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1 Introduction

Pharmaceuticals are essential for modern healthcare, yet their widespread and continuous use results in the release of active pharmaceutical ingredients (APIs) into the environment. Following consumption and excretion, or through direct disposal, these substances enter wastewater systems and may subsequently reach surface waters, sediments, and soils. While regulatory environmental risk assessments are routinely conducted for new medicinal products, many legacy or widely used existing pharmaceuticals were authorised before current environmental regulatory requirements were established. As a result, there remains a need to better characterise their environmental exposure and associated risks under real-world conditions.

This report presents an environmental risk assessment of existing pharmaceutical compounds, integrating monitoring data, emissions modelling, and multimedia fate modelling. The work includes measured environmental concentrations (MECs) and predicted environmental concentrations (PECs) derived from spatially resolved emissions estimates and continental-scale fate modelling. By comparing empirical observations with modelled exposure estimates, the study aims to evaluate the (in)consistency between measurement- and model-based approaches, highlighting areas for future research.

The risk assessment is based on a collation of monitoring data across a broad selection of databases and literature, covering surface waters and soils. It compares these MECs to hazard values from a recently published library of species sensitivity distributions (Posthuma et al., 2019) and other sources, alongside detection frequencies, to rank APIs in terms of those that present the highest risk to the environment. These results are compared to other risk ranking exercises, and placed in the context of PECs from the exposure modelling work. Finally, we use our findings to highlight priorities for future research towards better understanding of pharmaceuticals in the environment.

2 Collation of monitoring and hazard data

To predict the pan-European risk of in-use pharmaceuticals to the environment exposure monitoring data alongside ecotoxicological data has been collated from numerous sources for freshwaters and soils. Available freshwater and soil data for APIs and their transformation products for both human and veterinary use were collated, excluding personal care and medical imaging products.

2.1 Freshwater

For freshwaters, available temporal exposure monitoring data (from 1994-2022) was collected from the Environment Agency (EA) Water Quality archive, EA LC-MS and EA GC-MS datasets (n=114,190 across 156 APIs), Germany Environment Agency UBA database (n=53,457 across 618 APIs), NORMAN database (n=33,675 across 119 APIs), UK Water Industry Research Chemical Investigation Program archive (n=31,985 across 148 APIs), European Commission Navigation and Inland waterway Action and Development in Europe (NAIADES) (n= >100,000 across 154 APIs) and scientific literature (n=2,815 across 42 APIs). In total, freshwater measurements were gathered across 33 European countries (Austria, Belgium, Bulgaria, Croatia, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Luxembourg, Malta, Moldova, Netherlands, Norway, Poland, Portugal, Romania, Serbia, Slovakia, Spain, Sweden, Switzerland, Ukraine and United Kingdom) for 677 APIs. Ecotoxicological data was gathered from an available freshwater species sensitivity distributions (SSDs) resource (Posthuma et al., 2019) for 829 APIs. The top 5 APIs (with hazard data) with the highest exposure concentrations in freshwaters were cetirizine (antihistamine), cotinine (nicotine metabolite), furosemide (diuretic), azithromycin (antibiotic) and caffeine (stimulant) (Figure 1).

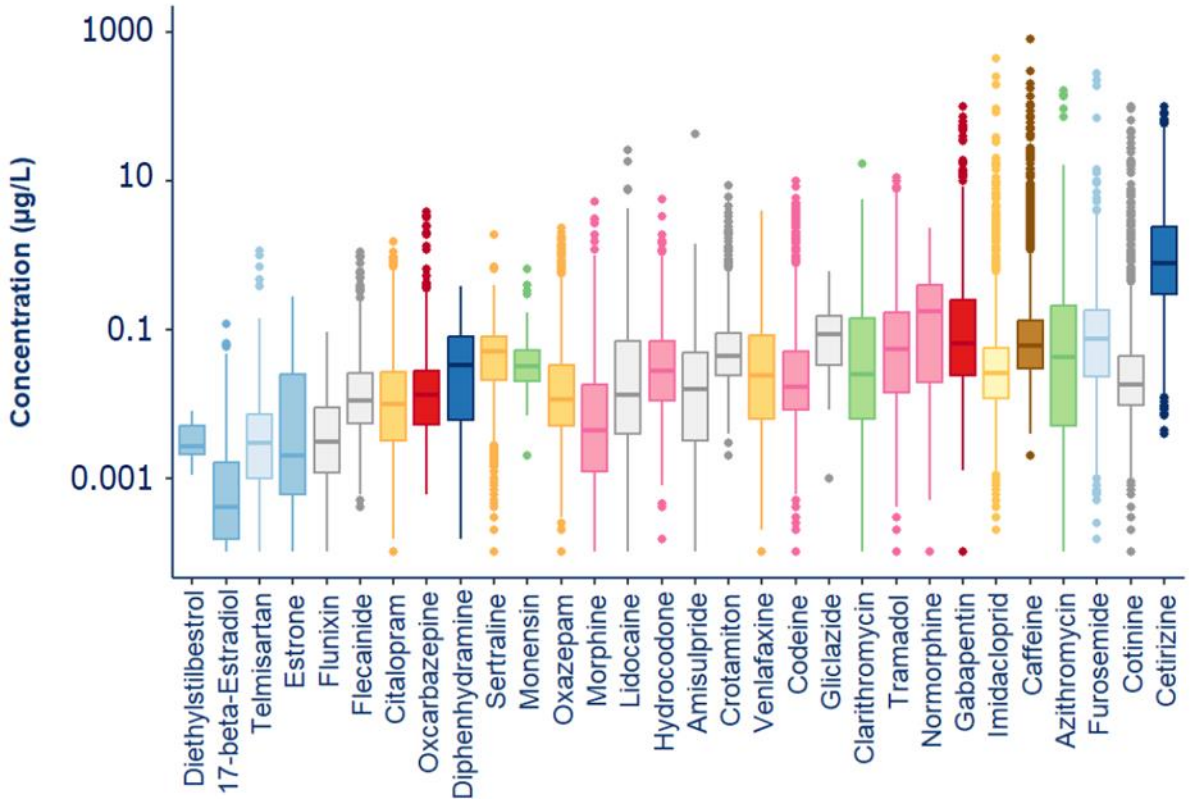


Figure 1. Concentration range of top 30 APIs detected in freshwaters

2.2 Soils

For soils, available temporal exposure monitoring data (from 2000-2015) was collected from the Germany Environment Agency UBA database (n=677 across 93 APIs), from 10 countries across Europe, including the United Kingdom. Ecotoxicological data was gathered from the literature in Web of Science to collect published studies on EC_{50} concentrations for earthworms (*Eisenia* species) in terrestrial environments, using the following search string:

TS=(eisenia) AND (TS=(toxic*) OR TS=(dose response)) AND (TS=(soil*) OR TS=(terrestrial)) AND (TS=(pharma*) OR TS=(drug*) OR TS=(antibiotics)) (search conducted on 13/11/2025).

A total of 122 papers were screened for relevance, and 11 papers passed the criteria with reporting studies with 3 or more concentrations tested within the *Eisenia* API ecotoxicity tests. Available ecotoxicological data (EC_{50} and LC_{50}) for mortality and reproduction endpoints were extracted for 16 APIs across the analgesic, antibiotic, beta-blockers, lipid-lowering, UV filter and

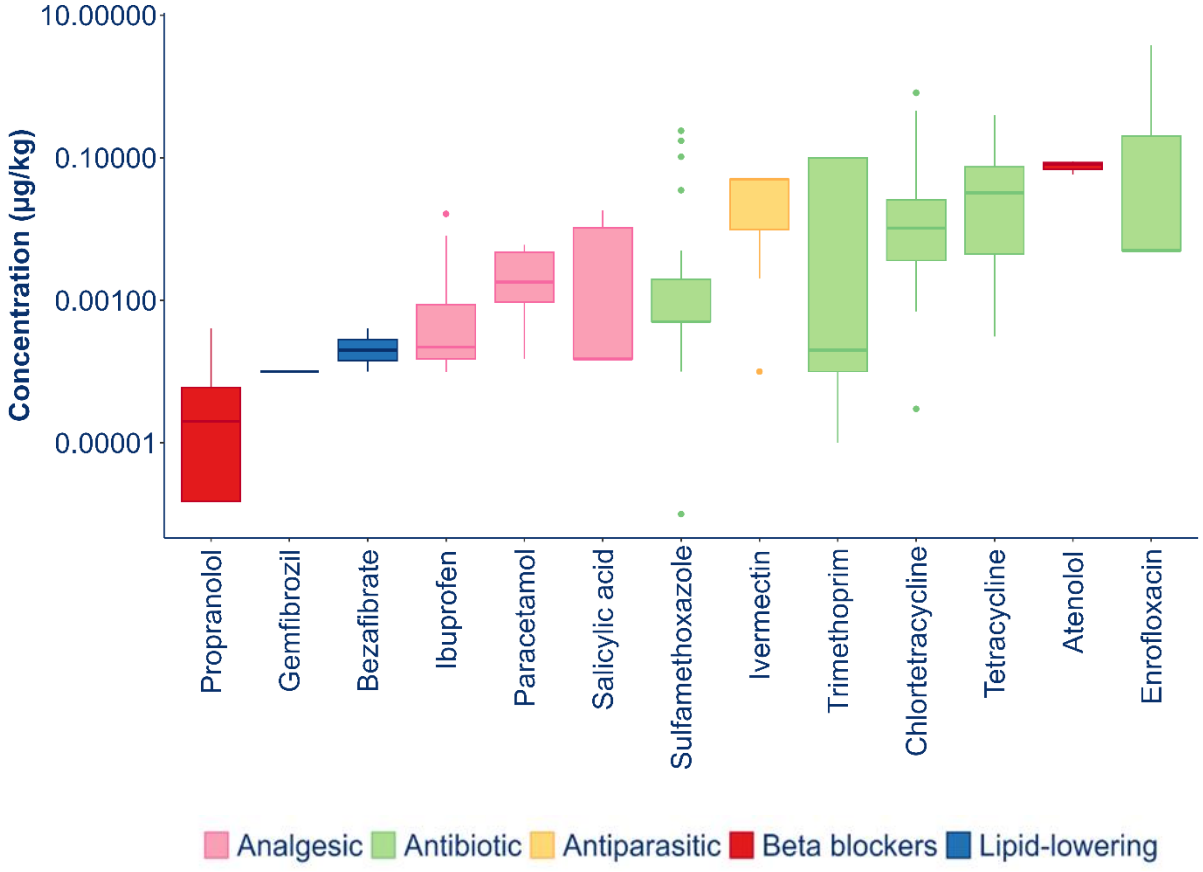


Figure 2. Concentration range of all APIs detected in soils with hazard data

veterinary drug groups. Ecotoxicological data was also collated from the USA EPA ECOTOX database using Standartox, to extract effect concentrations (EC_{50} and LC_{50}) for mortality, growth and reproduction endpoints for *Eisenia* species for 25 APIs. In total, 13 APIs had both soil ecotoxicological data (XX_{50}) and soil exposure measurements. The top 5 APIs (with hazard data) with the highest exposure concentrations in soils were antibiotics (enrofloxacin, chlortetracycline, tetracycline and trimethoprim) and beta blockers (atenolol) (Figure 2).

3 Emissions and exposure modelling

As detailed in Deliverable 4.3, we previously formulated a list of priority in-use pharmaceuticals, based on risk ranking from monitoring and ecotoxicological data (Section 4.1), previous risk ranking and prioritisation exercises (Spurgeon et al 2022, Spilsbury et al 2024) and ensuring representation of different therapeutic classes. As the ETERNAL project focuses on medicines for human use, we excluded pharmaceuticals that are only used for veterinary purposes. This list is shown in Table 1.

Table 1. Priority in-use pharmaceuticals selected for study within the ETERNAL project, based on our risk ranking, other risk ranking and prioritisation exercises and ensuring representation of different therapeutic classes. Description of MOA/s taken from Drug Bank (https://go.drugbank.com/) unless additional reference is given.

Compound	Usage	MOA/s	DrugBank ID	CAS No.	Justification for selection
Amitriptyline	A tricyclic antidepressant that treats depressive illness and relieve depression associated anxiety.	Inhibitor of sodium-dependent noradrenaline transporter. Inhibitor of sodium-dependent serotonin transporter. Antagonist of 5-hydroxytryptamine receptor 2A.	DB00321	549-18-8	Highest hazard in our hazard ranking. Represents antidepressants.
Rifaximin	Antibiotic for treating bacterial infections, including traveler's diarrhea and irritable bowel syndrome.	Inhibits DNA-directed RNA polymerase subunit beta (Escherichia coli - strain K12). Agonist of Pregnane X receptor (PXR) activator (human).	DB01220	80621-81-4	Highest risk in our risk ranking. Represents antibiotics.
Gliclazide	Used to lower blood sugars in patients with type 2 diabetes.	Binds to ATP-binding cassette sub-family C member 8.	DB01120	21187-98-4	11th highest risk in our risk ranking. Represents antidiabetics.
Diclofenac	Used to treat various types of arthritis.	Inhibitor of Prostaglandin G/H synthase 2. Inhibitor of Prostaglandin G/H synthase 1.	DB00586	81811-14-5, 78213-16-8, 119623-66-4, 15307-81-0, 15307-79-6	Ranks highly in other risk rankings (e.g. 4th highest risk in Spilsbury et al 2024). Represents commonly used non-steroidal anti-inflammatories.

Ibuprofen	Used to reduce fever, pain, and inflammation.	Inhibitor of Prostaglandin G/H synthase 2. Inhibitor of Prostaglandin G/H synthase 1.	DB01050	57469-82-6, 57469-77-9, 79261-49-7, 527688-20-6	Ranks highly in other risk rankings (e.g. 18th highest risk in Spilsbury et al 2024). Represents commonly used non-steroidal anti-inflammatories.
Altrenogest	Altrenogest is a steroidal progestin that is widely used in veterinary medicine to suppress estrus in animals.	Agonist of the Progesterone and Androgen Receptors (McRobb et al 2008; Gillon et al 2021).	DB11372	850-52-2	Identified as a priority pharmaceutical by the EMA
Isoeugenol	Added to many commercially available products, and may have antimicrobial activity.	Uncertain: Isoeugenol has a non-disruptive detergent-like mechanism of action (Hyldgaard et al 2015).	DB14188	97-54-1	Identified as a priority pharmaceutical by the EMA

Owing to the demanding nature of predicting emissions and exposure, we further prioritised this list to focus our modelling efforts on. We selected **Amitriptyline, Rifaximin, Gliclazide, Diclofenac and Ibuprofen**, again based on their position in our hazard and risk ranking, and wanting to ensure coverage across therapeutic classes and commonly-used pharmaceuticals.

3.1 Spatial predictions of emissions to waters and soils

3.1.1 Overview

This Section presents the methodology and results of a spatiotemporal modelling framework designed to estimate emissions of priority in-use pharmaceuticals to aquatic and terrestrial environments across Europe. These emissions serve as inputs for downstream pharmaceutical exposure models.

The targeted active pharmaceutical ingredients (APIs) include Amitriptyline (an antidepressant), Rifaximin (an antibiotic), Gliclazide (an anti-diabetic), Diclofenac (an anti-inflammatory/anti-arthritis), and Ibuprofen (an anti-inflammatory). Among these, Amitriptyline, Rifaximin, and Gliclazide are prescription-only medicines (POMs), while Diclofenac and Ibuprofen are also available over the counter in the United Kingdom (UK).

Two separate emission models were developed for these categories by modifying the emission component of ePiE, a high-resolution spatial model for pharmaceutical exposure in European surface waters (Oldenkamp et al., 2018). These models were calibrated and validated using UK data and subsequently applied to predict emissions to both surface waters and soils across European countries.

The primary data source is general practitioner (GP) prescription data from the UK National Health Service (NHS). To generate reliable pharmaceutical usage estimates for emission modelling, NHS GP prescription data were extracted and pre-processed. Where significant usage data were missing, estimation techniques were applied to ensure completeness.

The following subsections describe the methodology and results in detail, structured around two key components: (1) data preparation (including extraction and preprocessing), and (2) emission modelling (covering model development, calibration, and validation) and expanding.

3.1.2 Methodology

3.1.2.1 DATA EXTRACTION

Our GP prescription data is sourced from the four separate National Health Services in the UK: NHS England, NHS Scotland, NHS Wales, and Health and Social Care (HSC) Northern Ireland. Due to variations in data availability and structure, particularly regarding the volume of publicly accessible data, different data extraction methods were employed. These include manual downloading, scripted downloads, and programmatic access via Application Programming Interfaces (APIs).

NHS England, covering approximately 84% of the UK population, is the largest of the four systems. Given the volume and granularity of its prescription dataset, an API-based approach was adopted to extract pharmaceutical prescription data. Each priority active pharmaceutical ingredient (API) in our study may correspond to one or more drug entries, identified by their respective British National Formulary (BNF) codes. Table 2 lists the BNF codes of the drugs associated with all targeted APIs.

We found these BNF codes from NHS Business Services Authority (NHSBSA)'s browser for the Dictionary of Medicines and Devices, the UK national standard for medicines information, and checked DrugBank at https://go.drugbank.com for pre-drugs (a prodrug is a compound that is inactive (or less active) when administered but is converted into an active drug through metabolism in the body.

Table 2. Targeted APIs, their associated drugs and BNF codes

APIs	Drug/Pre-drug	BNF Codes	Oral/Topical
Amitriptyline	Amitriptyline Hydrochloride	0403010B0	Oral
Rifaximin	Rifaximin	0501070X0	Oral
Gliclazide	Gliclazide	0601021M0	Oral
Diclofenac	Aceclofenac (pre-drug)	100101080	Oral
	Diclofenac Diethyl	1003020AF	Topical
	Diclofenac Potassium	1001010AG	Oral
	Diclofenac Sodium A	1108020A0	Topical
	Diclofenac Sodium C	1001010C0	Oral
	Diclofenac Sodium U	1003020U0	Topical
	Diclofenac Sodium W	1308010W0	Topical
Ibuprofen	Ibuprofen_J	1001010J0	Oral
	Ibuprofen_P	1003020P0	Topical
	Ibuprofen Lysine	1001010AD	Oral
	Ibuprofen Sodium Dihydrate	1001010AP	Oral

Our data extraction script was adapted from the official NHS API program, with modifications to:

- request individual GP-level prescription data for each BNF-coded drug,
- retrieve data by year and by postcode area or sub-area, and
- ensure that data is downloaded in manageable chunks to prevent interruption, as large requests often fail.

This customised process enabled efficient access to high-resolution prescription data across both time and geography, while maintaining robustness and completeness.

The pseudocode extracting NHS Prescription Data by Year and Postcode is given below:

1. Set the base API and endpoints for:
   a) Listing datasets; b) Accessing dataset metadata; c) Querying data using SQL
2. Define:
   a) The dataset ID (English Prescribing Dataset);

b) The target drug (e.g., Ibuprofen) and its BNF code;
c) A list of postcode areas (e.g., 'B1', 'M1', etc.)
3. Download the metadata to get a list of available monthly files
4. For each postcode area:
For each year in the desired range:
a) Identify the monthly files for that year
b) For each month (e.g., Nov and Dec):
Build a SQL query to get records:
• Matching the BNF code
• Where postcode starts with the current area
Send the API request
If the request is successful:
Extract the data
c) Combine the data for that year
d) Save the data and list of drug descriptions to CSV files

Monthly prescription data from NHS Scotland and HSC Northern Ireland were downloaded programmatically using scripts, with BNF codes applied as filters. In contrast, data from NHS Wales were downloaded manually in bulk, after which the relevant records were extracted using BNF codes.

Although the data formats in these systems differ somewhat from that of NHS England, key variables, such as BNF_DESCRIPTION, TOTAL_QUANTITY, Date, and Address, are present across all datasets, albeit sometimes under different names. This consistency enables effective integration and comparative analysis.

3.1.2.2 DATA PRE-PROCESSING

Summarising Data Over Time and Space

The individual GP prescription data downloaded from the four national NHS systems were summarised both temporally and spatially. This summarisation produced monthly and yearly usage data for each active pharmaceutical ingredient (API) at the national level. For England, where prescription data are available at postcode area or sub-area levels, additional regional-level summaries were generated.

The summarisation process involved two main steps:

- Calculating the usage volume for each GP prescription by multiplying the total quantity prescribed by the mass per unit of the drug.
- Aggregating these usage volumes across all GP practices within the relevant spatial temporal unit.

Table 3 presents two exemplary drug descriptions, representing a typical oral formulation and a topical formulation in the NHS systems. To extract the mass values embedded in the prescription descriptions, regular expressions (regex) were applied within the R processing script.

Table 3. Drug descriptions representing typical oral and topical formulations in the NHS

Ibuprofen J (oral)	Ibuprofen P (topical)
Ibuprofen 100mg/5ml oral suspension sugar free	Ibuprofen 5% gel
Ibuprofen 400mg capsules	Fenbid 5% gel
Ibuprofen 200mg tablets	Ibuprofen 5% spray
Ibuprofen 400mg tablets	Ibuprofen 10% gel
Ibuprofen 100mg/5ml oral suspension	Ibuleve 5% gel
Ibuprofen 600mg tablets	Ibugel Forte 10% gel
Ibuprofen 800mg modified-release tablets	Ibuleve Maximum Strength 10% gel
Ibuprofen 200mg / Codeine 12.8mg tablets	Fenbid Forte 10% gel
Ibuprofen 200mg orodispersible tablets sugar free	Phorpain 5% gel
	Ibugel 5% gel
Nurofen 200mg liquid capsules	Ibuleve Speed Relief 5% spray

Ibuprofen 200mg capsules Ibuprofen 600mg effervescent granules sachets Ibuprofen 300mg modified-release capsules Nurofen Express 200mg liquid capsules Nurofen for Children 100mg/5ml oral suspension orange Nurofen for Children 100mg/5ml oral suspension strawberry Nurofen Plus tablets Cuprofen Maximum Strength 400mg tablets Ibuprofen 200mg/5ml oral suspension sugar free …	Ibuspray 5% spray Deep Relief gel Phorpain Maximum Strength 10% gel Ibuprofen 5% / Levomenthol 3% gel Ibuprofen Pain Relief Maximum Strength 10% gel Ibuleve 5% spray Mentholatum Ibuprofen 5% gel Ibuprofen 5% cream Radian B Ibuprofen 5% gel Ibuderm 5% gel Nurofen 5% gel ...

Calculation of Per Capita Volumes

Per capita volumes of prescribed drugs are calculated by dividing the total mass of prescribed pharmaceuticals within each spatial unit by the corresponding population totals. To ensure temporal consistency, population time series data from the UK's Office for National Statistics (ONS) are used, matched to the relevant spatial and temporal scales.

