration in sewage sludge (Table 5) and assuming a sewage sludge application rate of 25 tonnes/ha and mixing in the top 20 cm of soil.

Table 6. Assumed "unit world" for fugacity modelling.

	Air	**Water**	**Soil**	**Sediment**
Area [ha]	865,800	240,000	625,800	240,000
Depth [m]	1000	20	0.2	0.05
Organic carbon content [g/g]	-	-	0.03	0.04
Bulk density [kg/m^3]	1.19	1000	1500	1280
Water volume fraction	-	1	0.3	0.8

Air volume fraction	1	-	0.2	-
Solid volume fraction	0	5e-6	0.5	0.2
Biota volume fraction	-	1e-6	-	-

5.3.2 Risk to surface water and aquatic organisms

The concentrations reported for surface water in Table 5 can be directly compared to the PNEC values in Table 4 to give an indication of the risk to surface water and aquatic organisms (cf. Equation 1.3). This comparison shows that the average concentrations of all 5 pharmaceuticals have been observed to be higher than the PNEC and hence suggest that there is an unacceptable risk to surface waters. The review showed that around 90% of the reported concentrations of ibuprofen in surface water were above the PNEC, while the same was the case for about 30%, 15%, 25% and 10% of the average concentrations of EE2, erythromycin, diclofenac and clarithromycin, respectively (Helwig *et al.,* 2022). It should also be noted that the measured concentrations in surface water might be biased towards higher concentrations as previous studies and sampling campaigns are likely to have focussed on higher risk areas. Also, most of the measured concentrations were generally taken just outside the mixing zone of a WWTW with low dilution and hence likely to misrepresent the true situation as further down the reach of rivers, risk will have reduced owing to additional dilution, degradation and partitioning. This agrees with the fact that the concentrations in water calculated using multimedia modelling were in general lower than the measured ones and about 1-2 orders of magnitude below the PNEC values. However, as already mentioned, the modelled concentrations are dependent on a vast range of assumptions and hence associated with large uncertainty.

5.3.3 Risk to human health

5.3.3.1 Ingestion of food crops

The human exposure to hazardous agents via intake of food crops is calculated as:

$$ADD_{\text{crop}} = \frac{C_{crop} R_{\text{crop}}}{BW} \qquad (3.1)$$

where ADD_{crop} (mg kg^{-1} day^{-1}) is the Average Daily Dose through ingestion of crops, C_{crop} (mg kg^{-1}) is the concentration of the specific pharmaceutical in the ingested crop as estimated through the modelling (Table 5), R_{crop} (kg day^{-1}) is the ingestion rate of crops and BW (kg) is the body weight of the human receptor (Table 7). It is assumed that all crop produce is eaten raw.

ADD_{crop} has been calculated for two different human receptor groups (Table 7) and using the calculated concentration in crops based on both the Level III and the realistic worst-case calculation (Table 5).

The results of this scenario are shown in Figure 4 – Figure 5. It is found that when using the crop concentrations based on the Level III calculations, the estimated doses for each of the pharmaceuticals are well below their respective reference doses and hence do not pose a risk to human health (i.e. HQ<1, cf. Eq. 1.4).

If the predicted crop concentrations from the worst-case scenario are used instead, the estimated doses increase by approximately 2 orders of magnitude due to the significantly higher concentrations in soil. While the HQ for an average person remain below 1, it is found that the HQ of clarithromycin, diclofenac and ibuprofen are above 1 for the highly exposed infant receptor group. This could suggest that there might be a potential risk to more vulnerable receptor groups from these three pharmaceuticals but given the uncertainties and limitations of the QRA method, further investigations are required to confirm this. It should also be noted that for the worst-case scenario the estimated pharmaceutical concentrations in the applied sewage sludge and the resulting concentrations in soil are much higher than the concentration levels reported in the literature (Section 2). It is assumed that all vegetables eaten are from similarly treated and exposed fields, which is unlikely to be the case in real life with local foodstuffs making up only a small proportion of an individual's diet in the UK. It is also assumed that the entire crop is eaten raw, which is only relevant for some foodstuffs. Finally, as already mentioned, the fugacity calculations used for estimating the concentrations in the different media are associated with considerable uncertainty and will be strongly affected by the properties used as inputs (Table 4). As discussed previously, the influence of

dissociation is not accounted for, which can have a strong impact on how the pharmaceutical partitions in the environment.