Monthly and yearly per capita usage values are generated for:

- UK regions (for selected drugs),
- Each of the four nations (for all drugs), and
- The entire United Kingdom, calculated as a population-weighted average of the national values.

These results enable meaningful comparisons of drug usage trends across regions and nations.

Estimation of Over the Counter (OTC) Usage

OTC usage estimation was applied exclusively to APIs that are available in both prescription and over the counter (OTC) formulations, specifically diclofenac and ibuprofen.

OTC usage was estimated based on the findings of Austin et al. (2021), who utilised commercial data assumed to be reliable. Specifically, the estimation relied on the reported proportions of OTC use relative to (i) total usage and (ii) prescription-only usage (see Table 4). For example, OTC diclofenac accounted for 55.65% of total topical diclofenac use and 35.10% of total diclofenac use.

As the data from Austin et al. (2021) cover only a single year, applying the two approaches resulted in identical OTC usage estimates for that year. However, when these two proportions were applied to all study years, they generated two distinct time series of estimated OTC usage. The final OTC time series was therefore derived by averaging the two resulting estimates.

Table 4. Total masses of sold OTC and prescribed (2016-17) in England and Wales, and ratios (based on Austin et al. 2021)

	Ibuprofen	**Diclofenac**	**Ibuprofen**	**Diclofenac**	**Ibuprofen**	**Diclofenac**
	kg/year	kg/year				
Total	**409463**	**8458**				
Topical	32466	5335				
Oral	376997	3123				
Prescription	**9631**	**5489**				
Topical	26639	2366	82.05%	44.35%	6.51%	27.97%
Oral	70992	3123	18.83%	100.00%	17.34%	36.92%
OTC	**311831**	**2969**				
Topical	5827	2969	17.95%	55.65%	1.42%	35.10%
Oral	306004	0.002	81.17%	0.00%	74.73%	0.00%

3.1.2.3 EMISSION MODELLING

Emission models represent the potential pathways through which pharmaceuticals are released into the environment, from usage to emission. A simplified schematic of these pathways is provided in Figure 3.

The modelling process begins with usage data, which includes prescription data, over the counter (OTC) usage, and, where available, other sources such as commercial market volume. However, the availability of such data varies significantly by region. In data-poor areas, it is often necessary to apply assumptions, such as a uniform per capita usage rate, to estimate pharmaceutical consumption. In such cases, population data are used as a proxy to interpolate usage and, consequently, estimate emissions.

Pharmaceuticals that are either prescribed or purchased over the counter may enter one of several pathways: human use, improper disposal (e.g. disposal down the drain), veterinary use, or other proper disposal methods (e.g. incineration or return to pharmacies). The latter is assumed to represent a loss from the system, with no environmental emissions.

For human use, a proportion of the taken pharmaceutical is excreted, and a proportion of the topical pharmaceutical is washed off, and, together with any quantities disposed of down the drain, enters the wastewater treatment system. During treatment, a fraction is partitioned into biosolids, while the remaining portion is discharged into surface waters, representing aquatic emissions.

Depending on regional policies, biosolids may be incinerated or applied to agricultural land. The latter contributes to emissions to soils. In the case of veterinary use, it is assumed that the excreted fraction is released directly to agricultural soils, contributing to terrestrial emissions.

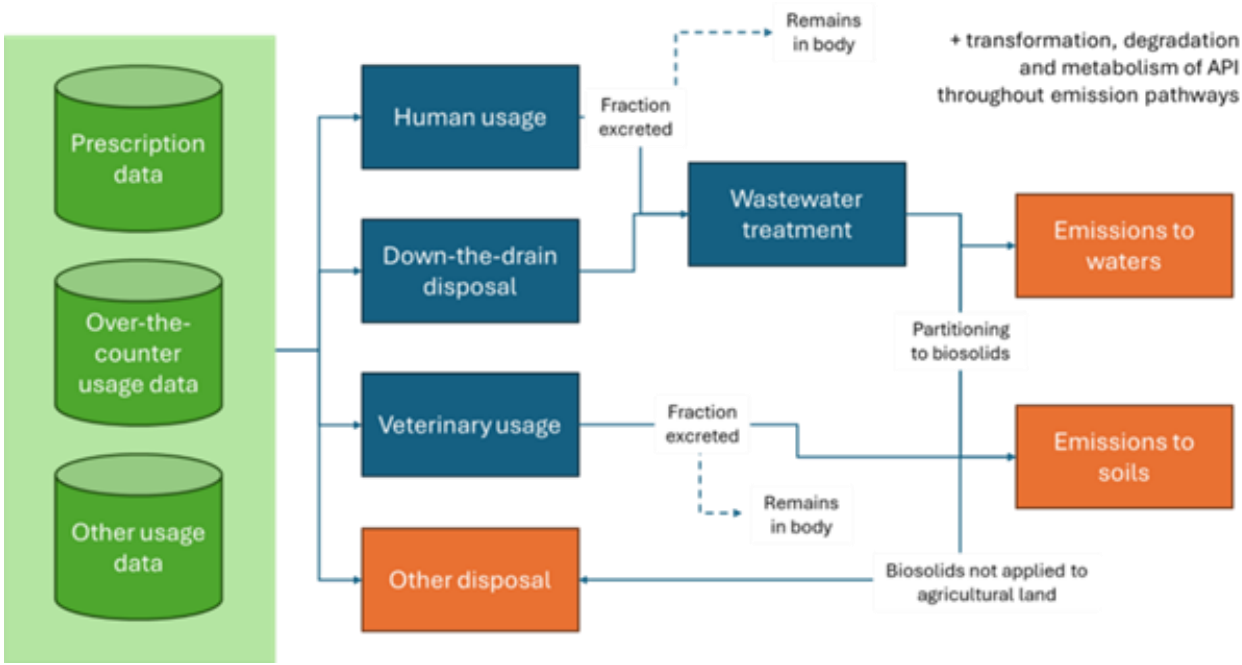


Figure 3. Simplified schematic of emissions pathways used in our model, which tracks the flow of APIs and their transformation products from usage to environmental emissions into surface waters and soils.

Model Formula and calculation

Following the pathways of the pharmaceuticals entering the surface water and soil from their usage, our model formula for calculating emissions to wastewater treatment plants and then discharge into rivers and soils are formed as following (note that veterinary usage is not incorporated into the

models, because none of the APIs assessed are licensed veterinary medicine in the UK, and therefore their veterinary use is negligible):

$$E_{w,wwtp} = \left(\left(M_{oral} + M_{pdO} * f_{met} \right) * f_{pc} + M_{topi} * f_{woff} + M * f_{diso} \right) (1 - f_{rem}) \quad (1)$$

and

$$E_{soil} = \left(\left(M_{oral} + M_{pdO} * f_{met} \right) * f_{pc} + M_{topi} * f_{woff} + M * f_{diso} \right) * f_{rem} * f_{appl} \quad (2)$$

Where:

- Ew,wwtp : Yearly emission into the river network from WWTPs (kg/year)
- Moral: Annual consumption of the (parent) API (oral) by human being (kg/year)
- MpdO : Annual consumption of the prodrug (kg/year)
- fmet: Fraction of prodrug metabolized into the API
- fpc : Fraction of parent API excreted unchanged or as reversible conjugates
- Mtopi: Annual consumption of the (parent) API (topical) by human (kg/year)
- Fwoff: wash-off rate of topical products
- M: all API (kg/year) including both prescribed and bought over the counter
- Fdiso: the rate of unproper down the drain disposal
- frem : WWTP removal efficiency for the API
- fappi: application rate of sludge to agricultural fields

In the emission model, the parameter fdiso, the rate of unproper down the drain disposal, is set to 0 for prescription-only medicines (POMs), (Amitriptyline, Rifaximin, and Gliclazide), indicating that improper disposal is not considered for these substances. For APIs that are available both as POMs and over the counter (OTC), such as Diclofenac and Ibuprofen, fdiso must be estimated using environmental monitoring data, as disposal rates reported in the literature vary widely and cannot be reliably selected at random. The values of other model parameters are derived from peer-reviewed literature and authoritative sources or from the calculation using measured data (see Table 5).

Table 5. Assigned values of model parameters, excluding the disposal rate

Priority API	Parent drugs/Pre-drug	Oral/Topical	OTC	Excreted unchanged	Wash-off	WwTP removal rate
Rifaximin	Rifaximin	Oral	POM	97%		0
Amitriptyline	Amitriptyline Hydrochloride	Oral	POM	<5% (2%)		65%
Gliclazide	Gliclazide	Oral	POM	<1%		75%
Diclofenac	Aceclofenac (Pre drugs)	Oral	POM	2.00%		35.8% (calculated)
	Diclofenac diethylamine	Topical	OTC (55%)		30%	
	Diclofenac potassium	Oral	POM	2.00%		
	Diclofenac sodium A	Topical	OTC (55%)		30%	
	Diclofenac sodium C	Oral	POM	2.00%		
	Diclofenac sodium U	Topical	OTC (55%)		30%	
	Diclofenac sodium W	Topical	OTC (55%)		30%	
Ibuprofen	Ibuprofen_J	Oral	OTC(81%)	10.70%		99% (calculated)
	Ibuprofen_P	Topical	OTC(18%)		50%	
	Ibuprofen lysine	Oral		10.70%		
	Ibuprofen sodium	Topical			50%	

References:

Rifaximin - Scarpignato and Pelosini (2005); Su et al., (2006); DrugBank Online (2025); Thornley (2023)

Amitriptyline – Rutkowska and Piekoszewski (1999); DrugBank Online (2025); Zhang et al. (2023); Wu et al. (2021)
Gliclazide - Iancu et al., 2021; DrugBank Online (2025); Campbell, R. K. (2004)
Diclofenac - Austin et al, 2021; Petrović and Barceló (2010); DrugBank Online (2025); Haltner-Ukomadu et al. (2019)
Ibuprofen - Austin et al, 2021; Petrović and Barceló (2010); DrugBank Online (2025); Bound and Voulvoulis (2005)

Note that, instead of relying on removal rates reported in the literature for Diclofenac and Ibuprofen, empirically derived values were used based on measured data provided by the UK Environment Agency. This decision was made because hundreds of concentration measurements are available for both APIs, including paired influent and effluent values across numerous wastewater treatment plants (WWTPs), meaning this provided a more robust estimate of real-world removal rates. The median of the removal rates, calculated from these WWTPs, was adopted as the model parameter for each API.

Using Model (1) and the parameters listed in Table 5, pharmaceutical emissions to wastewater treatment plants (WWTPs) via the identified pathways can be estimated. For orally administered drugs, the emissions are based on the fraction of the parent API excreted unchanged. For topically applied drugs, the portion washed off into wastewater is estimated. For APIs available in OTC products, emissions resulting from down-the-drain disposal are also included. By applying the relevant removal rates, the resulting effluent emission fluxes can be calculated, representing emissions to surface waters.

Concentrations can be estimated either by dividing the total emissions by the total volume of wastewater, or by dividing the per capita emissions by the per capita wastewater volume. In this study, the latter approach is used. First, per capita emissions are calculated by dividing the total emissions by the corresponding population. Then, assuming a daily per capita wastewater volume of 180 litres in the UK, the concentration of each API is estimated by dividing the per capita emissions by the annual per capita wastewater volume (i.e., 180 L/day × 365 days).

The portion of pharmaceuticals removed during wastewater treatment is transferred to biosolids. Using Model (2), emissions to soils are estimated by multiplying this removed fraction by the parameter fappl, which represents the application rate of sludge to agricultural land. In cases where biosolids are incinerated or disposed of by other means, they are considered lost from the system. This fappl parameter reflects regional policies on biosolid reuse. For example, in the UK, a circular economy approach is promoted, and approximately 89% of sewage sludge is applied to agricultural fields.

Model Calibration

Model calibration is the process of adjusting model parameters so that the model outputs align as closely as possible with observed data. In this study, the key parameter calibrated is the rate of improper down the drain disposal, which is both uncertain and highly sensitive, for Diclofenac and Ibuprofen, which are OTC available. Literature values for this parameter range from 0.5% to 5% (Bound & Voulvoulis, 2005), and as APIs disposed of down the drain enter the environment directly, this parameter has a significant influence on the calculated environmental concentrations.

Our approach to model calibration relies on environmental monitoring data, specifically the measured concentrations of APIs in the influents of wastewater treatment plants (WWTPs). By comparing the calculated influent concentrations to these measured values, we iteratively adjust the improper disposal rate using a trial-and-error method. The goal is to minimise the error, measured using Mean Absolute Error (MAE), to within an acceptable range.

Model Validation and Plausibility Checks

When full validation datasets are unavailable, or when monitoring data are sparse and highly variable, it is common practice to assess model performance through plausibility checks rather than strict statistical validation. In such cases, the objective is not to achieve precise predictions, but to evaluate whether the model outputs are reasonable and consistent with observed data.

Given the substantial variability in measured influent concentrations across sites and time, modelled concentrations in this study were evaluated against summary statistics of the observed data,

including the minimum, maximum, mean, and median values. A modelled value was considered plausible if it:

- Fell within the observed [min, max] range, indicating consistency with the general magnitude of observations—a weak criterion, but useful for bounding estimates;
- Was within one order of magnitude of the median, suggesting agreement with the central tendency despite measurement uncertainty;
- Was comparable to authoritative figures reported in the literature, where available.

This approach was adopted in recognition of the limited temporal resolution and inherent uncertainty in the monitoring data. Accordingly, the modelled influent concentrations for wastewater treatment plants (WWTPs), calculated using the specified and calibrated parameters, were assessed based on these criteria to determine their acceptability.

As no soil concentration data for pharmaceuticals are available, further validation against measured soil levels was not performed.

3.1.2.4 EXPANSION OF MODEL APPLICATION

As no GP prescription data in other European countries are as detailed or publicly accessible as those available in the UK, we applied the per capita emissions estimated using the calibrated and validated UK models to wastewater treatment plants (WWTPs) across Europe (see Figure 4 for their geographic distribution). Using mapped information on population served at each plant, these per capita values were scaled to estimate and spatialise pharmaceutical emissions to surface waters across the region.

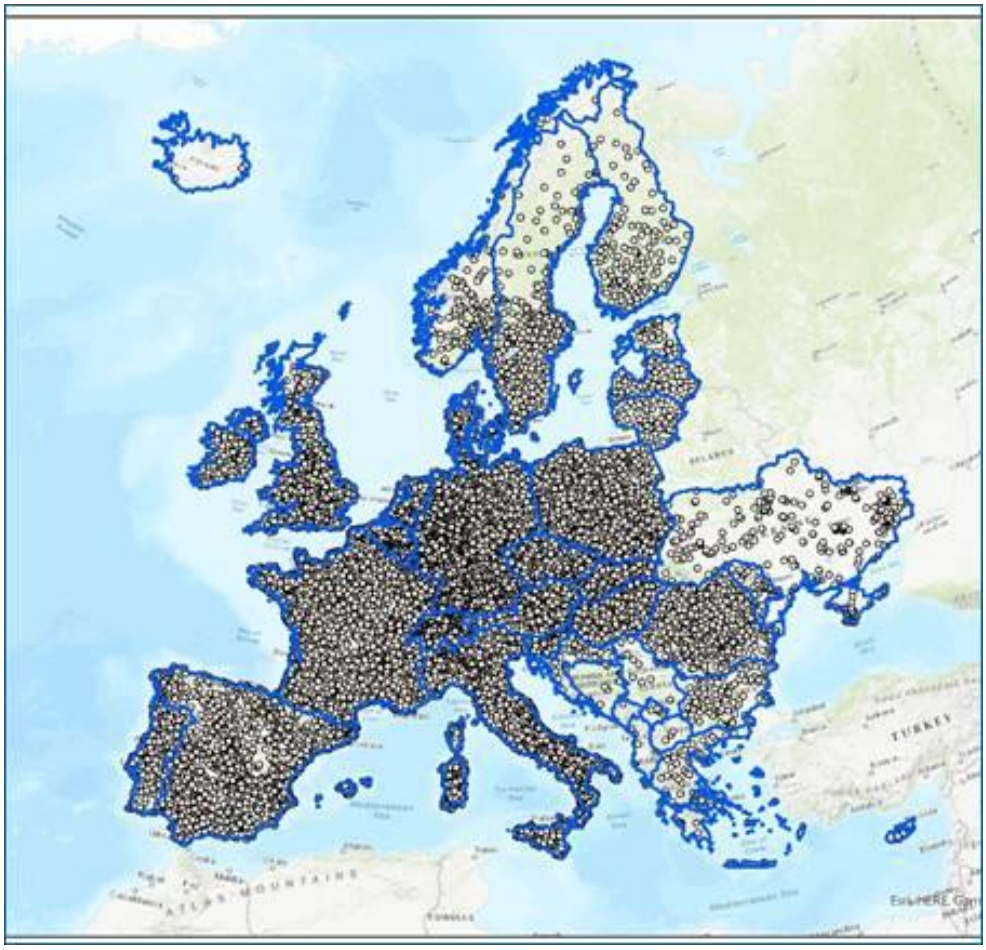


Figure 4. Geographic distribution of WwTPs in Europe

The portion of pharmaceuticals transferred to biosolids during wastewater treatment at these WWTPs is assumed to be evenly distributed over agricultural land within each country, depending on national sludge reuse policies. To support this spatial distribution, a 1 km × 1 km land use map of Europe (2019), containing 19 land use categories, was obtained through Python programming from the Global Land Analysis & Discovery Lab at the University of Maryland (Hansen et al., 2021). Based on this dataset, a cropland percentage map of 10 km × 10 km (see Figure 5) was generated to spatialise pharmaceutical emissions to soils.

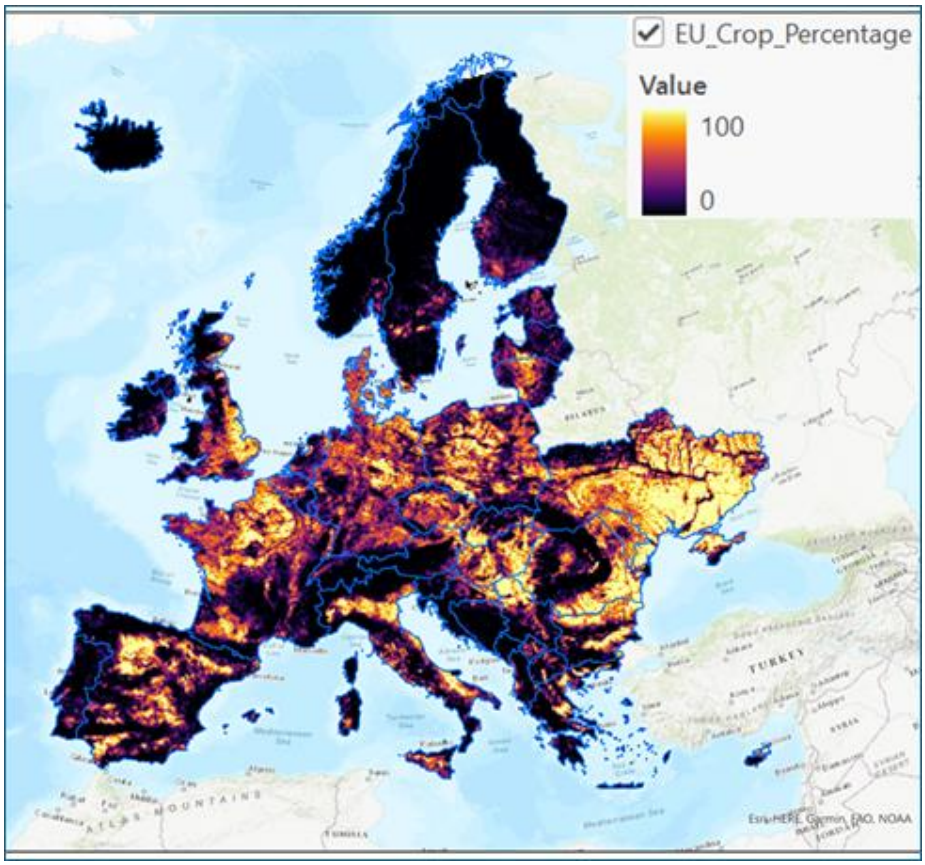


Figure 5. The cropland percentage map of Europe (2019)

The parameters reflecting national sludge reuse policies were obtained through further calculation based on EU statistical data, published literature, and national or local government reports. Using the EUROSTAT dataset on sewage sludge production and disposal, time series data from 2014 to 2023 were extracted to determine the percentage of sludge applied to agriculture, as shown in Figure 6. The corresponding average values are presented in Figure 7. For the United Kingdom, the figure was derived from a government report. For Ukraine, the value used in the spatialisation calculations, which is 5%, was sourced from a peer-reviewed academic publication.