5.3.3.2 *Ingestion of untreated surface water*

The human exposure to hazardous agents via ingestion of untreated surface water (e.g. for some private water supplies) is calculated as:

$$ADD_{\text{water}} = \frac{C_{water} R_{\text{water}}}{BW} \qquad (3.2)$$

where ADD_{warwe} (mg kg^{-1} day^{-1}) is the Average Daily Dose through ingestion of water, C_{water} (mg l^{-1}) is the concentration of the specific pharmaceutical in the private water supply sourced from surface water and R_{water} (l day^{-1}) is the ingestion rate of that water (Table 7). The concentration in water is assumed to be the measured concentration in surface water (Table 5), which is clearly a very conservative assumption as the pharmaceutical concentration is expected to be reduced by dilution in surface water; this can therefore be considered as worst-case scenario. Worst-case scenarios were considered for this work to ensure that risks were not under-estimated.

The results of this scenario are shown in Figure 4 – Figure 5. It is found that the estimated pharmaceutical doses through ingestion of surface water are well below their respective reference doses for both receptor groups (i.e. HQ<1), and this exposure pathway is therefore not considered to pose a risk to human health. The highest HQ is estimated for erythromycin at 0.004-0.02, which is also not deemed to be a risk.

5.3.3.3 *Dermal uptake through direct skin contact*

The chemical absorption through the skin largely occurs by diffusion from the contaminated media (water, soil etc.) in contact with the skin into the body tissue. The driving force for this process is the concentration gradient from the media in contact with the skin to the body tissue. As the concentration of most contaminants in the body tissue is usually considered negligible, the rate of adsorption is roughly proportional to the concentration in the media in contact with the skin (EA, 2009). Various factors affect skin

absorption of contaminants, including media type (e.g. soil or water), physico-chemical properties of the contaminant (e.g. lipophilicity) contact time, and skin-specific factors such as thickness, ageing and hydration (USEPA, 1992). Some studies suggest that contaminants that are highly soluble in both fat and water are most likely to be adsorbed through skin, but the process is complex and affected by a number of competing factors (e.g. lipophilic contaminants are more likely to penetrate skin, but are also more likely to adsorb to soil, if this is the media considered).

The Average Daily Dose through dermal uptake is calculated differently depending on what contaminated media the skin is in contact with. This study considers dermal uptake of pharmaceuticals from water during leisure activities such as wild swimming. The human exposure to hazardous agents via dermal uptake from water is calculated as (USEPA, 1992):

$$ADD_d^w = \frac{C_w \times K_p^w \times t_{event} \times EV \times A_{skin}}{BW} F_d \qquad (3.3)$$

where C_w (mg/ml) is the concentration of pharmaceuticals in surface water, K_p^w (cm hr^{-1}) is a contaminant-specific permeability coefficient through skin from water, t_{event} (hr/event) is the duration of the exposure event, EV is the number daily contact events, A_{skin} is the exposed skin area (cm^2) (Table 7) and F_d is fractional time of dermal exposure.

Experimentally derived K_p^w values for different contaminants can be found in the literature (e.g., USEPA, 1992; Bogen, 2013). Several regression models have also been developed to estimate K_p^w, mainly for organic contaminants, based on K_{ow} and molar weight (MW, g mol^{-1}). Because experimentally derived K_p^w values are not available for the 5 pharmaceuticals considered in this project, we have used the following regression model to estimate K_p^w (US EPA, 1992):

$$k_p^w = -2.72 + 0.71 \times logK_{ow} - 0.0061 \times MW \qquad (3.4)$$

It is assumed that a human receptor is doing leisure activities in surface water 50 times per year (i.e. about once a week every year) and for 1 hour every time. It is furthermore assumed that during the activity the human receptor accidentally ingest water at a rate given in Table 7.

The results are shown in Figure 4 – Figure 5. The estimated average daily doses of pharmaceutical through direct dermal contact are found to be much lower than the corresponding reference doses and this exposure scenario is therefore deemed very unlikely to pose any significant risk to human health.

Table 7. Input for risk assessment scenarios.

Receptor - Human health	**Average person**	**Highly exposed infant**
Body weight [kg] (Hough *et al.,* 2012)	74	13
Body surface area [m^2] (US EPA,2003)	1.82	1
Water ingestion rate [l/day] (US EPA,2003)	1.05	0.7
Root crop intake [kg/d] (Hough *et al.*, 2004)	0.1	0.1
Leafy green intake [kg/d] (Hough *et al.*, 2004)	0.1	0.1
Fruit intake [kg/d] (Hough *et al.*, 2004)	0.05	0.04
Water ingestion while swimming [l/hr] (US EPA)	0.02	0.12

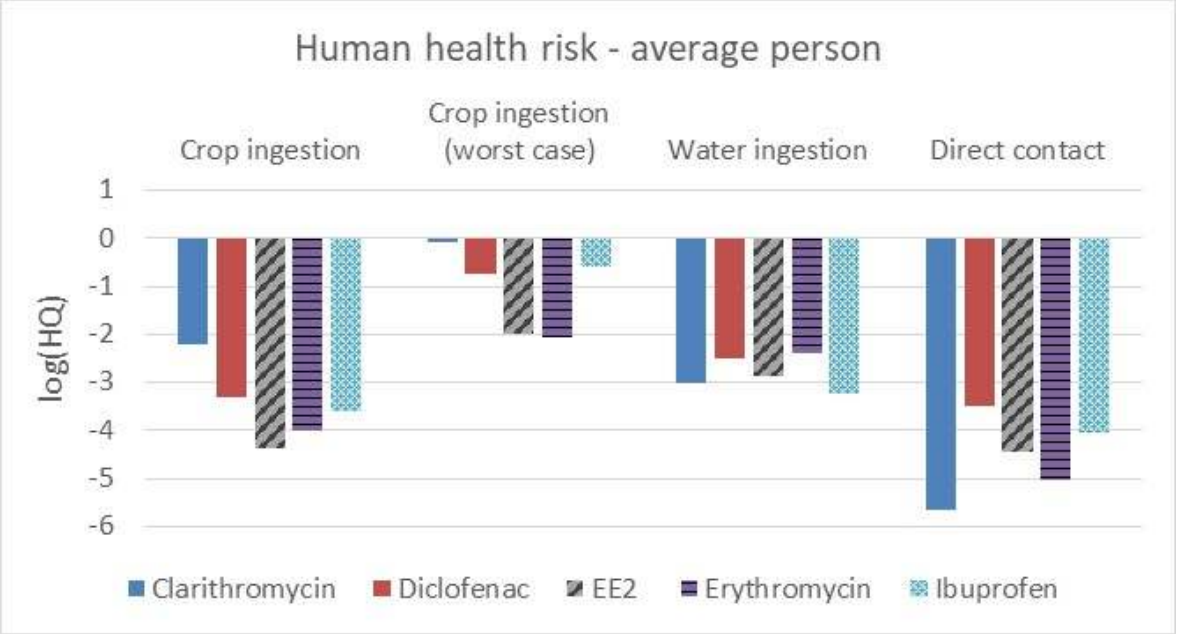

Figure 4. Risk assessment of an average human receptor (see definition in Table 7) exposed to pharmaceutical through three different exposure scenarios (crop ingestion, surface water ingestion and direct dermal contact). The risk is shown as estimates of the hazard quotient, log (HQ), for each pharmaceutical based on the ratio of the estimated average daily exposure dose to their respective reference doses (RfD) (Table 4). A log (HQ) > 0 indicates that further investigation may be required.