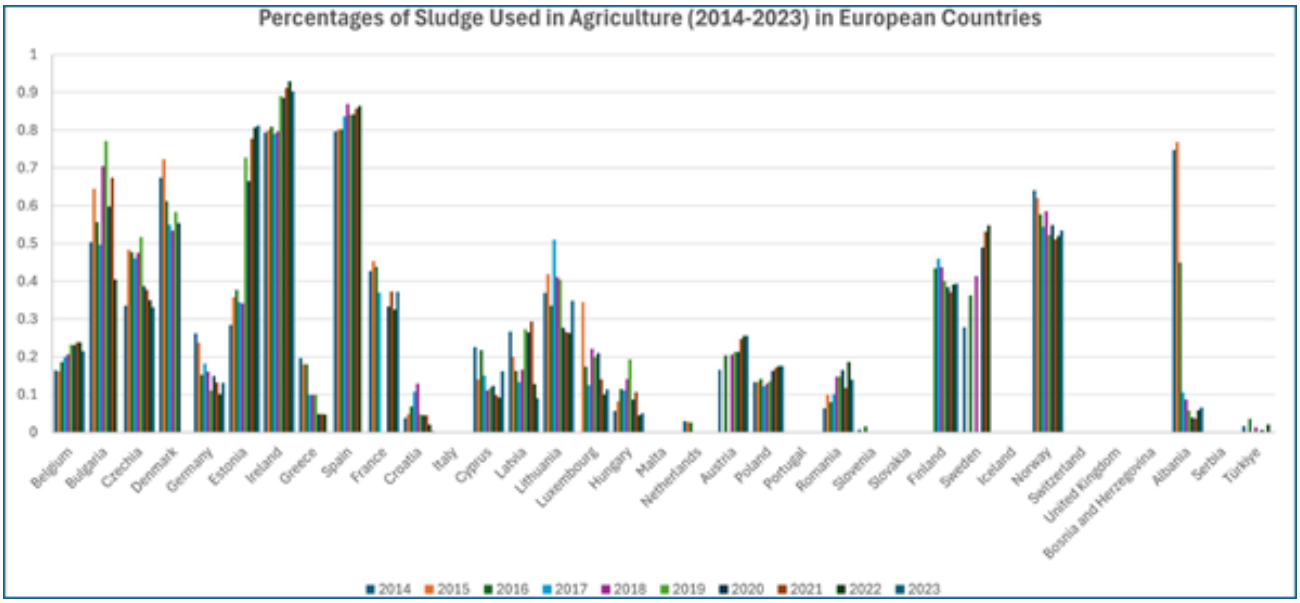


Figure 6. Annual percentages of sludge used in agriculture in Europe (2014-2023)

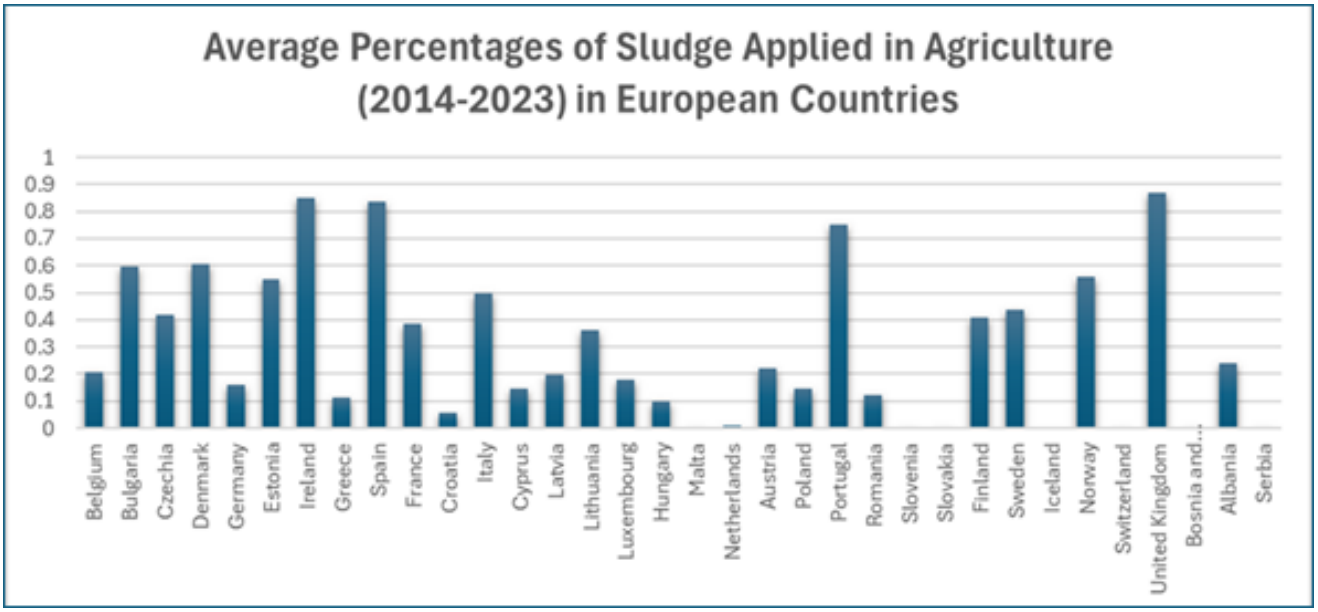


Figure 7. Average percentage of sludge used in agriculture across Europe

3.1.3 Results

General practitioner (GP) prescription data for the United Kingdom were obtained, and prescribed quantities were aggregated at temporal and spatial scales. After calculating per capita consumption of the five APIs, their per capita emissions were estimated using the emission model described above, which accounts for multiple pathways from pharmaceutical use to environmental release.

Model performance was evaluated by comparing predicted influent concentrations of APIs in wastewater treatment plants (WWTPs) with measured concentrations reported by the Environmental Agency. Following validation, the derived per capita emission factors were extrapolated to European countries to estimate total API emissions to surface waters and soils for the period 2018–2024.

This section presents:

1. Monthly and annual per capita consumption of the APIs and their associated drugs;
2. Estimated annual per capita emissions; and
3. Modelled emissions to surface waters and soils across Europe between 2018 and 2024.

Results are presented in the following order: Amitriptyline, Rifaximin, Gliclazide, Diclofenac, and Ibuprofen, each discussed in a dedicated subsection.

3.1.3.1 AMITRIPTYLINE

Per Capita Usage across UK Regions

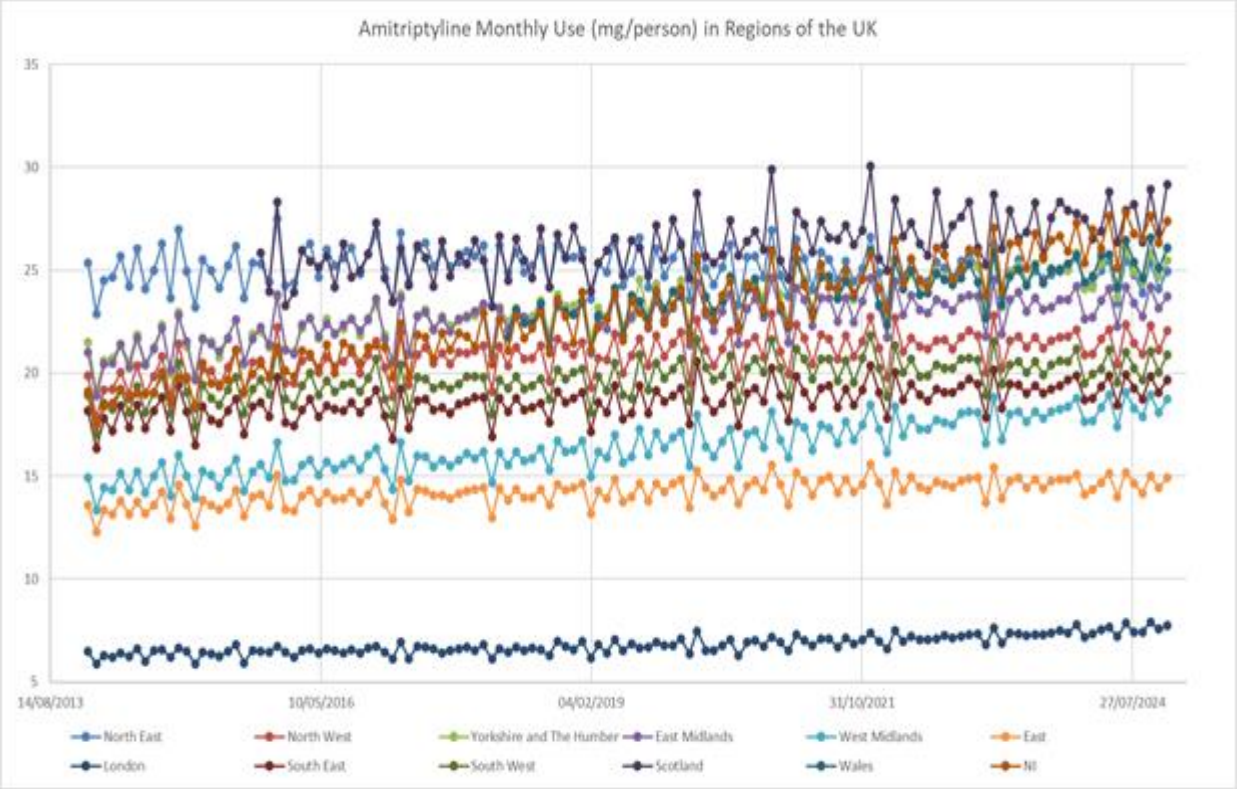


Figure 8. Monthly per capita use of Amitriptyline (mg/person) across UK regions

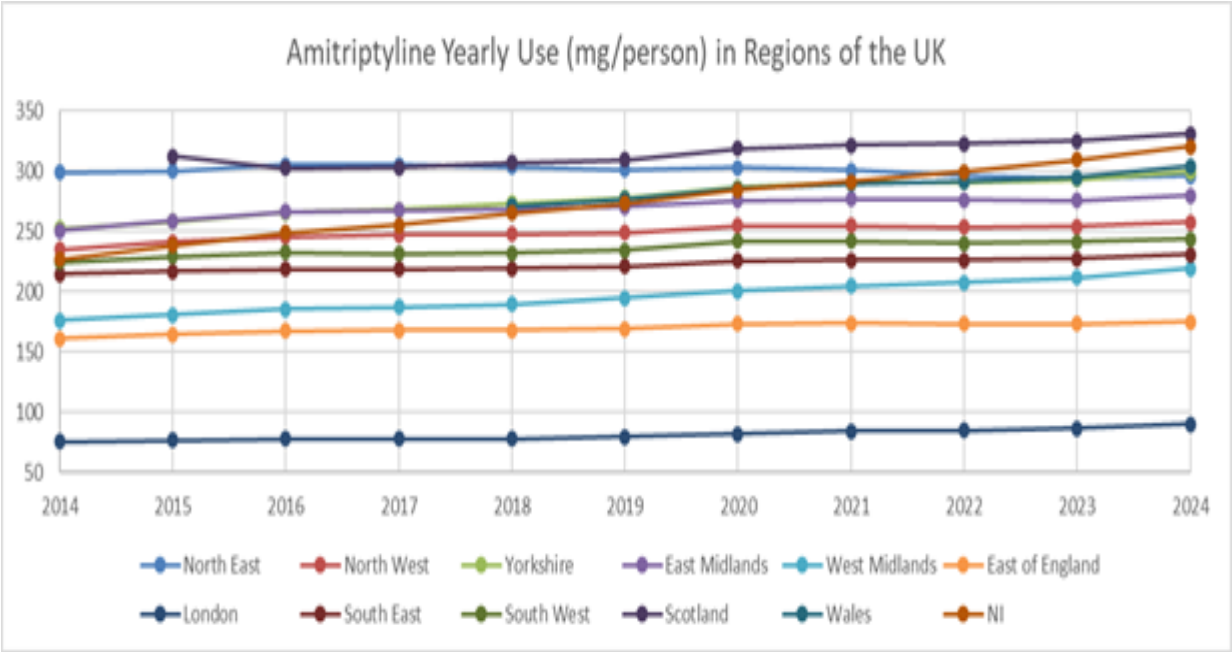


Figure 9. Yearly per capita use of Amitriptyline (mg/person) across UK regions

The monthly and annual per capita consumption across UK regions is presented in Figure 8 and Figure 9. As shown, the average per capita use of Amitriptyline in London is substantially lower than in other regions, whereas higher consumption levels are observed in northern regions. For example, in 2024, the annual per capita use of Amitriptyline exceeded 300 mg in Scotland, while it was below 100 mg in London.

Per Capita Usage in the Nations of the UK

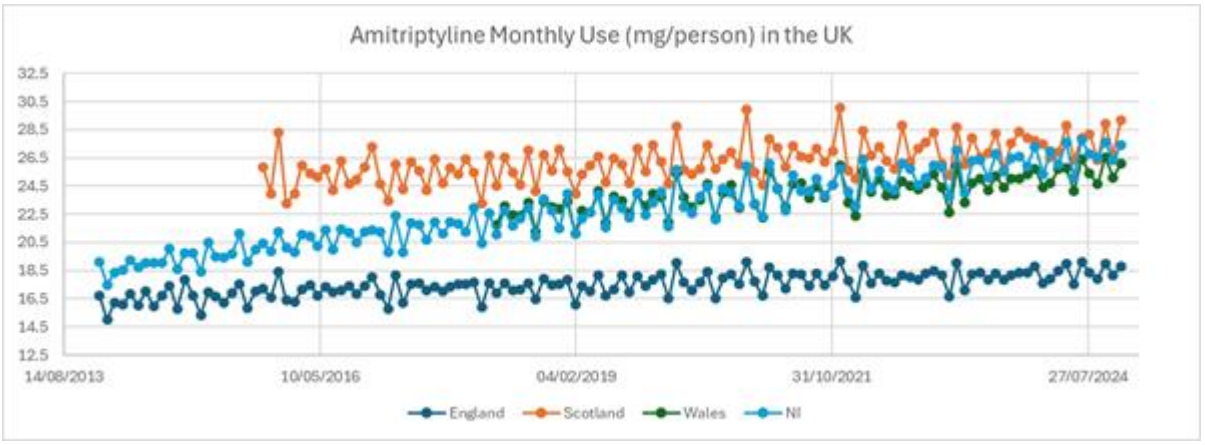


Figure 10. Monthly per capita use of Amitriptyline (mg/person) in the nations of the UK

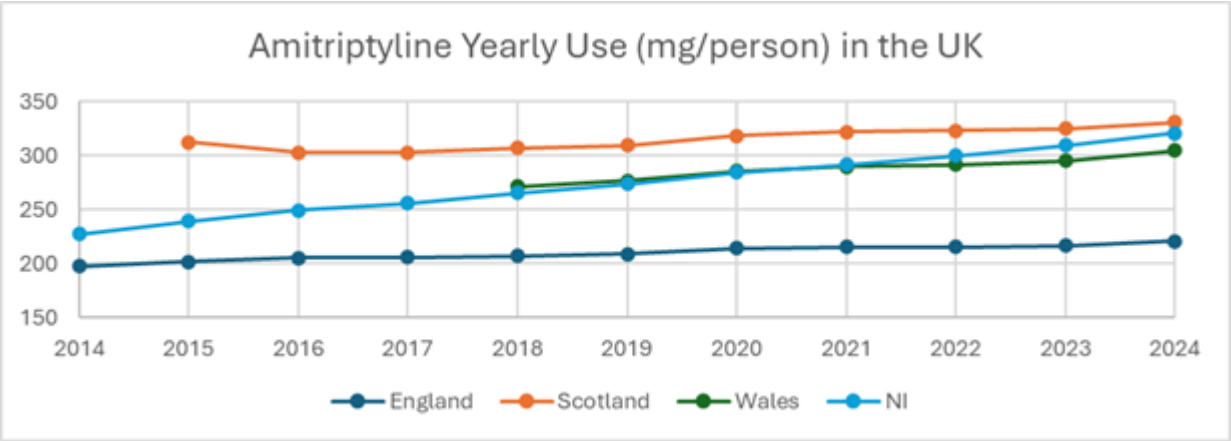


Figure 11. Yearly per capita use of Amitriptyline (mg/person) in the nations of the UK

From the national summarisation, see Figure 10 and Figure 11, the per capita usage of Amitriptyline is increasing in all nations, with increase more significantly in North Ireland. The amount of per capital use in London is lowest, and in Scotland the highest, with those in Wales and Northern Ireland catching up in recent year.

Calculated Average Emissions in the UK

Table 6. Per capita usage, emissions, and influent concentrations in WwTPs in the UK

EF =2%	Use	Influent Flux	Inf Conc.	Eff Conc.
PE (L/P/D)180	mg/P/Y	mg/P/Y	ug/L	ug/L
2018	219.6914797	4.393829593	0.066831388	0.023390986
2019	222.0151758	4.440303517	0.067538269	0.023638394
2020	227.773931	4.55547862	0.069290115	0.02425154
2021	229.7040213	4.594080427	0.06987726	0.024457041
2022	229.9895285	4.599790571	0.069964112	0.024487439
2023	231.5638448	4.631276897	0.070443028	0.02465506
2024	236.1941729	4.723883457	0.0718516	0.02514806

In Table 6, the highlighted average calculated concentration for 2019 closely aligns with the median of the measured values (0.066 µg/L). This suggests that the estimate is reasonably robust and appropriate for use in subsequent calculations across European countries. Furthermore, the result is consistent with values reported for England by Zhang et al. (2023).

Estimated Emissions to Surface Waters and Soils across Europe

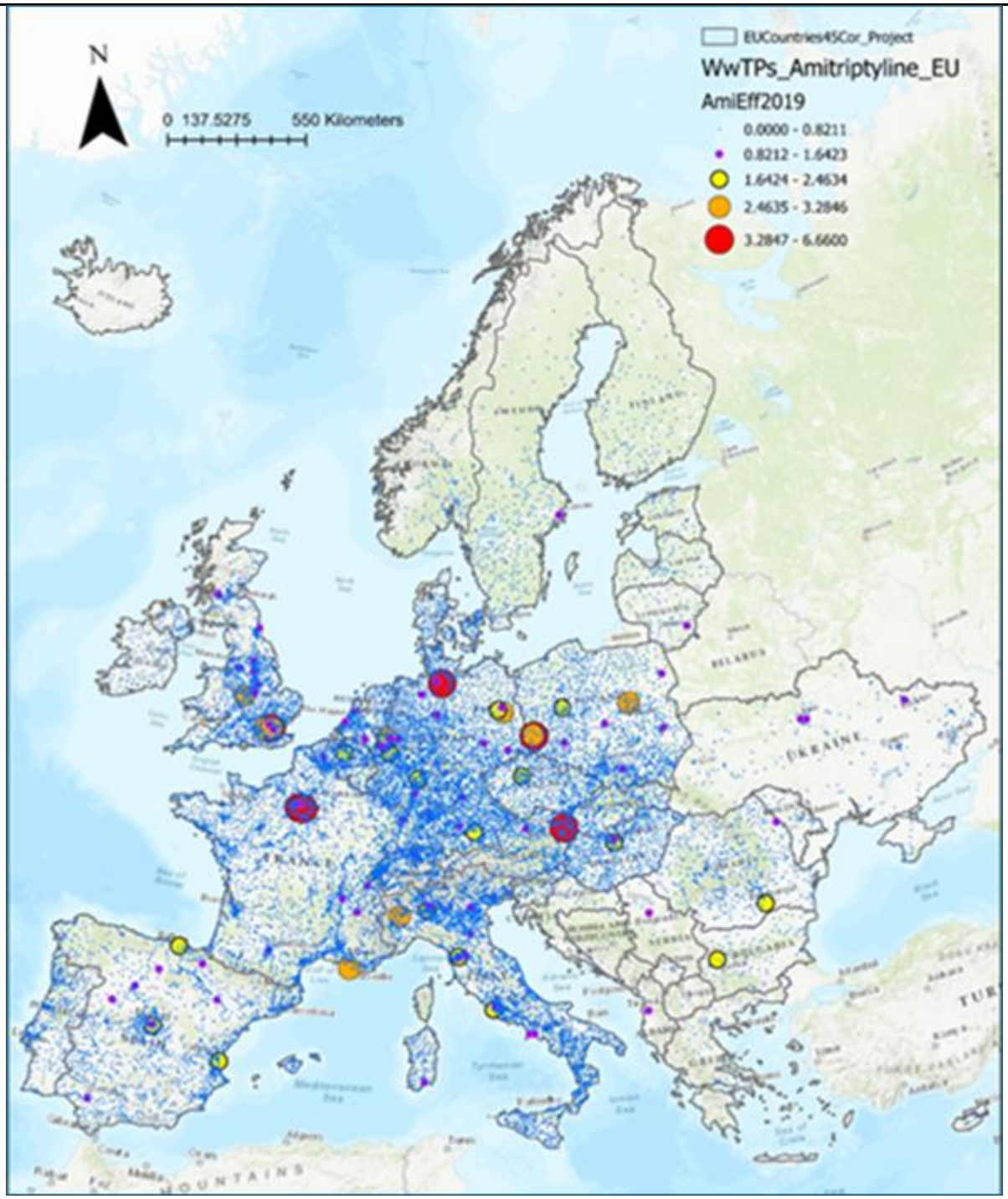


Figure 12. Estimated emissions of Amitriptyline to surface waters across Europe (kg/WwTP/year)

Estimated emissions of amitriptyline to surface waters and soils across Europe from 2018 to 2024 were calculated. Figure 12 presents amitriptyline emissions to surface waters in 2019 via wastewater treatment plant (WWTP) effluents. The highest emissions were observed at WWTPs serving the largest populations, with a maximum annual discharge of 6.66 kg from a single WWTP.

Figure 13 shows the estimated emissions to soils in 2019 via application to agricultural land. Higher emissions were concentrated in the eastern part of the UK, reaching up to 263 kg per 10 × 10 km grid cell in that year. Countries with relatively high emissions per grid cell include Portugal, Italy, and Spain.

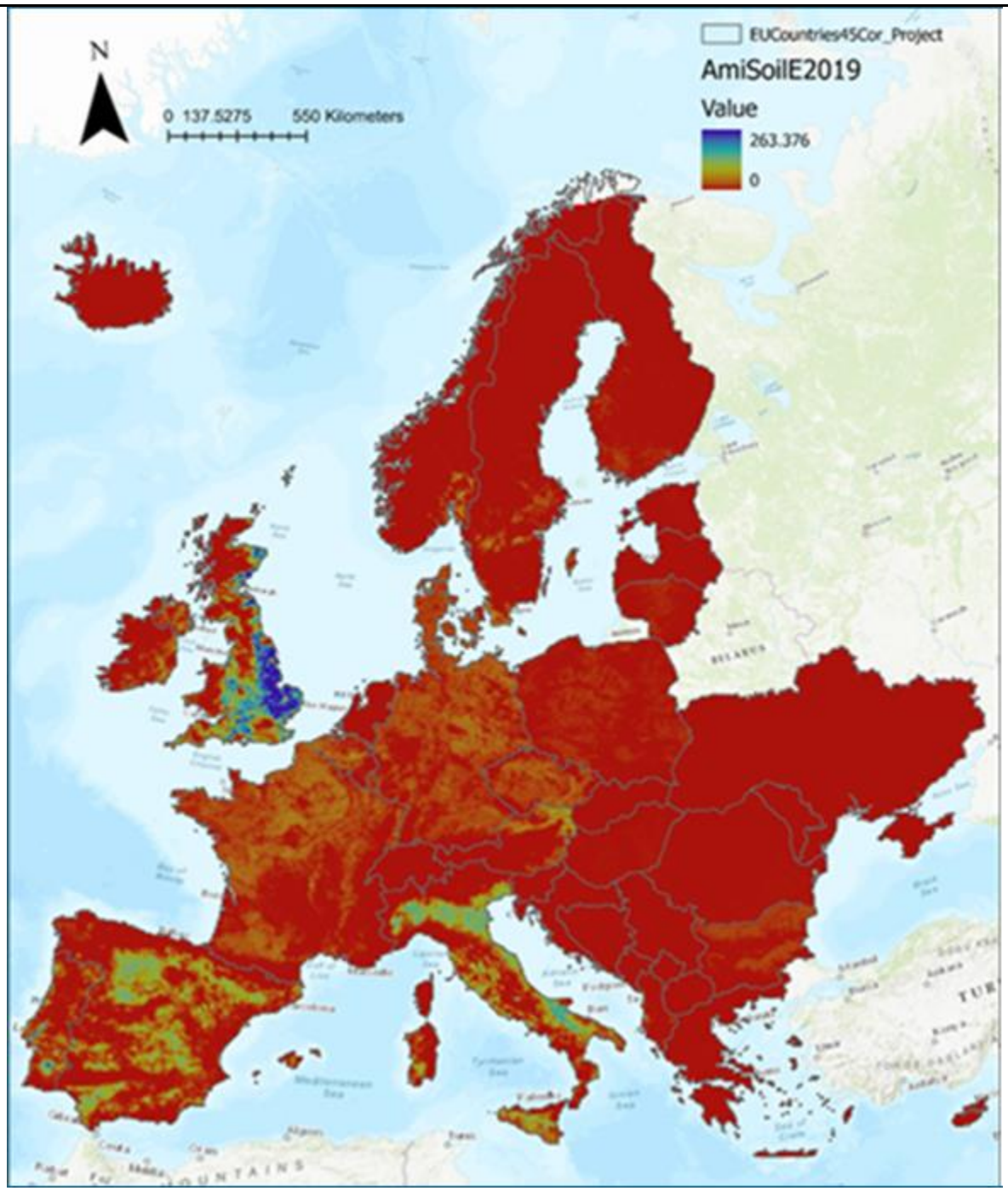


Figure 13. Estimated emissions of Amitriptyline to soils across Europe (g/cell/year)

3.1.3.2 RIFAXIMIN

Per Capita Usage across UK Regions

The monthly and annual per capita consumption of Rifaximin across UK regions is presented in Figure 14 and Figure 15. An increasing trend is observed across all regions, with the Northeast showing the largest rise, surpassing the Northwest in recent years to record the highest per capita

consumption. Over the study period, London consistently exhibits the lowest average per capita consumption of Rifaximin.