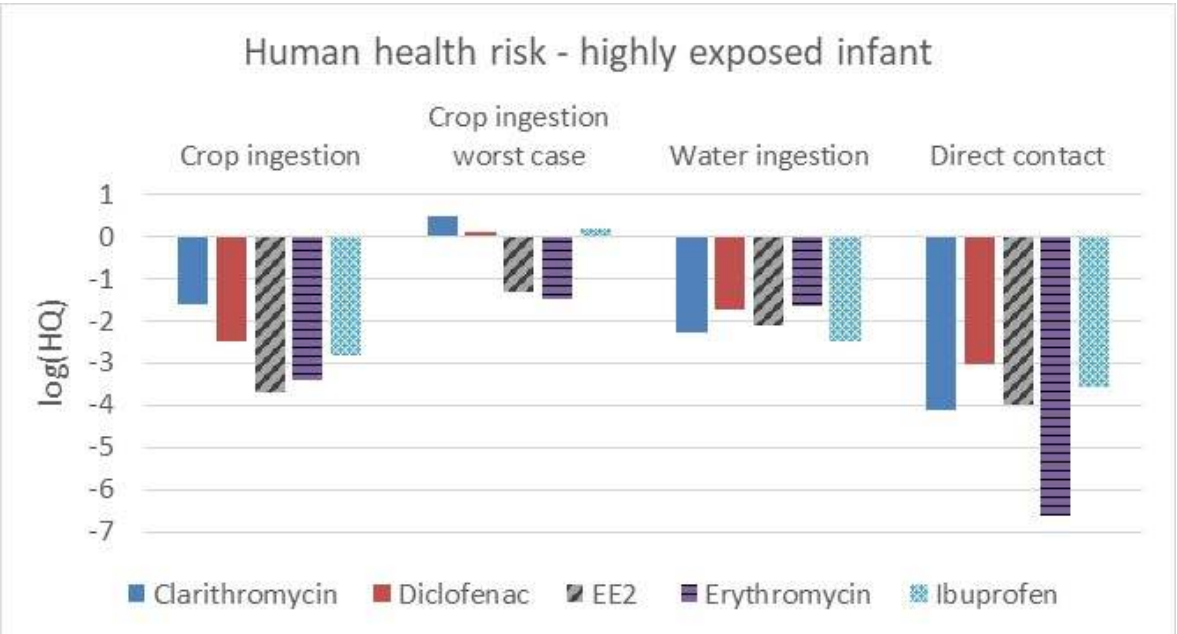

Figure 5. Risk assessment of a highly exposed infant receptor (see definition in Table 7) exposed to pharmaceutical through three different exposure scenarios (crop ingestion, water ingestion and direct dermal contact). The risk is shown as estimates of the hazard quotient, log (HQ), for

each pharmaceutical based on the ratio of the estimated average daily exposure dose to their respective reference doses (RfD) (Table 4). A log (HQ) > 0 indicates that further investigation may be required.

5.4 Summary

1. For all five short-listed pharmaceuticals (ibuprofen, clarithromycin, erythromycin, diclofenac and EE2), the measured concentrations in Scottish surface waters have at some point been observed to be above the Predicted No Effect Concentration (PNEC). This was especially the case for ibuprofen, for which the measured concentration (from the CREW database; Helwig *et al.*, 2022) in around 90% of the cases exceeded the PNEC. For the other 4 pharmaceuticals, the PNEC was exceeded generally between 10-30% of the cases. This suggests that there is a potential risk to surface waters and aquatic organisms, which merits further investigation. However, it should be noted that the measured concentrations in surface water are likely to be biased towards higher concentrations as many of the data have been taken just outside the mixing zone of a WWTW with low dilution, and hence unlikely to represent the true situation as dilution, degradation and partitioning further down the reach of the rivers are not accounted for. Further work is needed to understand how these results translate to the wider surface water environment.
2. The multimedia fugacity-based modelling could be used to estimate pharmaceutical concentrations in different environmental compartments and media (soil, water, air, sediment, plants, and fish) based on the physico-chemical properties of the pharmaceuticals and estimates of emissions to the environment. It was found that the modelled concentrations in water were generally within an order of magnitude of the measured ones, hence giving some confidence in the predicted concentrations in the other compartments. However, it was also found that there was a lack of reliable physico-chemical data required as input for the fugacity calculations. In many cases, it was necessary to use estimated values of key properties. More information and data are needed, as estimates of key properties for pharmaceuticals with functionality subject to e.g. dissociation introduce uncertainty into the predicted concentration estimates.

3. Due to the uncertainties associated with the risk assessments, worse case scenarios were used so that risks were not under-estimated. Under a worst-case scenario, vulnerable human receptor groups could experience a potential risk of unacceptable exposure to some pharmaceuticals through ingestion of food crops grown on land treated with sewage sludge, with the Hazard Quotient of clarithromycin, ibuprofen and diclofenac exceeding 1. However, this was based on a worst-case assumption regarding the concentrations of pharmaceutical in sewage sludge and amounts applied to land (e.g. reductions in pharmaceutical concentrations during the wastewater and sewage treatment process were not accounted for). The estimated concentrations in sewage sludge for this scenario were therefore generally much higher than what has been reported in previous studies (Section 2) and in the international literature (USEPA, 2009). Further investigations are required to confirm whether exposure through the food chain poses a risk.
4. Ingestion of untreated surface water (e.g. from private water supplies) and direct skin contact with surface water during leisure activities are unlikely to pose a risk to human health.
5. This work has highlighted that further research is required regarding risk via both the terrestrial and aquatic environment, with significant research required on the latter.

6. Recommendations

Based on the literature review, the following is recommended:

1. Due to the disparity between the diversity of pharmaceuticals studied in the aquatic vs the terrestrial environment, is it recommended that more research is focussed on pharmaceutical prevalence in terrestrial environments.
2. The literature review in this project did not consider the prevalence of veterinary pharmaceuticals, so this should be considered in further studies.

Based on the modelling and risk assessment, the following is recommended:

3. The presented QRA considered four exposure scenarios. However, future work could look at expanding this to consider other risk scenarios such as bioaccumulation in fish and subsequent entry in the human food chain, risk of exposure to livestock, and risk to terrestrial organism and wildlife. Future work could also look at modifying the presented QRA approach and run the model scenarios "in reverse", starting from the pre-defined acceptable risk level at the receptor point and back-calculate the corresponding acceptable concentration levels in the source (Troldborg *et al.*, 2017). In this way the QRA can be designed to inform the level of water treatment required to achieve an acceptable risk level.
4. The presented QRA method relies on a vast number of inputs and assumptions and the results are therefore associated with large uncertainties. The behaviour and fate of the considered pharmaceuticals are still not well-understood, and it was difficult to find reliable data on their physico-chemical and ecotoxicological properties on which the risk assessment is based. Due to the many uncertainties, conservative assumptions have been adopted throughout the QRA (as is commonplace) to ensure that the risks are not underestimated. However, future work should aim to address the many sources of uncertainties in the QRA, for example by using probabilistic or possibilistic approaches to propagate uncertain inputs through the model (see e.g. (Troldborg *et al.*, 2017).
5. The assessment here only considers risk from individual pharmaceuticals. There is an increasing focus on the issue of mixtures of pharmaceuticals and their actions, but the evidence is still in its infancy, and comprehensive data are not

available for all combinations of chemicals possibly present in sewage sludge and effluent.

7. Appendix A: Modelling uptake of organic contaminants by plants

The application of sewage sludge to land, whether directly to the soil surface or through incorporation into the topsoil, will directly expose the soil and any associated crops to organic contaminants. The uptake of pollutants, in particular from soil to plants, could facilitate a potential entry pathway into the human food chain and subsequent human exposure. The magnitude of plant uptake, as well as the pathway by which organic contaminants enter vegetation is a function of the chemical and physical properties of each pollutant. Experiments and model simulations have shown that persistent, polar ($\log K_{ow} < 3$) and non-volatile contaminants generally have the highest potential for accumulation from soil into plants. Concentrations in roots and leaves may even exceed the concentrations in soil (in some cases by several orders of magnitude), which among other things is because the water content in roots (up to 95%) is usually higher than in soils (about 30%). Volatile contaminants have a low potential for accumulation because they quickly escape to air (Trapp and Legind, 2011).

The crop type influences which uptake processes are more likely to be dominant. For example, the accumulation of contaminants from soil will be higher for root crops than for tree fruits, while the uptake from air (if the pharmaceutical is likely to be volatile or airborne) is higher for fruits. The degree to which physiological plant-specific parameters such as leaf area, transpiration rate, water and lipid contents as well as growth rate affect the uptake is highly dependent on the properties of the contaminant of interest. Water soluble contaminants will usually be rapidly translocated from soil to leaves, and the accumulation in leaves will in this case almost entirely be decided by transpiration rate (Trapp and Legind, 2011).

The uptake of contaminants by plants can be estimated in different ways. A simple way of doing this is through bioconcentration factors (BCFs), which express the ratio of contaminant concentration in an organism (here, the crop plant) to contaminant concentration in the surrounding medium. Measurements of concentrations in plant tissues and concentrations in soil will yield a BCF plant to soil, given by:

$$BCF = \frac{C_{plant}}{C_{soil}} \quad \text{(A.1)}$$

where C_{plant} is the concentration in plant tissues and C_{soil} is the concentration in soil (ideally at steady state, but practically at harvest). BCFs (or regression equations relating BCF to contaminant-specific properties) are usually determined through controlled experiments in the laboratory or in the field. It is important to note that BCFs will only be valid for the exact conditions under which they are estimated, i.e. for the specific contaminant and soil type used for the determination.