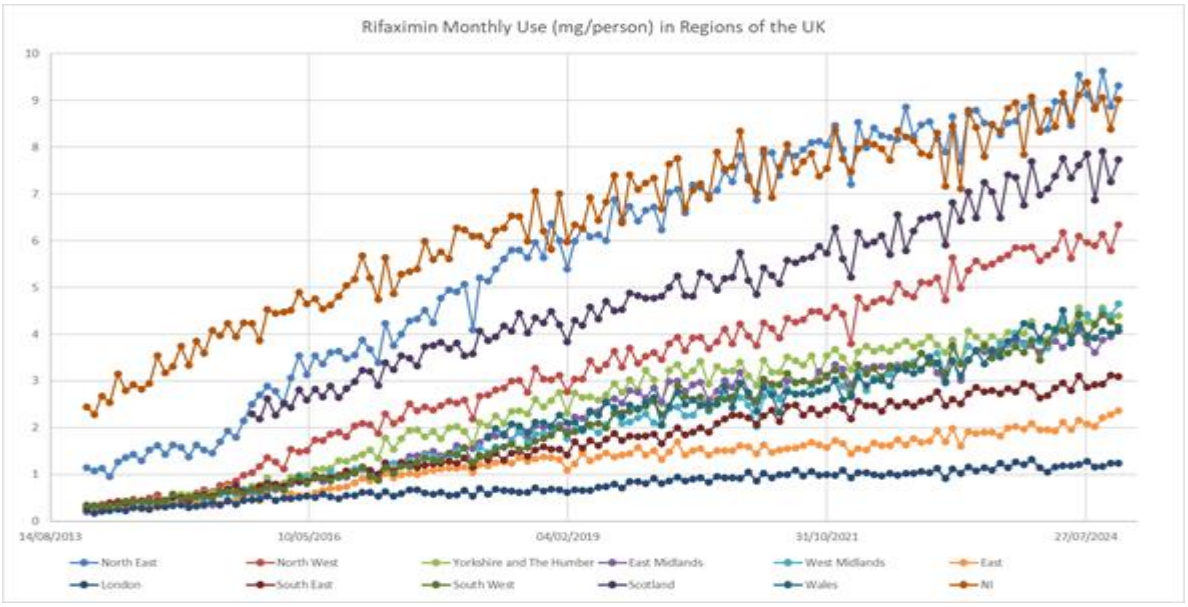


Figure 14. Monthly per capita use of Rifaximin (mg/person) across UK regions

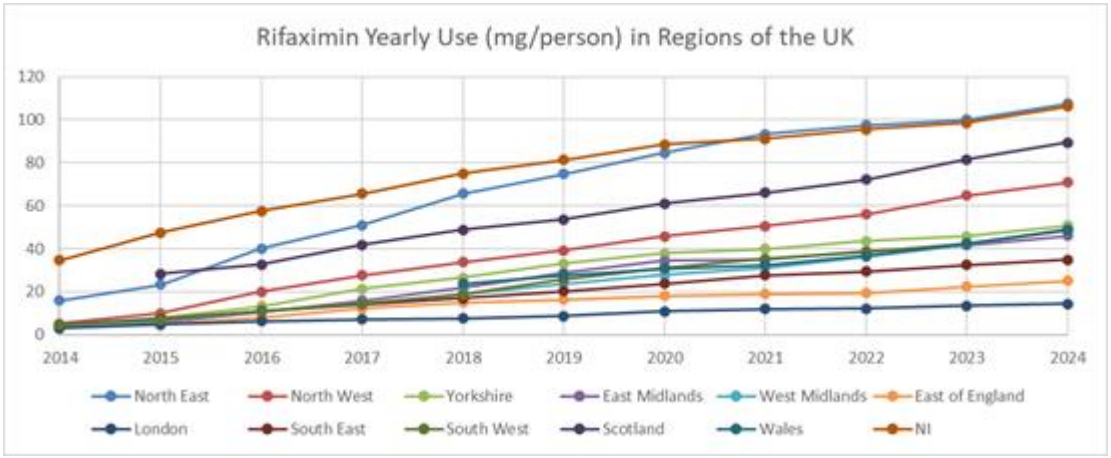


Figure 15. Yearly per capita use of Rifaximin (mg/person) across UK regions

Per Capita Usage in the Nations of the UK

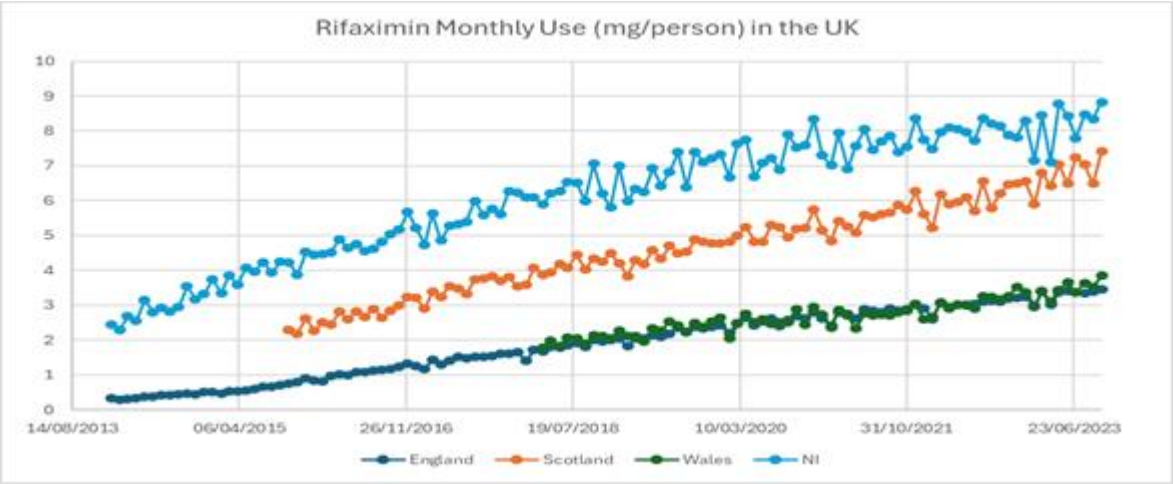


Figure 16. Monthly per capita use of Rifaximin (mg/person) in the nations of the UK

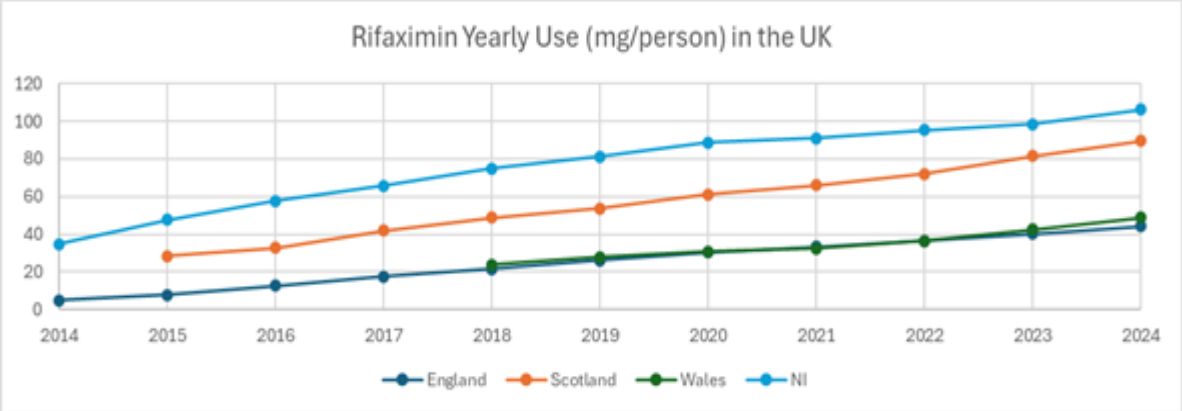


Figure 17. Yearly per capita use of Rifaximin (mg/person) in the nations of the UK

At the national level (Figure 16 and Figure 17), per capita consumption of Rifaximin increases at a similar rate across all nations. Northern Ireland records the highest per capita values, followed by Scotland. In contrast, per capita consumption in England and Wales is comparable and approximately half that observed in Northern Ireland and Scotland.

Calculated Average Emissions in the UK

Table 7. Per capita usage, emissions, and influent concentrations in WwTPs in the UK

EF =97%	Use	Influent Flux	Inf Conc.
PE (L/P/D)180	mg/P/Y	mg/P/Y	ug/L
2018	25.40443649	24.64230339	0.374816387
2019	29.91757028	29.02004317	0.441403045
2020	34.56103835	33.5242072	0.50991265
2021	37.63929998	36.51012098	0.555329241
2022	40.869983	39.64388351	0.602994654
2023	45.12422435	43.77049762	0.665761619
2024	49.86822935	48.37218247	0.735754544

The calculated average influent concentration in wastewater treatment plants (WWTPs) (e.g., 0.44 µg/L in 2019) approximates the median measured value of 0.74 µg/L and remains within the same order of magnitude, indicating that the estimate is reasonably robust. Therefore, it was applied in subsequent calculations for European countries.

Estimated Emissions to Surface Waters and Soils across Europe

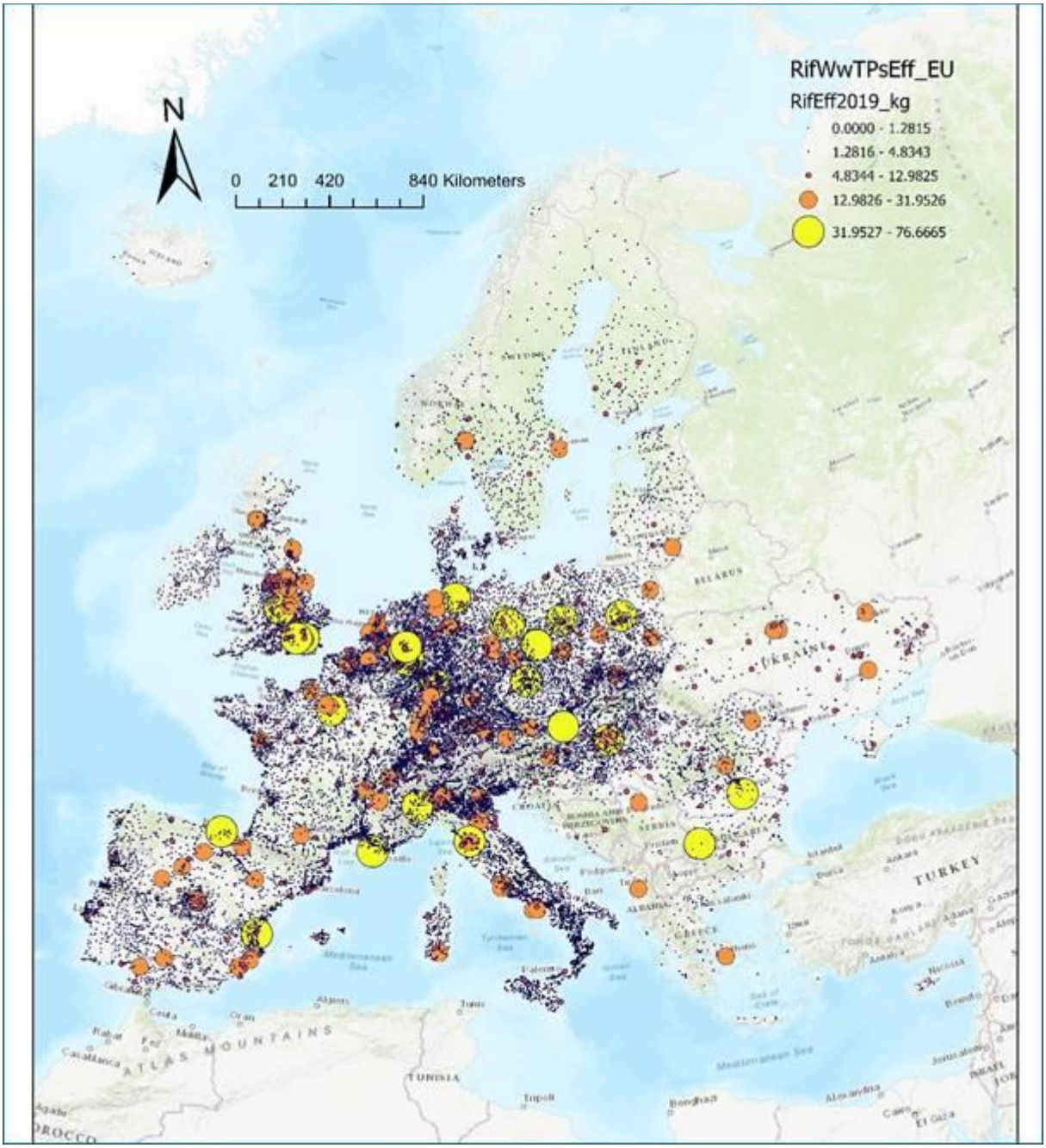


Figure 18. Estimated emissions of Rifaximin to surface waters across Europe (kg/WwTP/year)

Estimated emissions of Rifaximin to surface waters across Europe from 2018 to 2024 were calculated. As the removal rate of Rifaximin in wastewater treatment plants (WWTPs) was assumed to be zero, no fraction was retained in sludge for subsequent agricultural application; therefore, no emissions to soils were estimated. Figure 18 presents Rifaximin emissions to surface waters in 2019, with the maximum annual discharge from a single WWTP reaching 76.67 kg.

3.1.3.3 GLICLAZIDE

Per Capita Usage across UK Regions

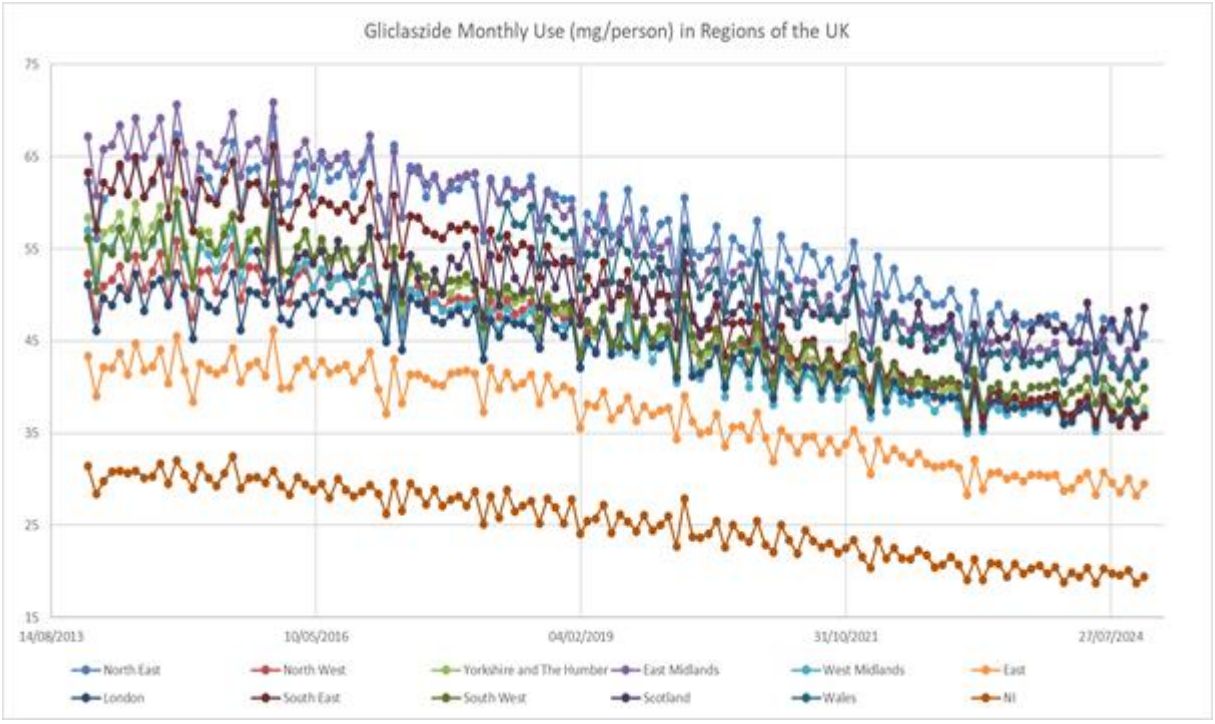


Figure 19. Monthly per capita use of Gliclazide (mg/person) across UK regions

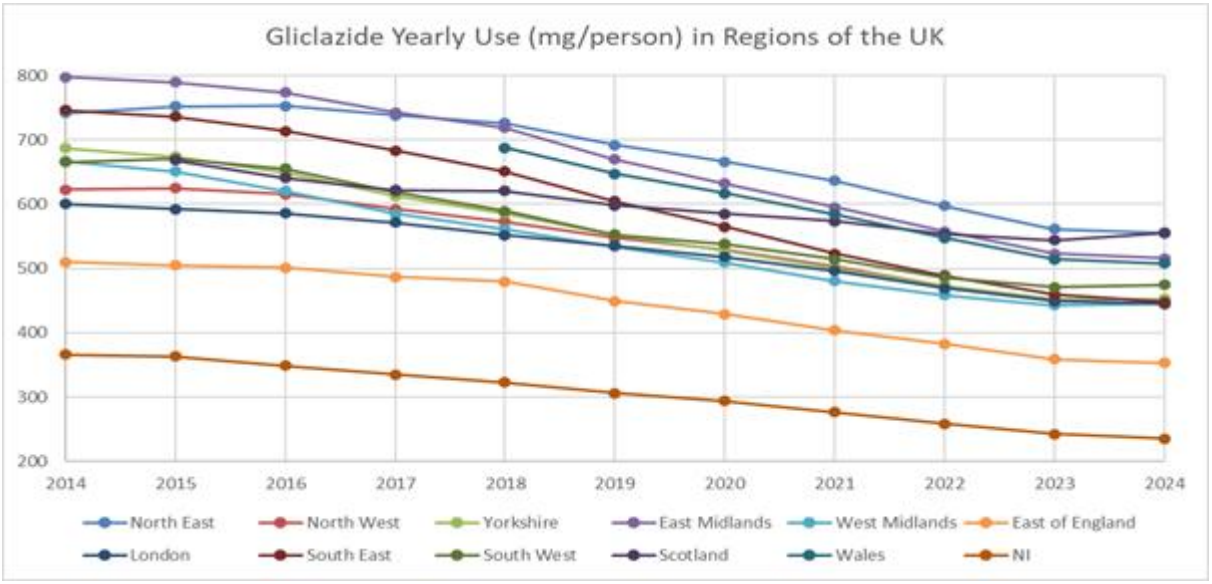


Figure 20. Yearly per capita use of Gliclazide (mg/person) across UK regions

The monthly and annual per capita consumption of Gliclazide across UK regions is presented in Figure 19 and Figure 20. Overall, a consistent declining trend is observed across most regions. Per capita consumption in Northern Ireland and the East of England is generally lower than in other regions, whereas higher values are observed in the Northeast, East Midlands, and Wales. Scotland shows the smallest decrease over time and records the highest per capita consumption by 2024, reaching approximately 560 mg per capita.

Per Capita Usage in the Nations of the UK

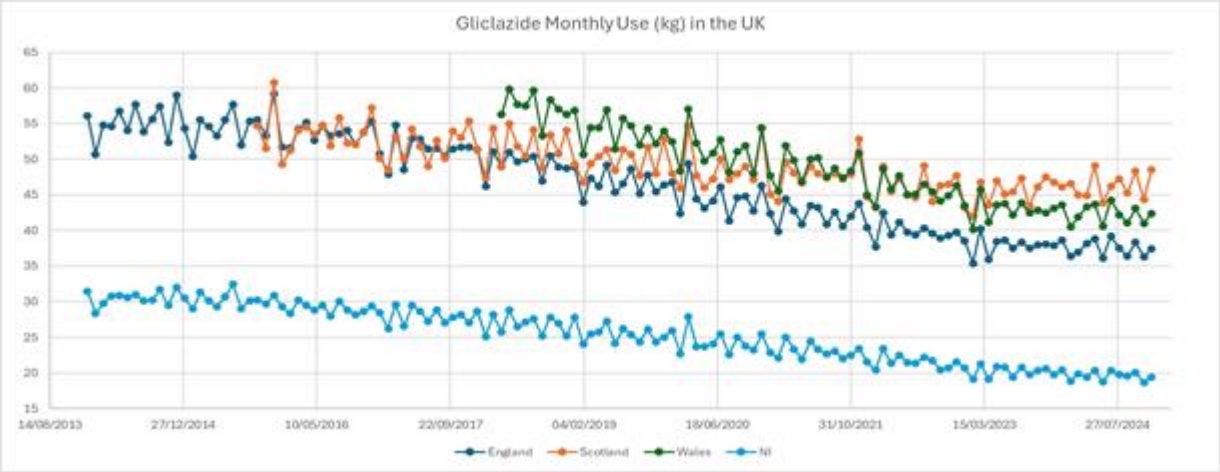


Figure 21. Monthly per capita use of Gliclazide (mg/person) in the nations of the UK

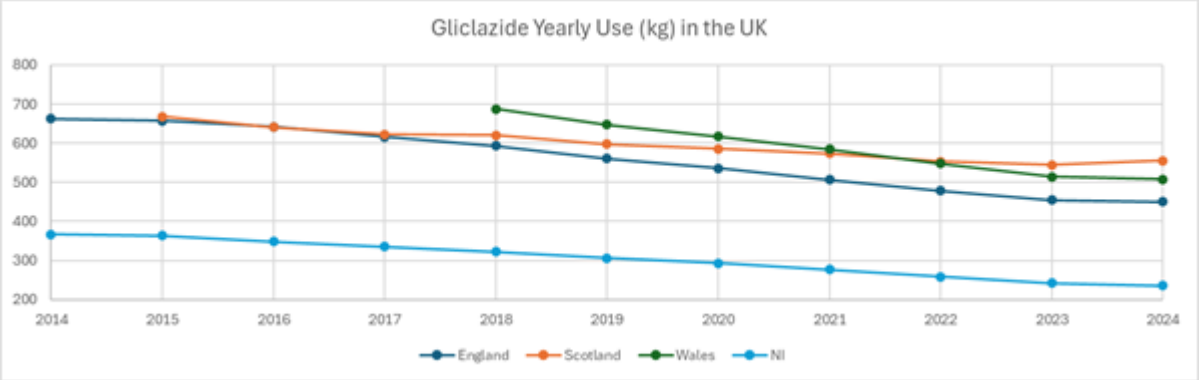


Figure 22. Yearly per capita use of Gliclazide (mg/person) in the nations of the UK

At the national level (Figure 21 and Figure 22), per capita consumption of Gliclazide shows a general decline across all nations over the study period, with some monthly variability. The absolute per capita consumption in England, Scotland, and Wales is comparable, decreasing from over 600 mg per year to approximately 500 mg per year. In contrast, per capita consumption in Northern Ireland is roughly half of those values.

Calculated Average Emissions in the UK

Table 8. Per capita usage, emissions, and influent concentrations in WwTPs in the UK

EF =1%	Use	Influent Flux	Inf Conc.	Eff Conc.
PE (L/P/D)180	mg/P/Y	mg/P/Y	ug/L	ug/L
2018	592.4360509	5.924360509	0.090111195	0.022527799
2019	560.6057769	5.606057769	0.08526972	0.02131743
2020	536.9391448	5.369391448	0.081669959	0.02041749
2021	509.2610889	5.092610889	0.077460049	0.019365012
2022	481.1291763	4.811291763	0.073181105	0.018295276

2023	458.3842944	4.583842944	0.069721545	0.017430386
2024	455.3076938	4.553076938	0.069253585	0.017313396

The calculated average influent concentration in wastewater treatment plants (WWTPs) for 2019 falls within the reported measured range (min = 0.001 µg/L; max = 0.6 µg/L). Although it is lower than the median value of 0.125 µg/L, it remains higher than the influent (and effluent) concentrations reported by Iancu et al. (2021). Overall, this comparison suggests that the estimate is reasonably plausible and was therefore applied in subsequent calculations for the UK and other European countries.

Emissions to surface waters and soils across the Europe

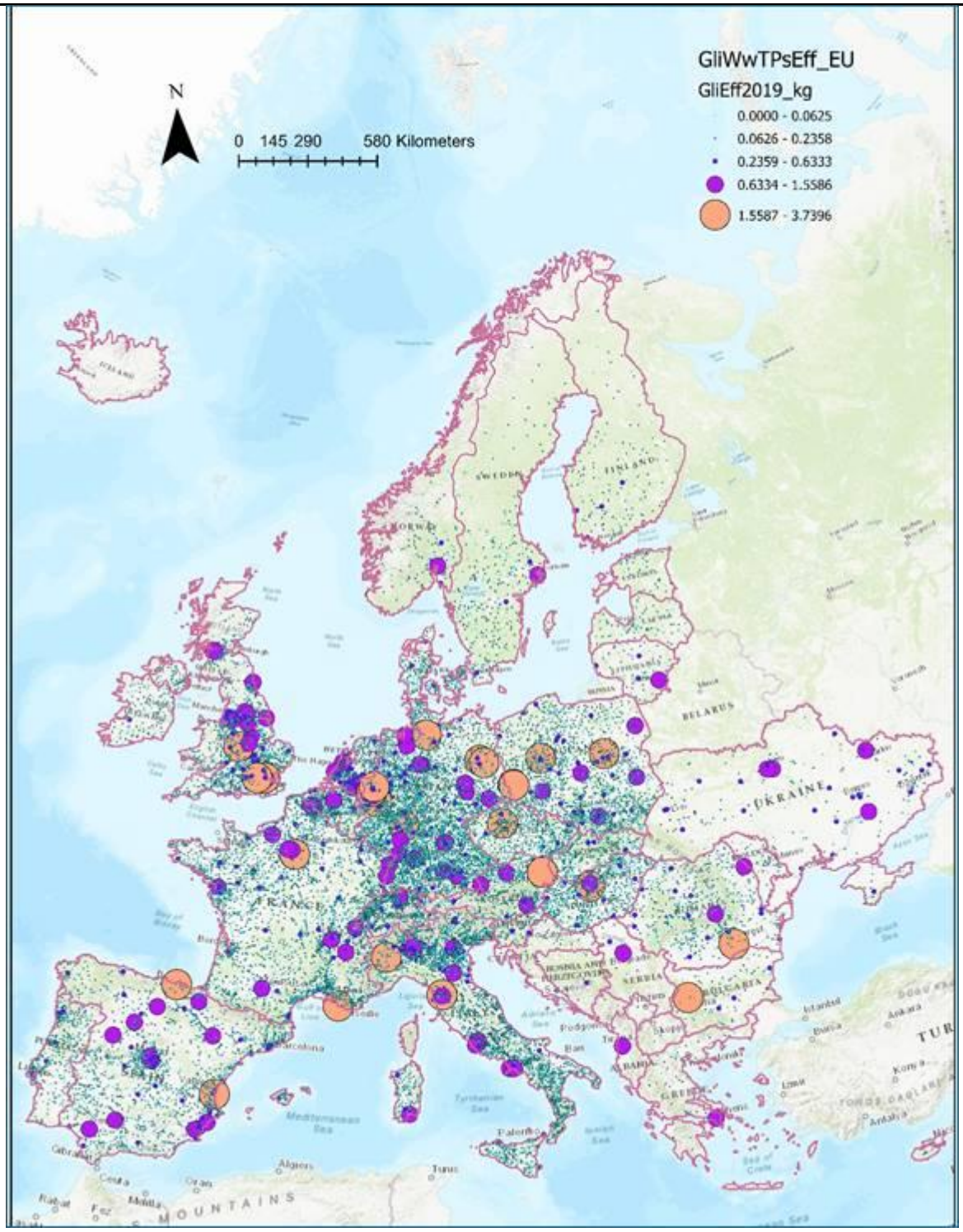


Figure 23. Estimated emissions of Gliclazide to surface waters across Europe (kg/WwTP/year)

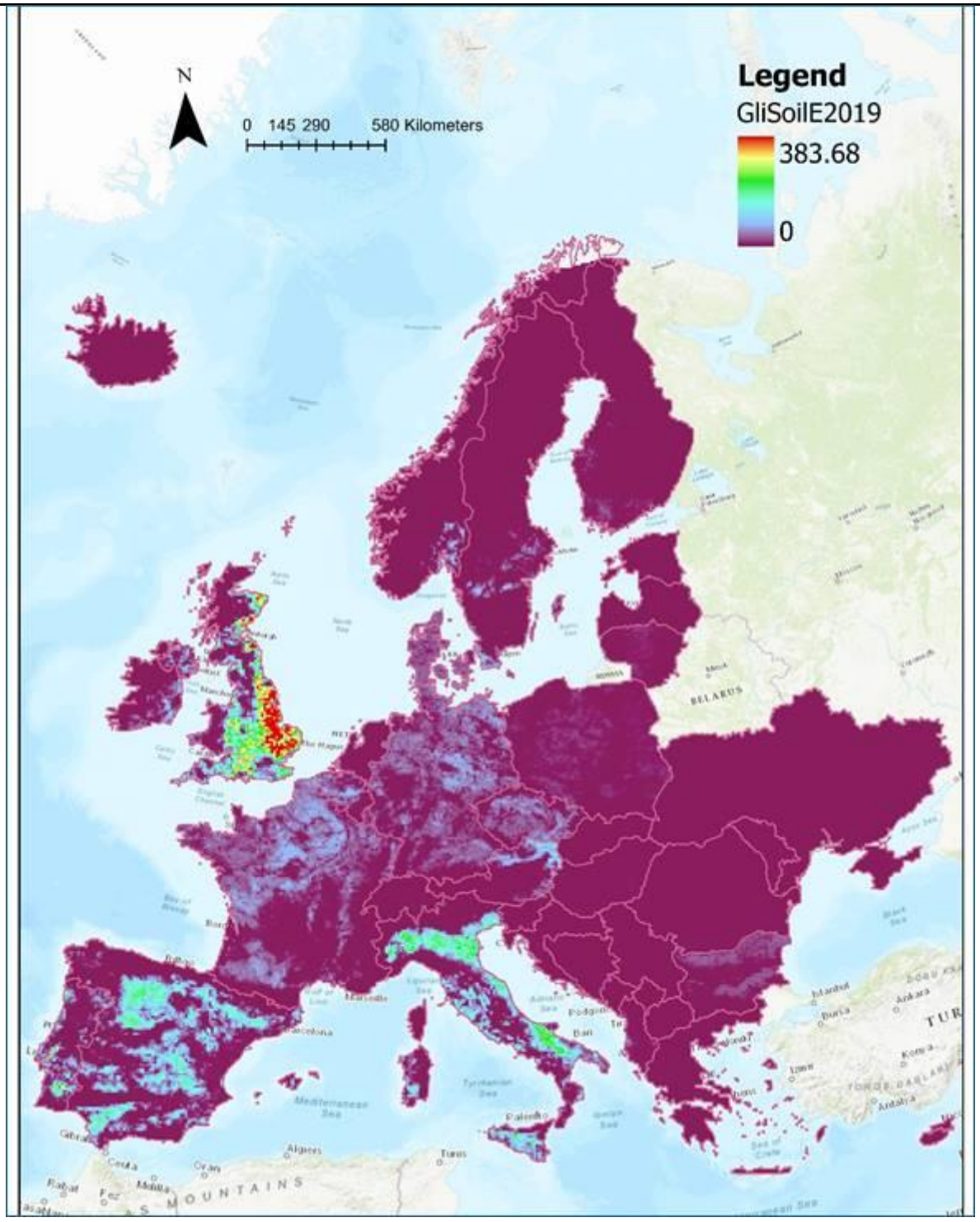


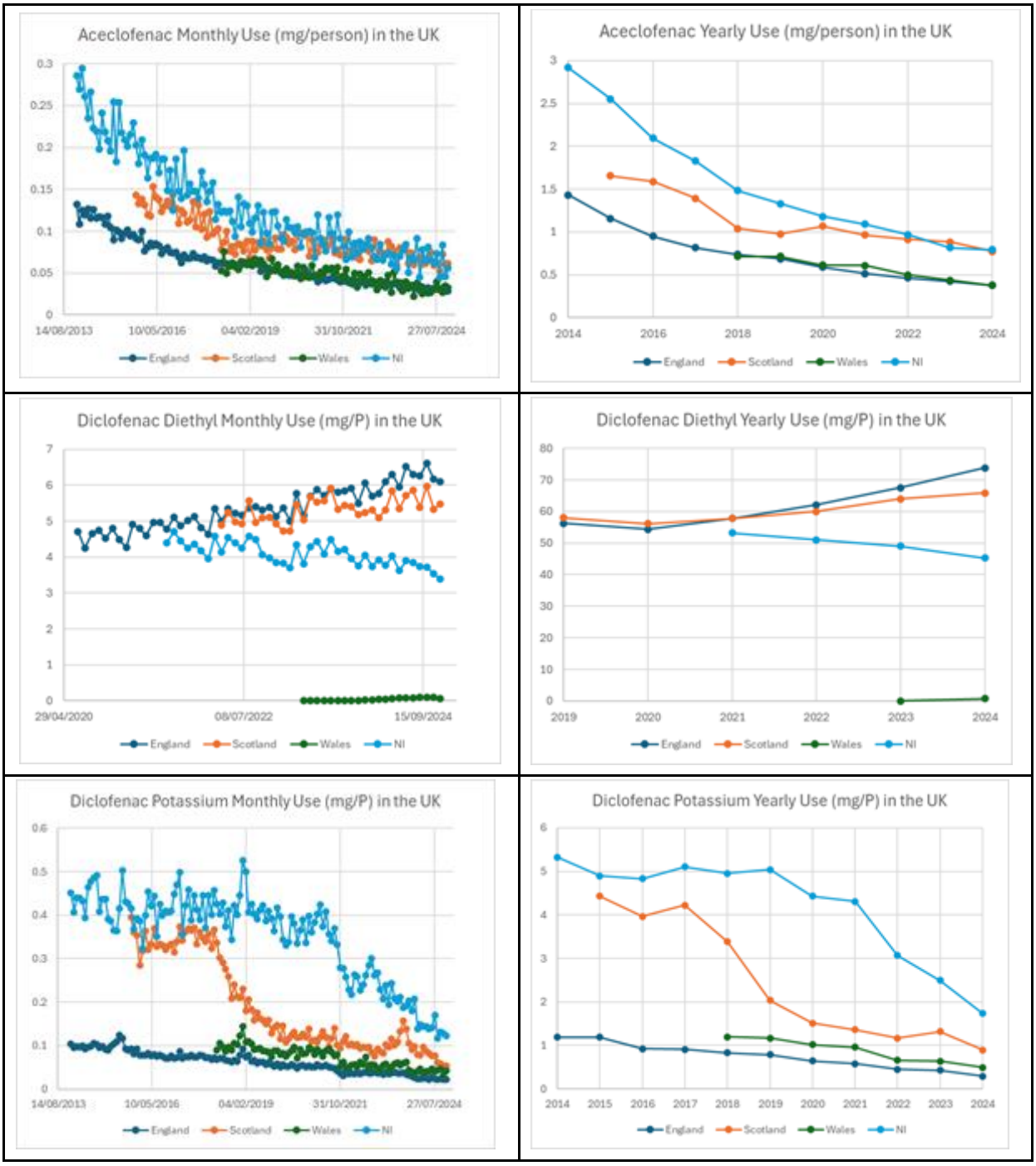
Figure 24. Estimated emissions of Gliclazide to soils Across Europe (g/cell/year)

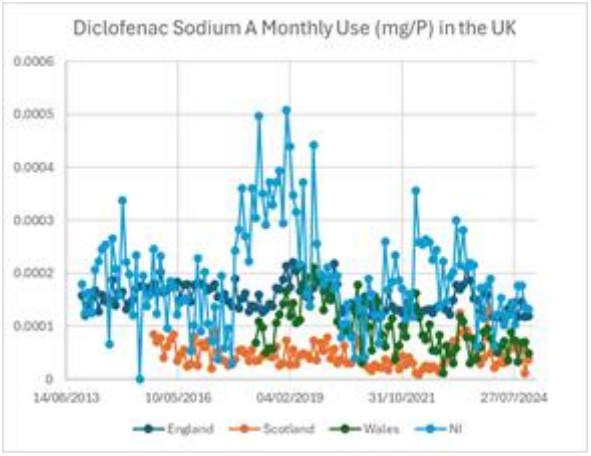
Estimated emissions of Gliclazide to surface waters and soils across Europe from 2018 to 2024 were calculated. Figure 23 presents Gliclazide emissions to surface waters in 2019 via WWTP effluents. The highest emissions were observed at WWTPs serving the largest populations, reaching approximately 3.74 kg per year per WWTP. Figure 24 shows the estimated emissions to soils in 2019 resulting from the agricultural application of WWTP sludge. Higher emissions were concentrated in the eastern arable regions of the UK, reaching up to 383.68 g per 10 × 10 km grid cell in that year. Similar to Amitriptyline, countries with relatively high emissions per grid cell include Portugal, Italy, and Spain.

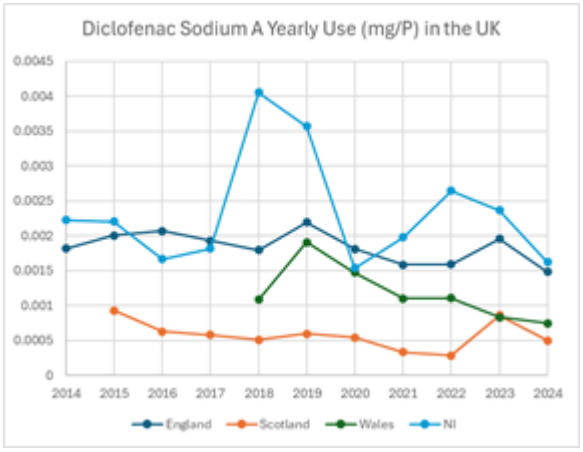
3.1.3.4 DICLOFENAC

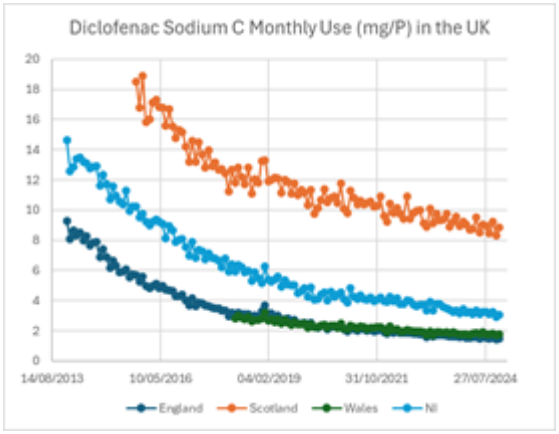
3.1.3.4.1 Drugs - per Capita Usage in the Nations of the UK

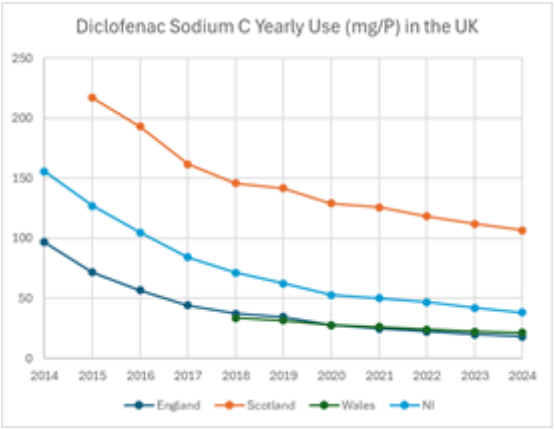
Figure 25 presents the monthly and annual per capita consumption of all prescribed drugs associated with the API Diclofenac. As shown, per capita consumption of oral formulations declines over time, with Diclofenac Sodium C being the predominant oral product throughout the study period. In contrast, the use of topical formulations generally increases over time. The data for Diclofenac Diethyl and Diclofenac Sodium U are complementary and should therefore be interpreted jointly. The topical formulation Diclofenac Sodium W also exhibits seasonal variation, although an overall increasing trend is observed.