A range of mechanistic models capable of simulating plant uptake of organic contaminants furthermore exists (e.g., Fujisawa, 2002; Hung and Mackay, 1997; Passuello *et al.*, 2010; Paterson *et al.*, 1994; Rein et al., 2011; Trapp, 2004; Trapp and Matthies, 1996). These models vary in complexity and usually aim at determining the uptake for specific crop types. Many of these models are based on a multimedia modelling principle, where mass balances are set up and combined for the different compartments considered (e.g., soil, roots, and leaves) assuming equilibrium partitioning. These models are then used to simulate the partitioning, transfer, and fate of chemical pollutants within and between the different plant compartments. The processes and their parameterization depend on the type of crop and the contaminant properties.

For the pharmaceuticals considered in this project, published BCF factors were not available in the literature, and the standard plant uptake model described in (Trapp and Legind, 2011) was therefore applied instead. The standard plant uptake model includes the compartments soil, roots and leaves (or grains) and is able of accounting: i) continuous and/or pulse input to all compartments, ii) uptake into roots with the transpiration water, iii) translocation from roots to leaves/grains with the transpiration stream, iv) loss from leaves to air, v) deposition from air to leaves, vi) transport to leaves with attached soil, vii) growth dilution, degradation and metabolism in roots and viii) loss from soil due to degradation, leaching, run-off and plant uptake. To maintain the precautionary approach, only the steady-state solution for a continuous source concentration is applied here. Finally, because air-phase partitioning and transport is

very limited for the considered pharmaceuticals, deposition of particles on the surfaces of leaves or grains is neglected and uptake from air is assumed solely by diffusive exchange in the gas phase. The steady-state expressions are given by:

$$C_{\text{roots}} = \frac{Q}{\frac{Q}{K_{\text{rw}}} + k_r M_r} C_{w,\text{soil}} \qquad \text{(A.2)}$$

$$C_{\text{plant}} = \frac{\frac{Q_p}{K_{\text{pw}}} C_{\text{roots}} + A_p g_p C_{\text{air}}}{\frac{K_H}{K_{\text{pw}}} A_p g_p + k_p M_p} \qquad \text{(A.3)}$$

where C_{roots} and C_{plant} are respectively the concentrations in the roots and plant (here: leaves or grains), $C_{w,\text{soil}}$ and C_{air} are the concentrations in soil water and air, respectively, K_H is the dimensionless Henry's constant, and k_r and k_p are first-order growth rates of the roots and leaves/grains, respectively. K_{rw} and K_{pw} are the equilibrium partition coefficients between roots and water and between leaves/grains and water, respectively. These can be determined through the following empirical expressions:

$$K_{\text{xw}} = W_x + 1.22 L_x \qquad \text{(A.4)}$$

where W_x and L_x are the water and lipid content of either roots, leaves or grains and b is a correction factor for differences between solubility in octanol and sorption to plant lipids. Based on previous studies, b can be assumed to be 0.77 for roots and 0.95 for leaves/grains (Trapp and Legind, 2011). Plant specific parameters and inputs used for the calculation are shown in Table A1.1.

As seen from the above equation, the concentrations in soil water and air are needed to estimate the accumulated concentrations in roots and leaves/grains. These can be estimated using fugacity modelling (Mackay, 2001) as described in Section 5.2.

Although more sophisticated plant uptake models capable of simulating the dynamic behaviour of the soil-plant system exist, the above more simple approach for estimating the uptake of organic contaminants into crop plants is considered appropriate for risk assessment purposes. The steady-state solution is likely to overestimate the

concentrations in the crops by orders of magnitude, which is in line with the precautionary approach used throughout this project.

Table A1.1. Default input data set for the standard model for the calculation of plant uptake (normalised to 1 m² of soil). From (Trapp and Legind, 2011).

Symbol	Input [unit]	Value
Roots		
W_r	Water content of roots [L/kg]	0.89
L_r	Lipid content of roots [L/kg ww] [1]	0.025
Q	Transpiration stream [L/d]	1
M_r	Root mass [kg ww]	1
k_r	First-order growth rate [1/d]	0.1
Leaves/grains		
A_p	Area of leaves [m²]	5
	Area of grains [m²]	1
W_p	Water content of leaves [L/kg]	0.8
	Water content of grains [L/kg]	0.15
L_p	Lipid content of leaves/grains [L/kg ww]	0.02
M_p	Mass of leaves/grains [kg ww]	1
ρ_p	Density of leaves/grains [kg ww/L]	1
g_p	Conductance of leaves/grains [m/d]	86.4
k_p	First-order growth rate for leaves/grains [1/d]	0.035
Q_p	Transpiration stream for leaves [L/d]	1
	Transpiration stream for grains [L/d]	0.2

[1] ww = wet weight

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