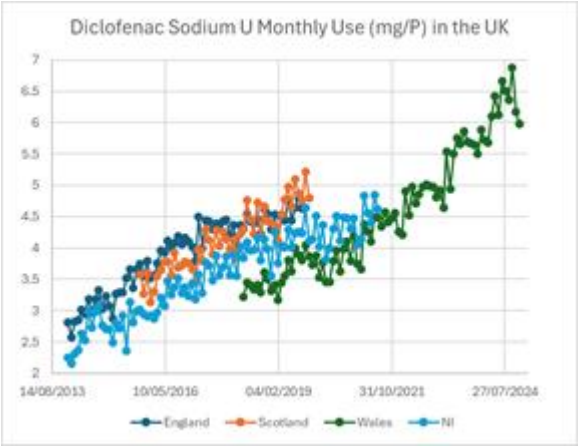


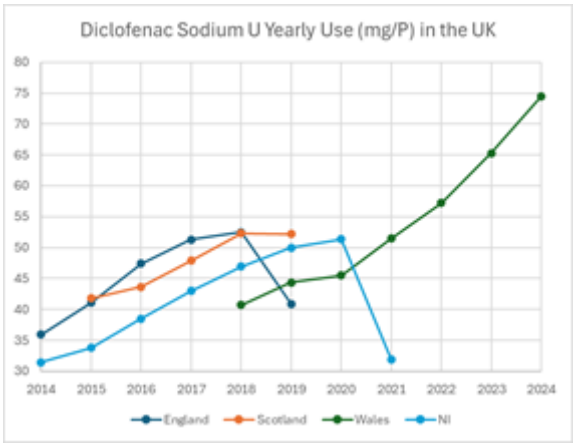

Diclofenac Sodium A Monthly Use (mg/P) in the UK
0.0006
0.0005
0.0004
0.0003
0.0002
0.0001
0
14/08/2013
10/05/2016
04/02/2019
31/10/2021
27/07/2024
England
Scotland
Wales
NI

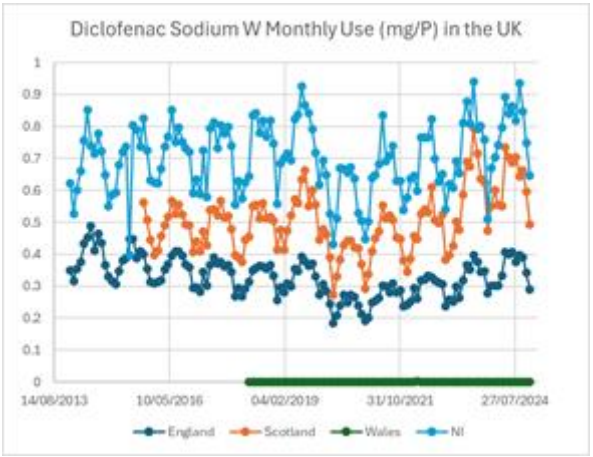

Diclofenac Sodium A Yearly Use (mg/P) in the UK
0.0045
0.004
0.0035
0.003
0.0025
0.002
0.0015
0.001
0.0005
0
2014
2015
2016
2017
2018
2019
2020
2021
2022
2023
2024
England
Scotland
Wales
NI


Diclofenac Sodium C Monthly Use (mg/P) in the UK
20
18
16
14
12
10
8
6
4
2
0
14/08/2013
10/05/2016
04/02/2019
31/10/2021
27/07/2024
England
Scotland
Wales
NI


Diclofenac Sodium C Yearly Use (mg/P) in the UK
250
200
150
100
50
0
2014
2015
2016
2017
2018
2019
2020
2021
2022
2023
2024
England
Scotland
Wales
NI


Diclofenac Sodium U Monthly Use (mg/P) in the UK
7
6.5
6
5.5
5
4.5
4
3.5
3
2.5
2
14/08/2013
10/05/2016
04/02/2019
31/10/2021
27/07/2024
England
Scotland
Wales
NI


Diclofenac Sodium U Yearly Use (mg/P) in the UK
80
75
70
65
60
55
50
45
40
35
30
2014
2015
2016
2017
2018
2019
2020
2021
2022
2023
2024
England
Scotland
Wales
NI


Diclofenac Sodium W Monthly Use (mg/P) in the UK
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
14/08/2013
10/05/2016
04/02/2019
31/10/2021
27/07/2024
England
Scotland
Wales
NI

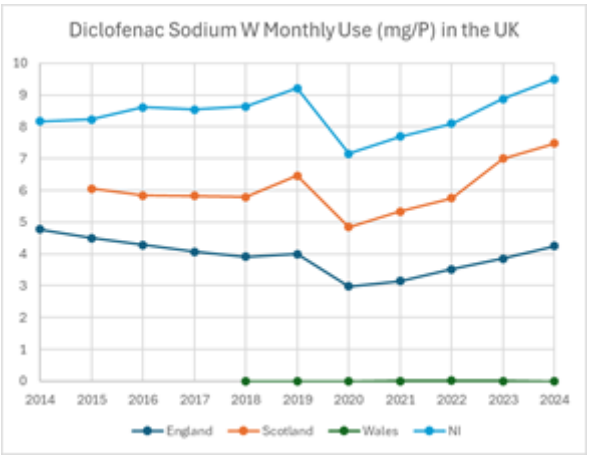

Diclofenac Sodium W Monthly Use (mg/P) in the UK
10
9
8
7
6
5
4
3
2
1
0
2014
2015
2016
2017
2018
2019
2020
2021
2022
2023
2024
England
Scotland
Wales
NI

Figure 25. Monthly and yearly per capita use of Diclofenac drugs (in an order of Aceclofenac (pre-drug), Diclofenac Diethyl, Diclofenac Potassium, Diclofenac Potassium, Diclofenac Sodium A, Diclofenac Sodium C, Diclofenac Sodium U, Diclofenac Sodium W) in the nations of the UK (mg/person)

3.1.3.4.2 Diclofenac API

Per Capita Usage in the Nations of the UK

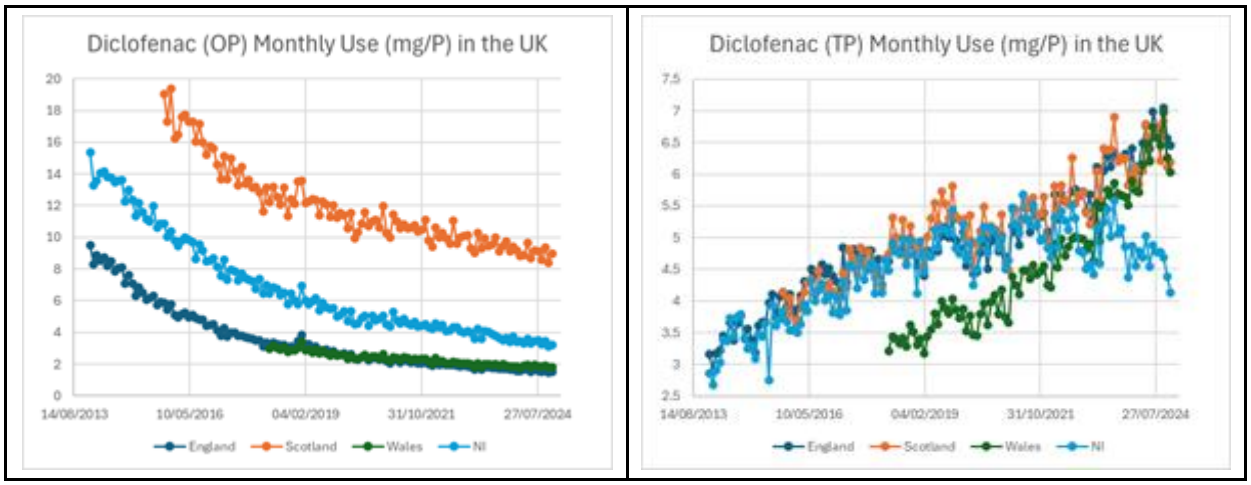


Figure 26. Monthly per capita prescription of oral and topical Diclofenac in the UK nations

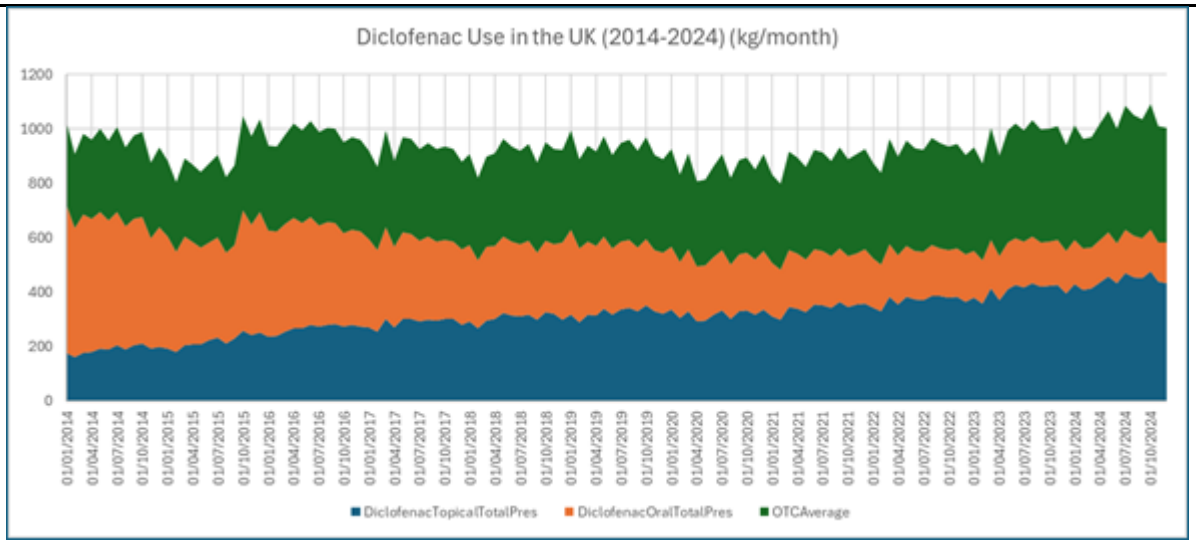


Figure 27. Monthly use of oral and topical Diclofenac drugs prescribed and those over the counter in the UK (kg/person)

Figure 26 presents the monthly per capita prescription of oral and topical Diclofenac across the UK nations (mg per person), aggregated from all associated drug formulations. Although oral Diclofenac prescriptions show an overall declining trend, Scotland consistently records the highest per capita consumption among the nations, followed by Northern Ireland. England and Wales exhibit similar and comparatively lower per capita values. Per capita prescriptions of topical Diclofenac are broadly comparable across nations. Wales shows lower values during the earlier period, whereas Northern Ireland records relatively lower values in more recent years.

Figure 27 is an area chart, presenting the total monthly consumption of oral and topical Diclofenac prescribed in the UK, together with OTC sales (topical formulations only, as oral formulations are not available OTC), expressed in kg per month. As shown, OTC consumption increases steadily over time and accounts for approximately one third of total Diclofenac use, which exceeds 1,000 kg per month in the most recent year. These findings are consistent with the Diclofenac data reported by Austin et al. (2021).

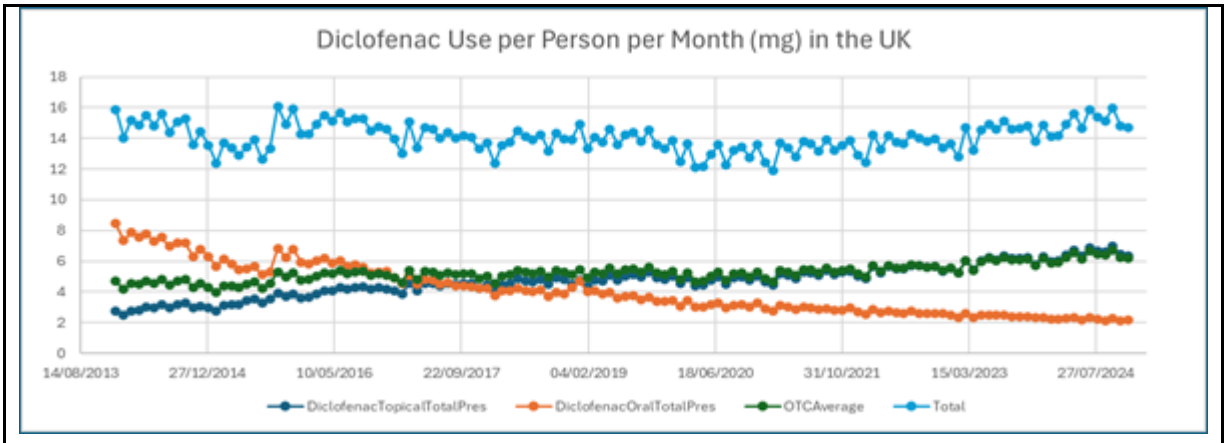


Figure 28. Diclofenac monthly per person use in the UK (mg/person)

Figure 28 shows the total monthly per capita consumption of Diclofenac in the UK. As shown, per capita use ranges from approximately 12 to 16 mg per person per month. The relative contributions of prescribed and over-the-counter products, as well as oral and topical formulations, vary over time in line with changes in the consumption of the associated drug formulations.

Calculated Average Emissions in the UK

Table 9. Per capita usage, emissions, and influent concentrations in WwTPs in the UK

	Topical TotalPres (mg/person)	Oral TotalPres (mg/person)	OTC Average (mg/person)	Influent flux (mg/person)	Influent Conc.(ug/L)	Effluent Conc. (ug/L)
2018	16.60	0.97	18.52	36.08	0.55	0.35
2019	17.59	0.91	19.17	37.67	0.57	0.37
2020	17.19	0.76	18.20	36.15	0.55	0.35
2021	18.33	0.70	18.97	38.00	0.58	0.37
2022	19.67	0.64	19.90	40.20	0.61	0.39
2023	21.42	0.58	21.21	43.21	0.66	0.42
2024	23.31	0.54	22.69	46.54	0.71	0.45

Table 10. Statistics of measured concentrations in WwTPs in the UK

Name	Influent Mean (ug/L)	Influent Median (ug/L)	Effluent Mean (ug/L)	Effluent Median (ug/L)	Number of measurements
Diclofenac	0.64	0.44	0.41	0.33	976/1149

The calibrated disposal rate was 1%. The calculated influent and effluent concentrations for the period 2018–2024 are presented in Table 9. A comparison with the summary statistics of measured concentrations in UK wastewater treatment plants (WWTPs), provided in Table 10, shows that the

calculated concentrations (both influent and effluent) closely approximate the median measured values and remain within the same order of magnitude. This agreement indicates that the estimates are reasonably robust and therefore suitable for use in subsequent calculations for European countries.

Emissions to surface waters and soils across the Europe

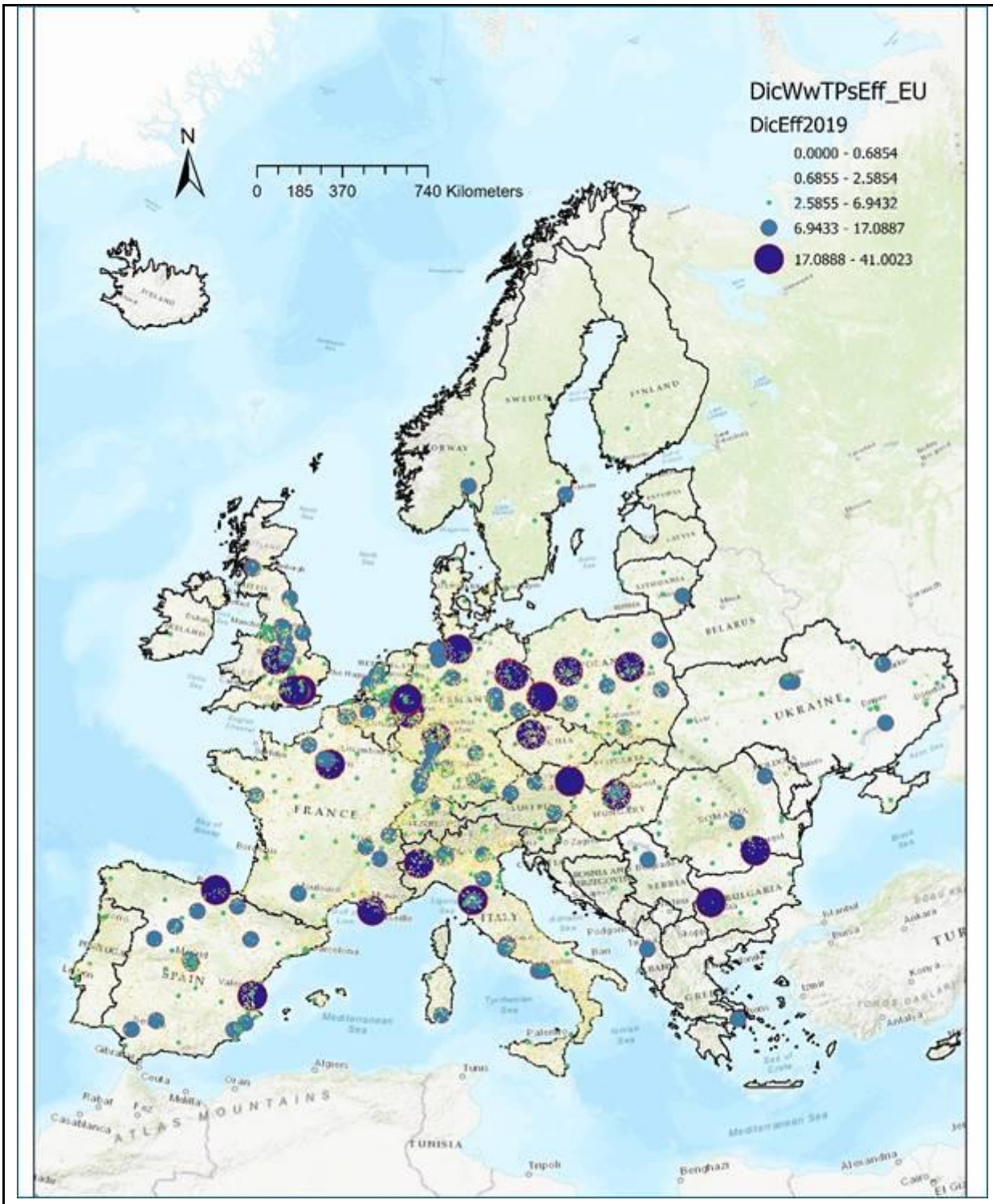


Figure 29. Estimated emissions of Diclofenac to surface waters across Europe (kg/WwTP/year)

Estimated emissions of Diclofenac to surface waters and soils across Europe from 2018 to 2024 were calculated. Figure 29 presents Diclofenac emissions to surface waters in 2019 via WWTP effluents. The highest emissions were observed at WWTPs serving the largest populations, reaching approximately 41 kg per year per WWTP. Figure 30 shows the estimated emissions to soils in 2019. The spatial distribution follows a pattern similar to that observed for the previous two APIs; however,

the maximum Diclofenac emission reaches up to 791 g per 10 × 10 km grid cell in the eastern arable regions of the UK.

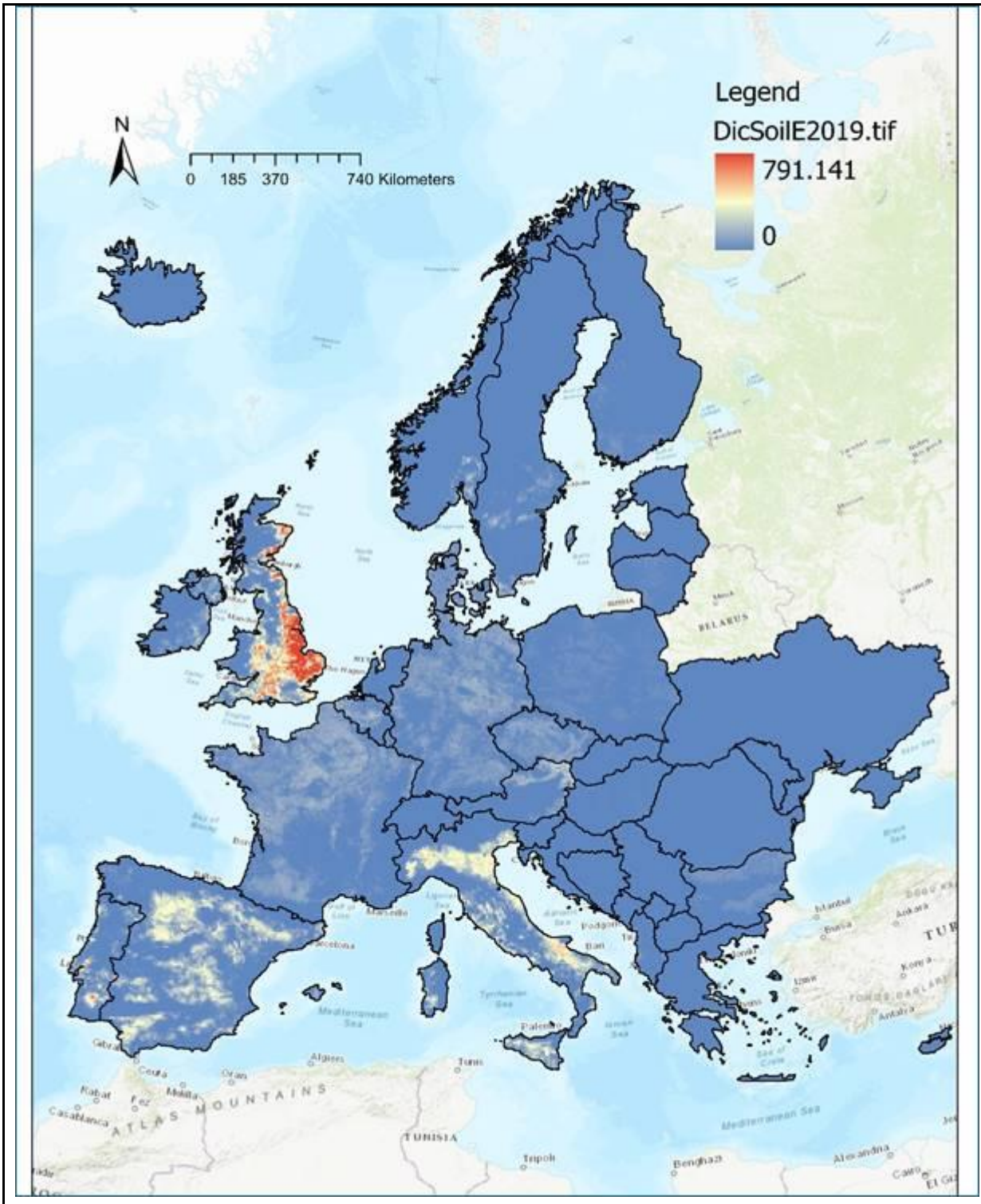


Figure 30. Estimated emissions of Diclofenac to soils Across Europe (g/cell/year)

3.1.3.5 IBUPROFEN

3.1.3.5.1 Drugs

Per Capita Usage across UK Regions

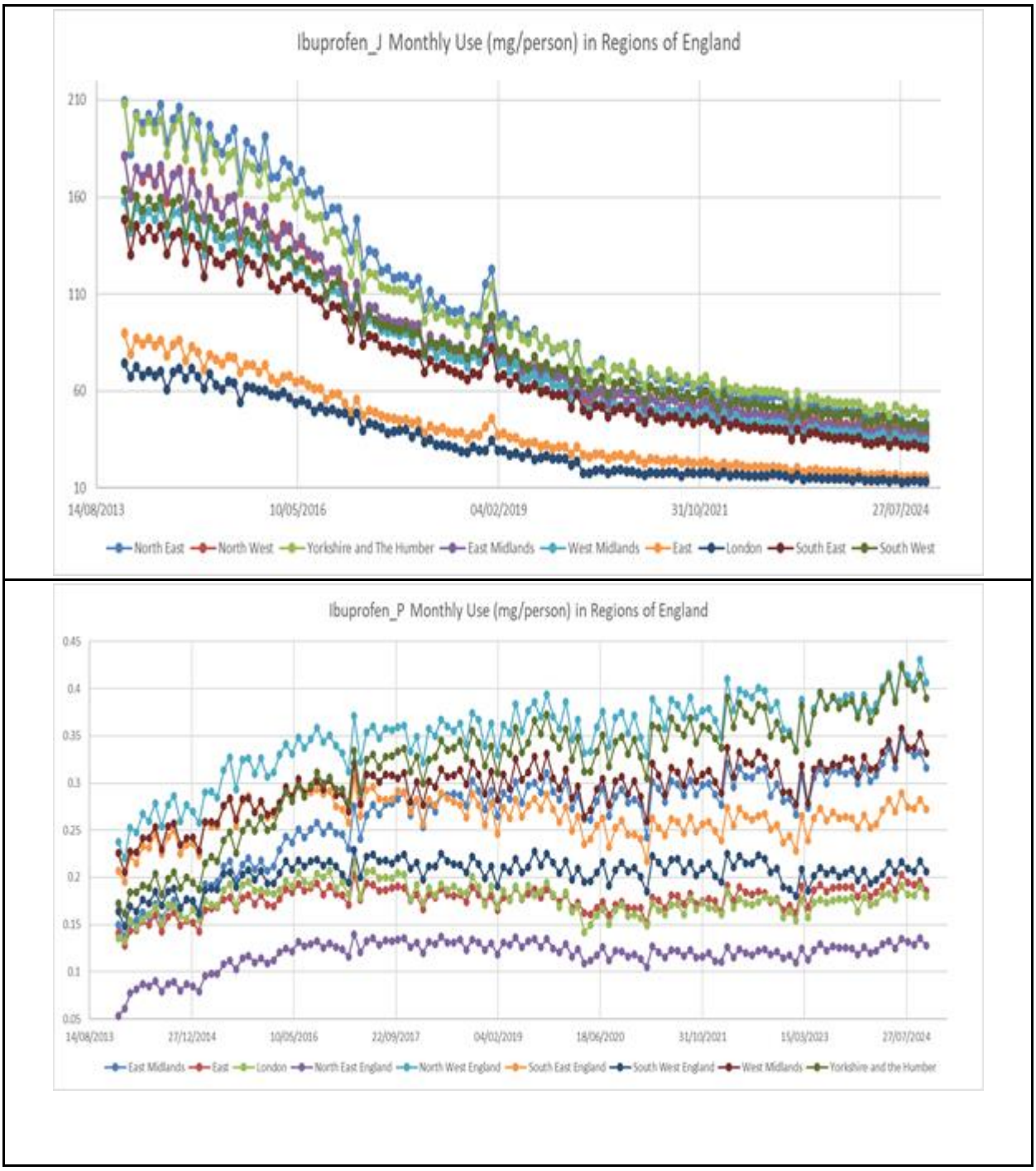
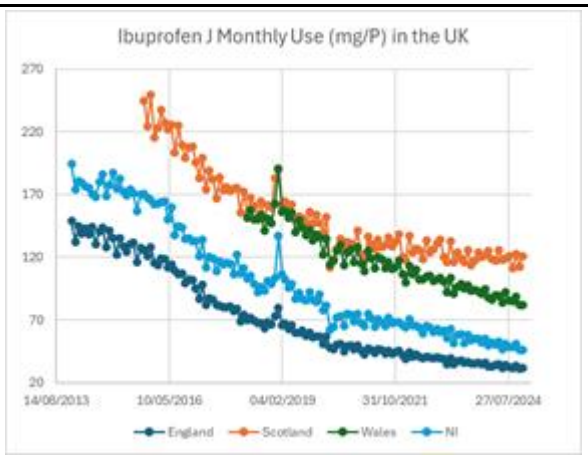
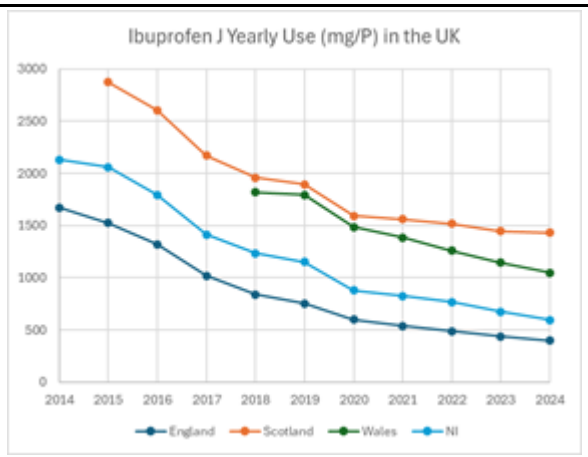


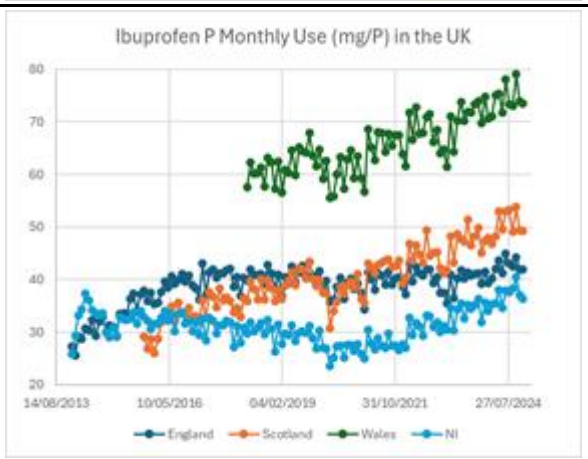
Figure 31. Monthly per capita use of Ibuprofen (J and P) across UK regions (mg/person)

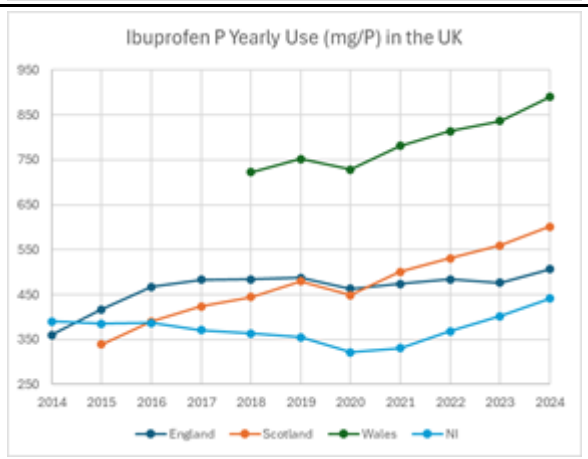
Figure 31 presents the monthly per capita prescription of Ibuprofen across regions in England. The upper panel represents the principal oral formulation (Ibuprofen J), while the lower panel shows the main topical formulation, with minor products excluded from the analysis. As shown, prescribed oral Ibuprofen declines across all regions over time, with a steeper decrease observed in the first half of the study period compared with the second. On average, per capita prescriptions are lower in London and the East of England than in other regions. In contrast, prescribed topical Ibuprofen exhibits a relatively stable but slightly increasing trend over time.

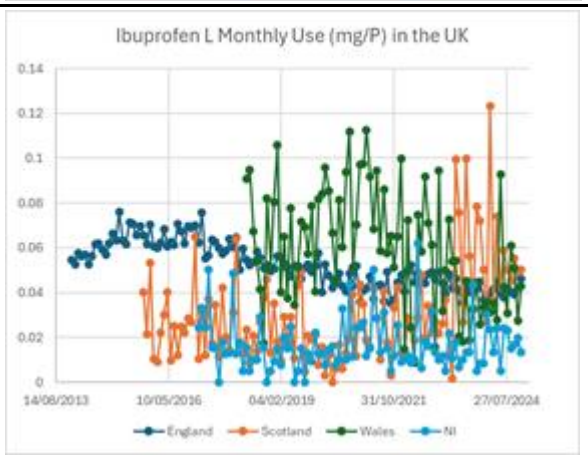
Per Capita Usage in the Nations of the UK

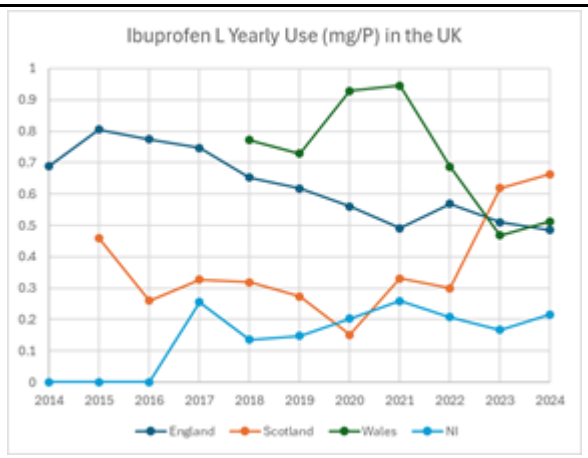

Ibuprofen J Monthly Use (mg/P) in the UK
270
220
170
120
70
20
14/08/2013
10/05/2016
04/02/2019
31/10/2021
27/07/2024
England
Scotland
Wales
NI

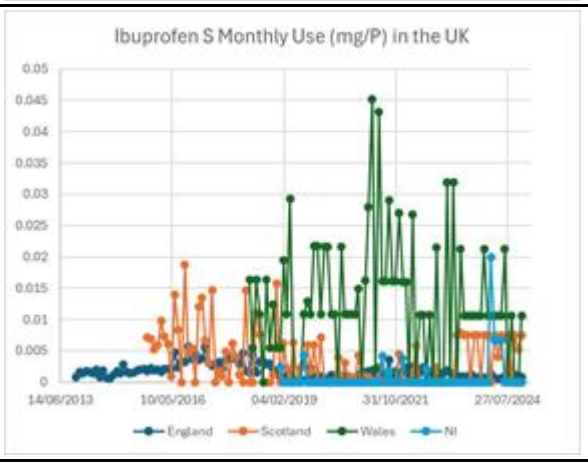

Ibuprofen J Yearly Use (mg/P) in the UK
3000
2500
2000
1500
1000
500
0
2014
2015
2016
2017
2018
2019
2020
2021
2022
2023
2024
England
Scotland
Wales
NI


Ibuprofen P Monthly Use (mg/P) in the UK
80
70
60
50
40
30
20
14/08/2013
10/05/2016
04/02/2019
31/10/2021
27/07/2024
England
Scotland
Wales
NI


Ibuprofen P Yearly Use (mg/P) in the UK
950
850
750
650
550
450
350
250
2014
2015
2016
2017
2018
2019
2020
2021
2022
2023
2024
England
Scotland
Wales
NI


Ibuprofen L Monthly Use (mg/P) in the UK
0.14
0.12
0.1
0.08
0.06
0.04
0.02
0
14/08/2013
10/05/2016
04/02/2019
31/10/2021
27/07/2024
England
Scotland
Wales
NI


Ibuprofen L Yearly Use (mg/P) in the UK
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
2014
2015
2016
2017
2018
2019
2020
2021
2022
2023
2024
England
Scotland
Wales
NI


Ibuprofen S Monthly Use (mg/P) in the UK
0.05
0.045
0.04
0.035
0.03
0.025
0.02
0.015
0.01
0.005
0
14/08/2013
10/05/2016
04/02/2019
31/10/2021
27/07/2024
England
Scotland
Wales
NI

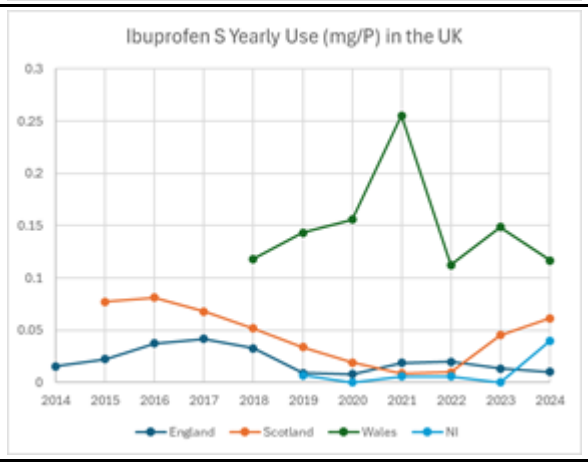

Ibuprofen S Yearly Use (mg/P) in the UK
0.3
0.25
0.2
0.15
0.1
0.05
0
2014
2015
2016
2017
2018
2019
2020
2021
2022
2023
2024
England
Scotland
Wales
NI

Figure 32. Monthly and yearly per capita use of Ibuprofen drugs in the UK (mg/person)

Figure 32 presents the monthly and annual per capita prescription of all drugs associated with the API Ibuprofen (prescribed products only). As shown, the per capita trends for the main oral and topical formulations across the four nations are similar to those observed for the regions in England. In contrast, the remaining two formulations do not exhibit consistent or stable trends across the nations.

3.1.3.5.2 Ibuprofen API

Per Capita Usage in the Nations of the UK (Prescribed):

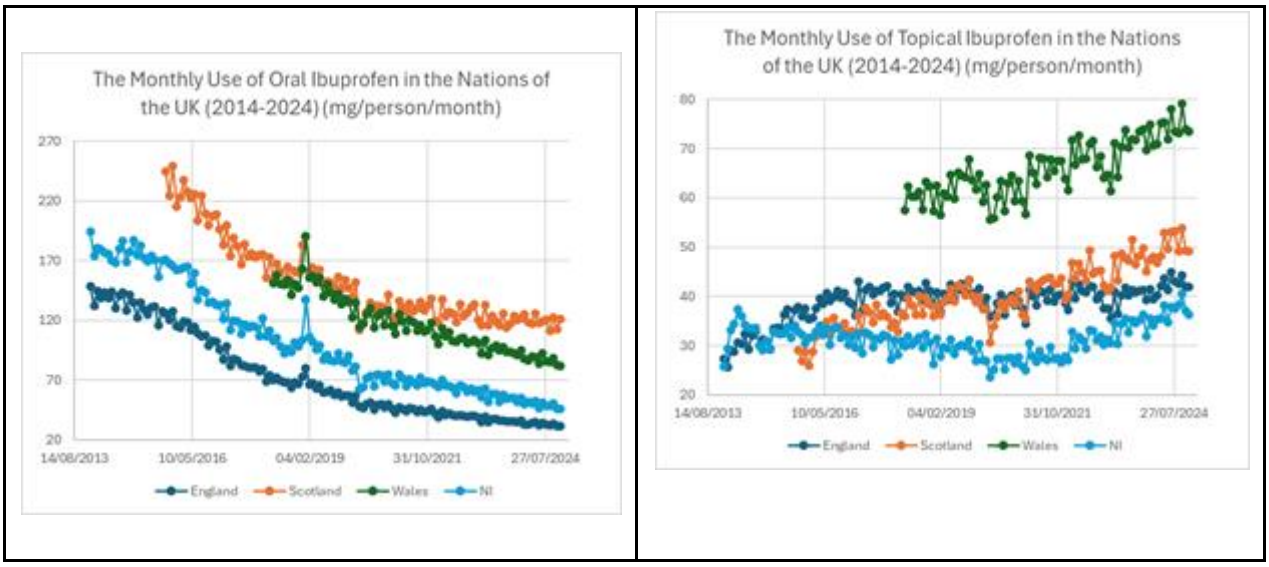


Figure 33. Monthly and yearly per capita prescription of oral and topical Ibuprofen in the UK nations (mg/person)

Figure 33 presents the monthly per capita prescription of oral and topical Ibuprofen across the UK nations, aggregated from all associated drug formulations (corresponding to the first two monthly trend charts in Figure 32). As shown, England records the lowest per capita prescription of oral Ibuprofen, whereas Wales exhibits the highest per capita use of topical Ibuprofen among the nations.

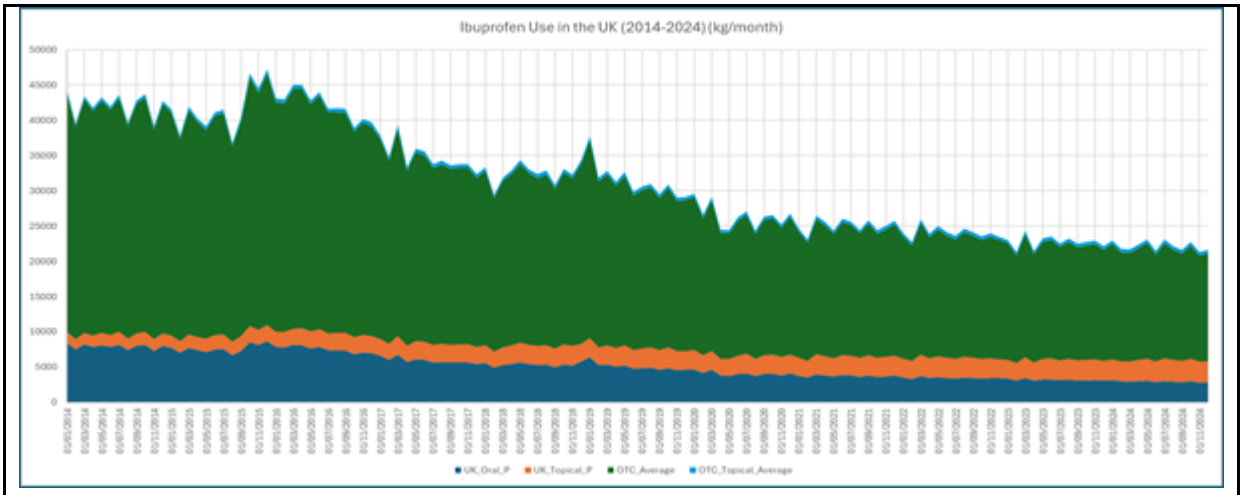


Figure 34. Ibuprofen Use in the UK (2014-2024) (kg/month) (prescribed + OTC)

Figure 34 presents the total monthly consumption of oral and topical Ibuprofen in the UK, including both prescribed and OTC products. As shown, OTC oral Ibuprofen accounts for the majority of total Ibuprofen consumption, reaching more than 45,000 kg per month in 2015 and declining to approximately 21,500 kg per month in 2024. These results are comparable with the Ibuprofen data reported by Austin et al. (2021).

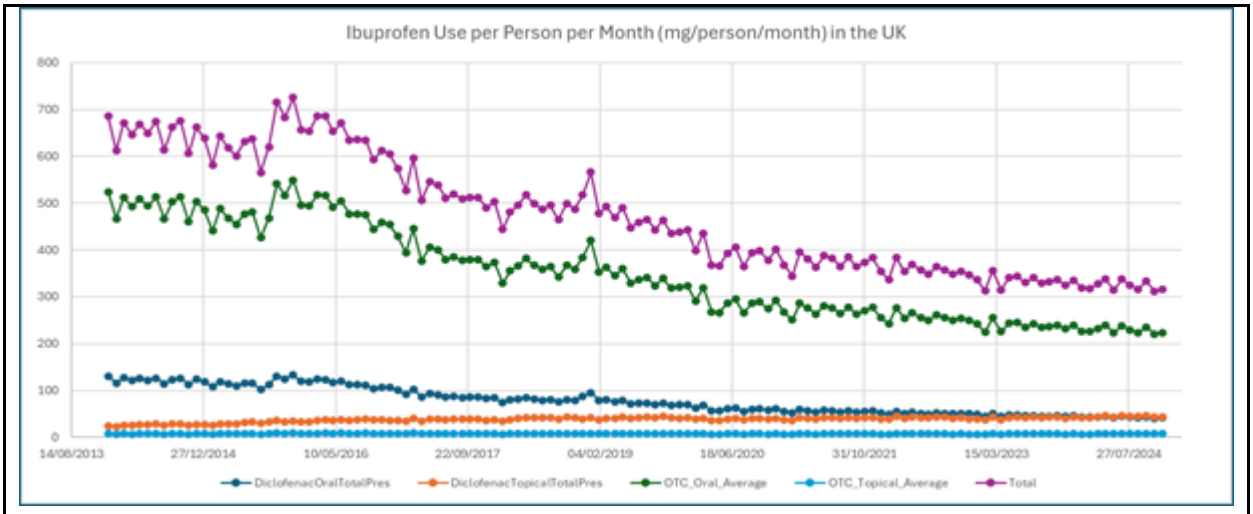


Figure 35. Ibuprofen monthly per person use in the UK (mg/person)

Figure 35 presents the total monthly per capita consumption of Ibuprofen in the UK (mg per person), including oral and topical formulations, both prescribed and OTC. Overall, total per capita consumption declines over time, decreasing from a peak of more than 700 mg per person per month to approximately 300 mg per person per month in 2024.

Calculated Average Emissions in the UK

Table 11. Per capita usage, emissions, and influent concentrations in WwTPs in the UK

	Oral_ Prescribed (mg/P/Y)	Topical_ Prescribed (mg/P/Y)	OTC_Oral_ Average (mg/P/Y)	OTC_Topical_ Average (mg/P/Y)	Disposal (down the drain 2% (mg/P/Y)	Influent Flux (mg/P/Y)	Influent Conc (ug/L)	Effluent Conc (ug/L)
2018	93.14	215.95	419.11	43.05	117.90	889.15	13.52	0.07
2019	87.32	222.86	399.78	43.20	112.99	866.16	13.17	0.07
2020	70.39	211.62	332.97	39.27	94.92	749.17	11.40	0.06
2021	64.48	218.62	313.34	39.43	89.94	725.80	11.04	0.06
2022	59.24	224.91	295.9	39.57	85.52	705.19	10.73	0.06
2023	53.77	223.87	275.23	38.66	80.00	671.53	10.21	0.05
2024	49.83	238.51	265.48	40.15	77.87	671.85	10.22	0.05

Table 12. Some statistics of measured concentrations in WwTPs in the UK

Sample Location Name	AvgOf Revised value	MinOf Revised value	MaxOf Revised value	StDevOf Revised value	Median	CountOf Revised value
Treatment Effluent	0.722	0.0025	56	3.385927	0.04	1132
Treatment Influent	18.171	0.005	766	28.10577	16.16	949

Compared with the measured data, the calculated concentrations (both influent and effuent) fall within the same order of magnitude as the median measured values. This agreement suggests that the estimates are reasonably robust and therefore suitable for use in subsequent calculations for European countries.

Emissions to surface waters and soils across the Europe

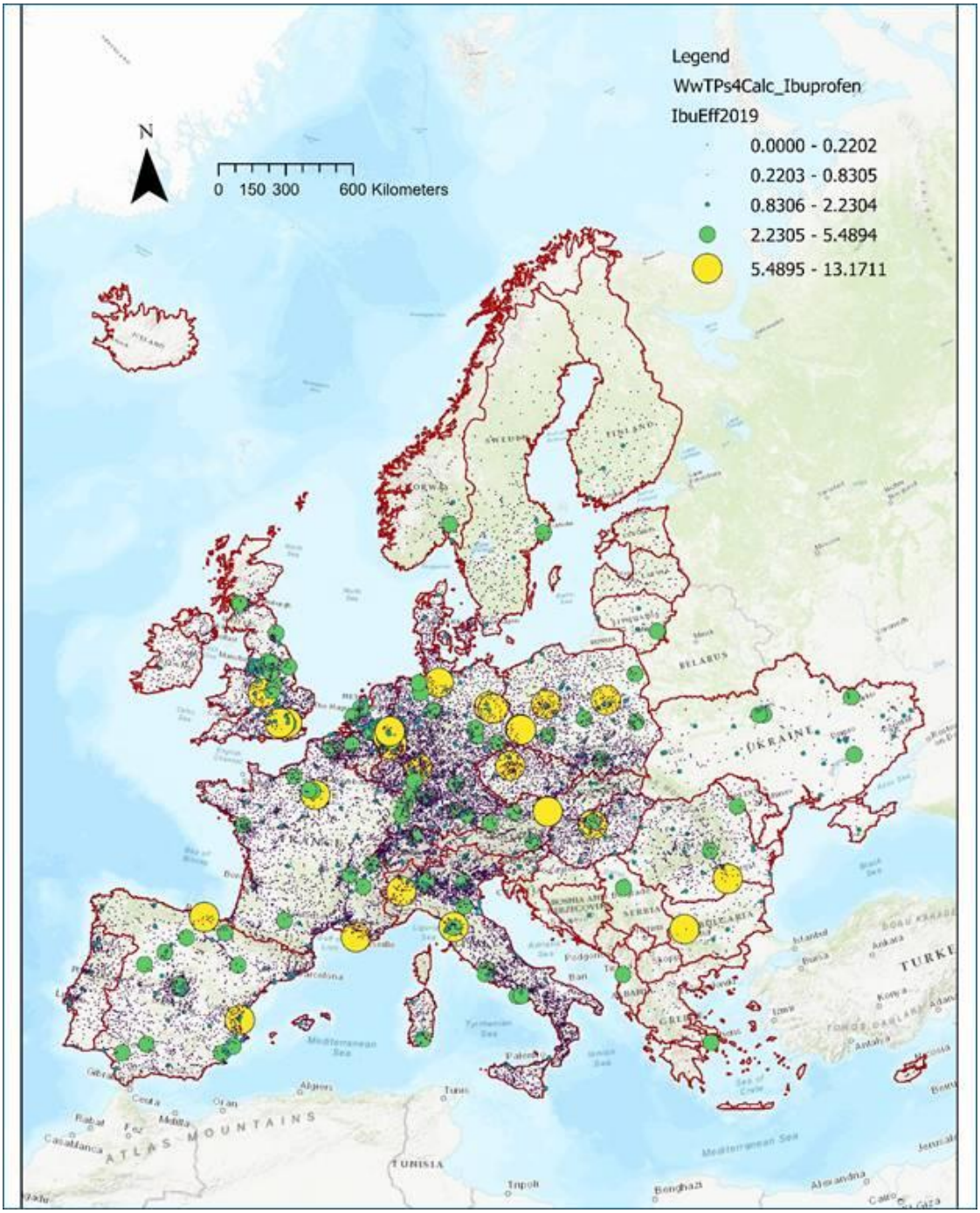


Figure 36. Estimated emissions of Ibuprofen to surface waters across Europe (kg/WwTP/year)

Estimated emissions of Ibuprofen to surface waters and soils across Europe from 2018 to 2024 were calculated. Figure 36 presents Ibuprofen emissions to surface waters in 2019 via WWTP effluents.

The highest emissions were observed at WWTPs serving the largest populations, reaching approximately 13.17 kg per year per WWTP. Figure 37 shows the estimated emissions to soils in 2019 resulting from the agricultural application of WWTP sludge. Higher emissions were concentrated in the eastern part of the UK, reaching up to 85 kg per 10 × 10 km grid cell in that year. Relatively high emissions per grid cell were also observed in countries such as Portugal, Italy, and Spain.

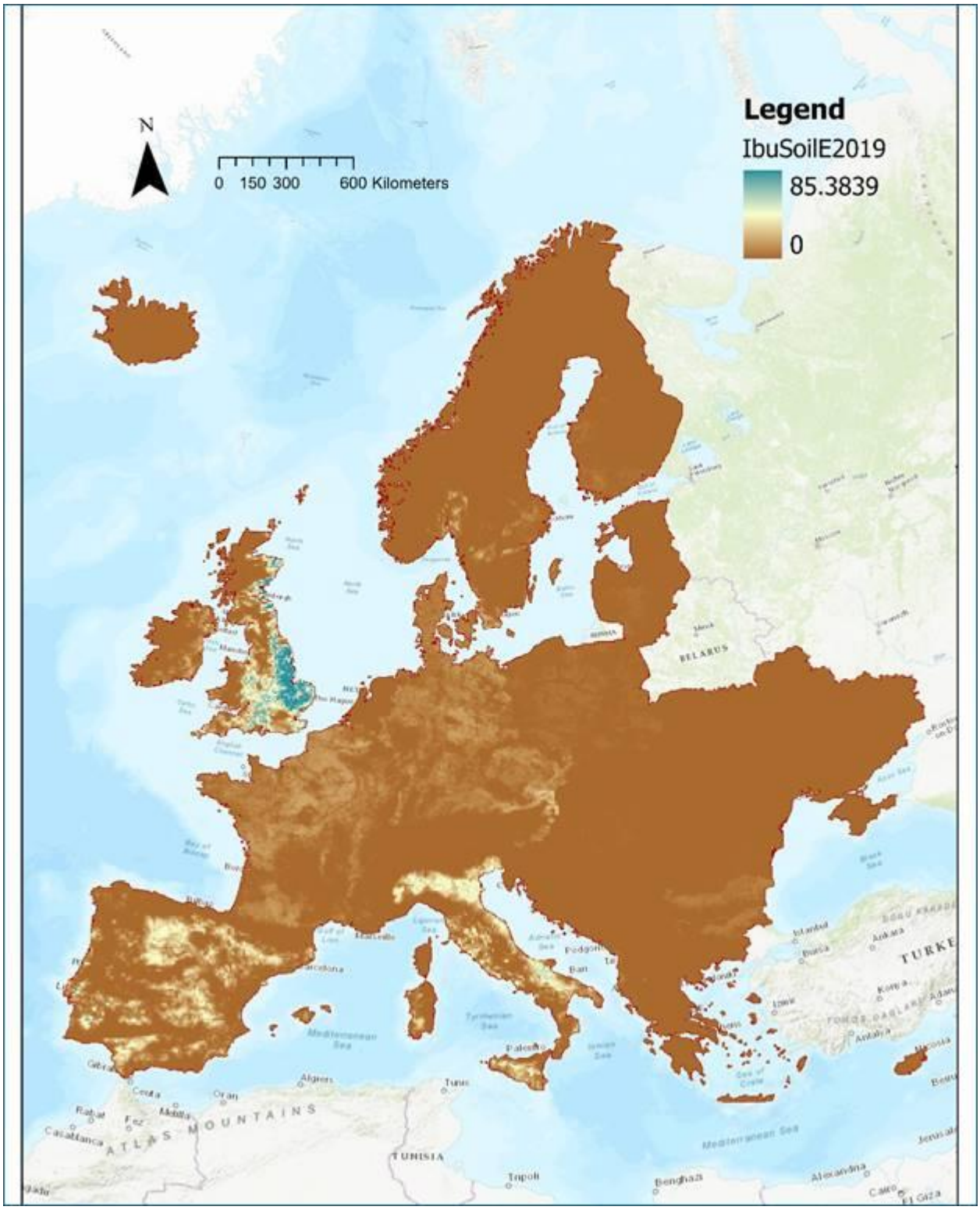


Figure 37. Estimated emissions of Ibuprofen to soils Across Europe (kg/cell/year)

3.2 Multimedia exposure predictions

3.2.1 Model framework

Multimedia environmental exposure predictions for the selected pharmaceuticals (amitriptyline, diclofenac, gliclazide, ibuprofen, and rifaximin) were generated using the SimpleBox multimedia fate model as implemented in the SBoo framework. SimpleBox is a mechanistic, steady-state and dynamic mass-balance box model that describes the environmental distribution, transport, and degradation of chemicals across interconnected environmental compartments at defined spatial scales. SimpleBox follows the "Mackay type" level III (steady-state, non-equilibrium) and level IV (dynamic, non-equilibrium) modelling principles. The model has been widely applied for chemical risk assessment in Europe and forms the basis of regulatory exposure tools used under REACH and related frameworks.

In this study, SimpleBox was applied at the continental (Europe) scale, treating the Europe as a single, well-mixed environmental system. The model represents the environment as a set of homogeneous compartments, including air, surface water, sediment, and agricultural soil, which are connected by advective transport and intermedia exchange processes. For molecular (non-particulate) substances such as pharmaceuticals, SimpleBox simulates fate processes including volatilisation, deposition, runoff, sedimentation, resuspension, and degradation. The model solves mass balance equations that account for:

- Emissions: Direct releases into specific compartments (e.g., WWTP effluents into surface water, biosolids application to agricultural soil).
- Transport: Advective (wind, water flow) and diffusive (volatilization, deposition) exchange between compartments.
- Transformation: Degradation processes (hydrolysis, photolysis, biodegradation) represented by first-order rate constants (k_{deg}).

3.2.2 Model compartments and system definition

Exposure predictions focused on the continental unbound compartments most relevant for pharmaceutical emissions:

- Agricultural soil (s2CU) – representing continental agricultural soils receiving diffuse inputs;
- River water (w1CU) – representing continental surface waters receiving point-source discharges.

The continental scale was selected to ensure consistency with the spatial aggregation of emission inventories and to allow comparison across substances using a harmonised modelling framework. Within SimpleBox, all grid-level emissions were spatially aggregated prior to modelling, and predicted environmental concentrations (PECs) therefore represent EU-average concentrations within each compartment.

The analysis was conducted in two phases:

- Steady-State Analysis (2018–2024): Calculating the equilibrium concentrations (PEC) for each individual year based on that year's specific emission loads.
- Dynamic Simulation (ODE): Solving the system of Ordinary Differential Equations (ODEs) over the 7-year period to capture time-varying accumulation or depletion effects.

Standard environmental parameters for the "Continental" scale provided within the SimpleBox database were utilised, including temperature (285 K), wind speed (3 m/s), and precipitation rates specific to the European climate zone. The system assumes a "closed" continental box nested within the global scales, allowing for background exchange but focusing primarily on intra-continental fate.

3.2.3 Model Parametrisation

Substance-specific physicochemical properties were defined in the SimpleBox input files (Substances.csv) based on literature data, regulatory dossiers, and peer-reviewed sources. Parameters included molecular weight, acid dissociation constant (pKa), vapour pressure, aqueous solubility, air–water partitioning coefficient (K_{aw}), and octanol–water partition coefficient (K_{ow}).

Environmental degradation was represented using first-order degradation rate constants (kdeg) for air, water, soil, and sediment compartments. Spatially distributed emission data were aggregated to the Continental scale, with annual emission loads (kg/year) derived from wastewater treatment plant (WWTP) effluents discharging into river water and contaminated sewage sludge (biosolids) applied to agricultural soil. To address uncertainty in degradation kinetics, a two-dimensional sensitivity analysis was performed by varying the half-lives (DT_{50}) of required pharmaceutical (such as gliclazide, rifaximin) in soil and water across a range of 1 to 1000 days, assessing the sensitivity of the Predicted Environmental Concentration (PEC) to determine whether exposure is driven primarily by persistence in the water phase, the soil phase, or an interaction of both.

3.2.4 Exposure outputs

3.2.4.1 MULTIMEDIA FATE AND EXPOSURE ASSESSMENT OF AMITRIPTYLINE

Emission Trends and Sources The annual aggregated emissions of amitriptyline to the European continental environment are presented in Figure 38. Amitriptyline emissions exhibited a steady increasing trend over the simulation period (2018–2024). Total emissions rose from approximately 1,365 kg/year in 2018 to nearly 1,430 kg/year in 2024. The release pathway profile was dominated by discharges to surface water, with wastewater treatment plant (WWTP) effluents accounting for approximately 59% of the total load, while the remaining 41% entered agricultural soil via biosolid application. The persistence of both emission pathways over time highlights the continuous environmental loading of amitriptyline and the relevance of both aquatic and terrestrial exposure routes.

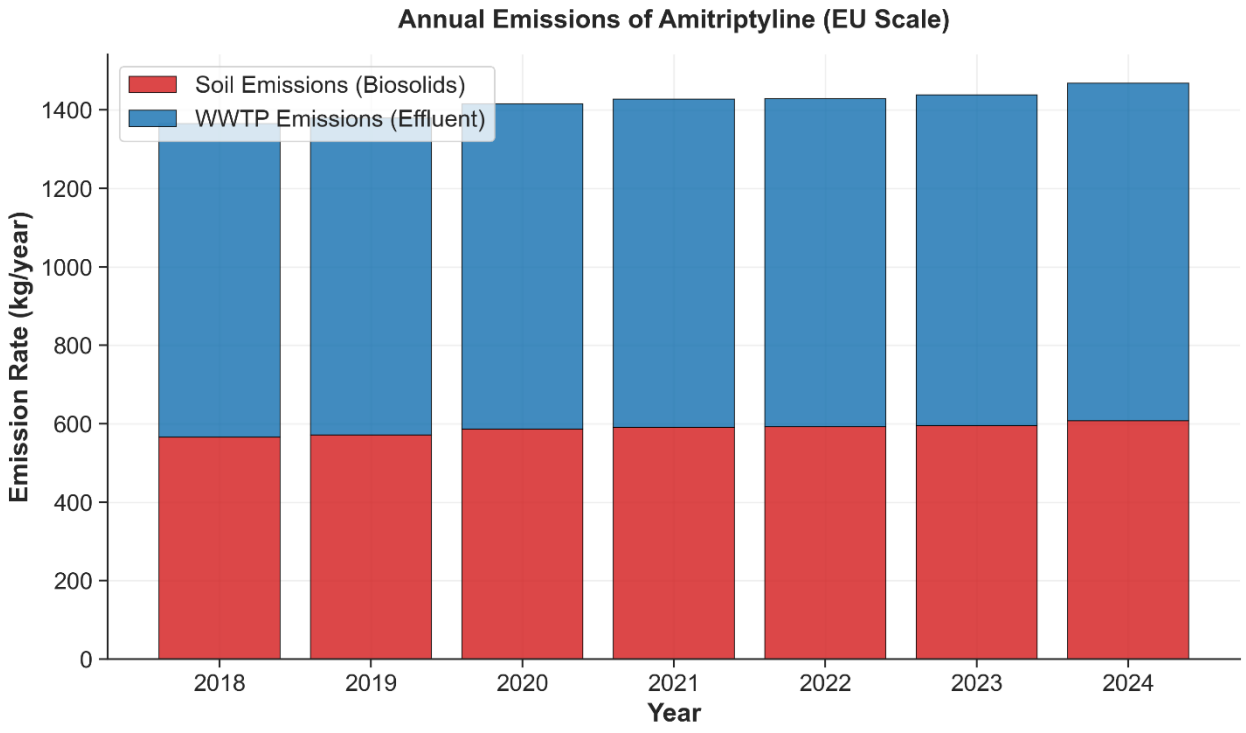


Figure 38. Annual aggregated emissions of amitriptyline to the European continental environment (2018–2024). Stacked bars represent direct releases to agricultural soil via biosolids (red) and surface water via WWTP effluents (blue).

Predicted Environmental Concentrations (PEC) Steady-state predicted environmental concentrations (PECs) indicate relatively stable but gradually increasing concentrations in both continental river water (w1CU) and agricultural soil (s2CU) over the 2018–2024 period (Figure 39). River water PECs ranged from approximately 0.35 to 0.38 ng L^{-1}, while soil PECs increased from about 4.5 to nearly 4.9 ng kg^{-1} (dry weight).

The parallel temporal trends in water and soil PECs reflect the shared emission drivers and the relatively slow degradation rates of amitriptyline in both compartments. Soil concentrations consistently exceeded aqueous concentrations by roughly an order of magnitude on a mass-normalised basis, consistent with the compound's moderate hydrophobicity and strong affinity for organic matter. These results suggest that agricultural soils act as a longer-term reservoir for amitriptyline, even when emissions are dominated by wastewater pathways.

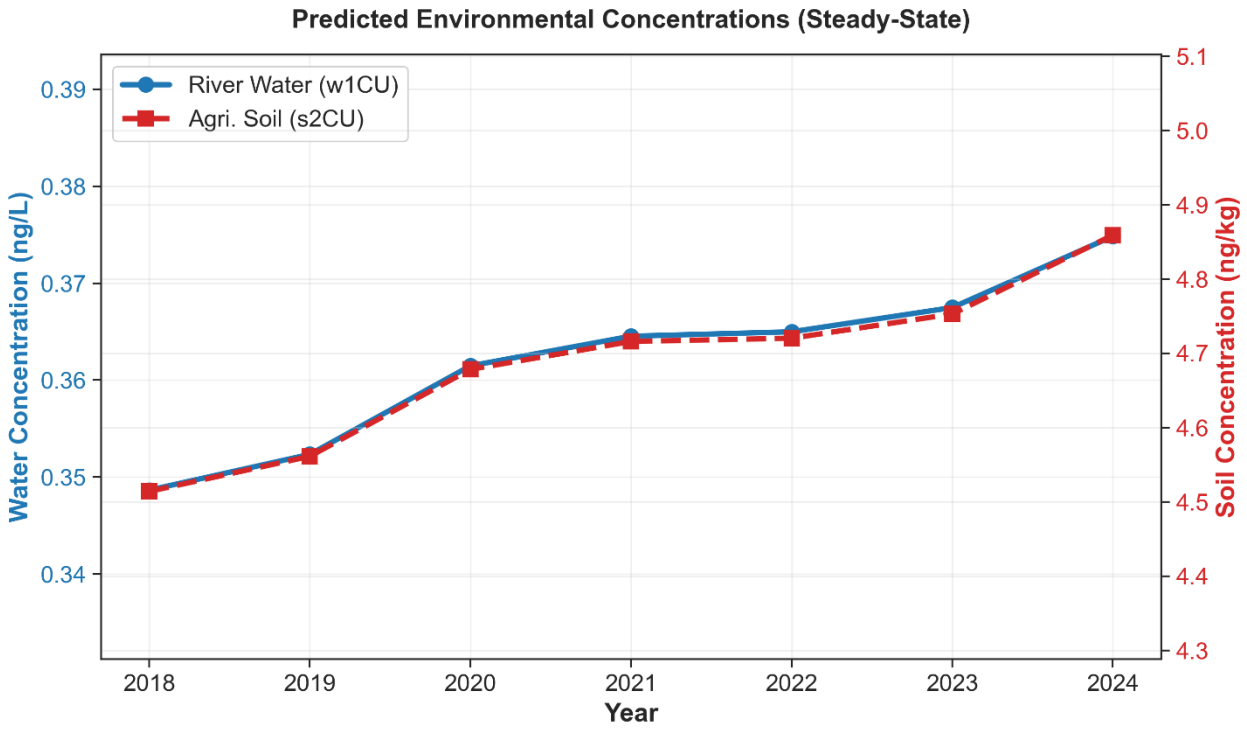


Figure 39. Trends in steady-state Predicted Environmental Concentrations (PEC) for amitriptyline (2018–2024). Left axis (blue solid line): Concentration in continental river water (ng/L). Right axis (red dashed line): Concentration in continental agricultural soil (ng/kg dw).

Dynamic vs. Steady-State Behaviour Dynamic simulations using the time-dependent SimpleBox ODE framework reveal that amitriptyline accumulates progressively in environmental compartments before approaching quasi-steady-state conditions (Figure 40).

The dynamic mass profile for river water overlaps almost perfectly with the steady-state predictions, indicating that the water compartment achieves equilibrium rapidly with annual emission fluxes.

In contrast, soil compartments exhibit much slower equilibration. Soil masses continue to increase throughout the simulation period and only begin to asymptotically approach steady-state values toward the end of the study window. This lagged response highlights the importance of dynamic modelling for terrestrial compartments, where assuming instantaneous steady-state conditions may underestimate transient accumulation and long-term exposure.

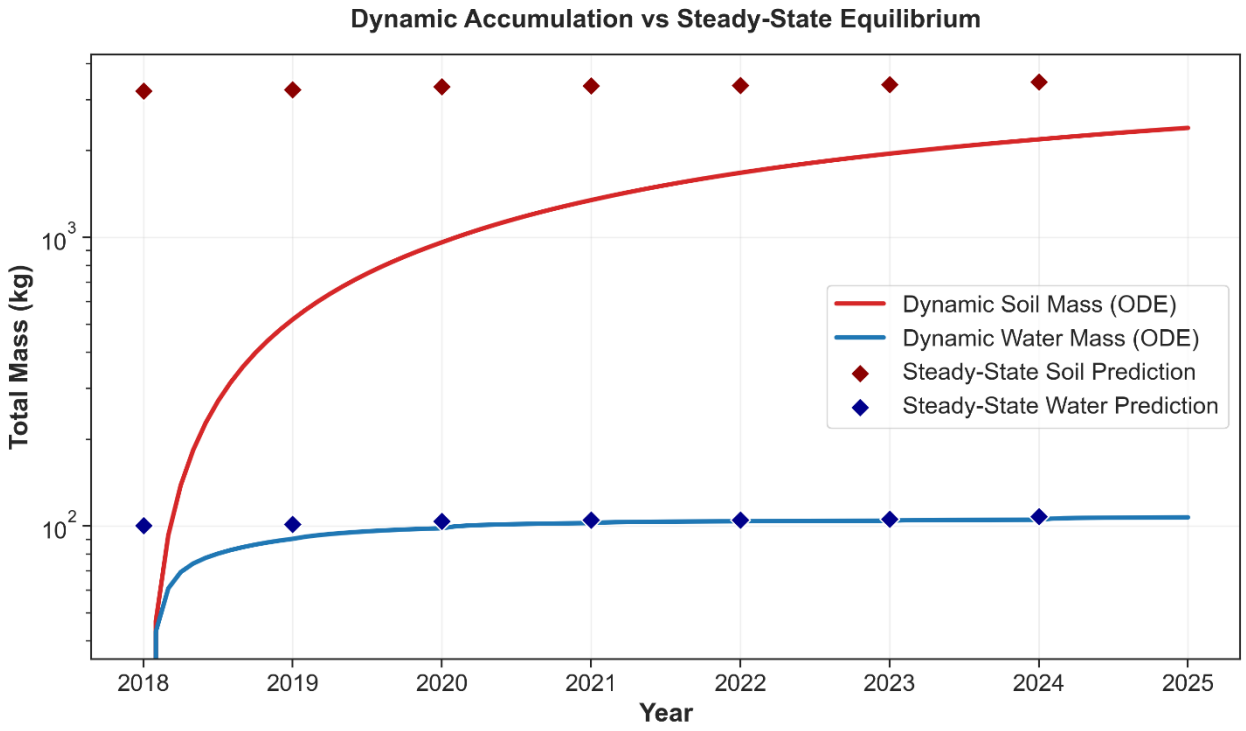


Figure 40. Comparison of dynamic (ODE) and steady-state mass simulations for amitriptyline. Continuous lines represent the dynamic mass accumulation over time; discrete markers represent the steady-state equilibrium mass calculated for each specific year. Note the logarithmic scale on the y-axis.

Environmental Mass Distribution Across Compartments The steady-state mass distribution for the year 2024 is detailed in Figure 41 and Figure 42. The system is characterised by strong retention in the lithosphere. Agricultural Soil is the primary environmental sink, holding approximately 3,455 kg (representing ~68% of the total environmental burden). This is significantly higher than the mass stored in Deep Ocean (479 kg), Freshwater Sediment (426 kg), or Sea Water (192 kg). Freshwater sediments rank among the top compartments, further reinforcing concerns regarding accumulation in depositional environments. River water itself contains comparatively smaller absolute masses, despite being the primary exposure medium for aquatic organisms, due to high throughflow rates and dilution. This distribution pattern suggests that amitriptyline's physicochemical properties (e.g., sorption coefficients) favour partitioning into soil and sediment matrices.

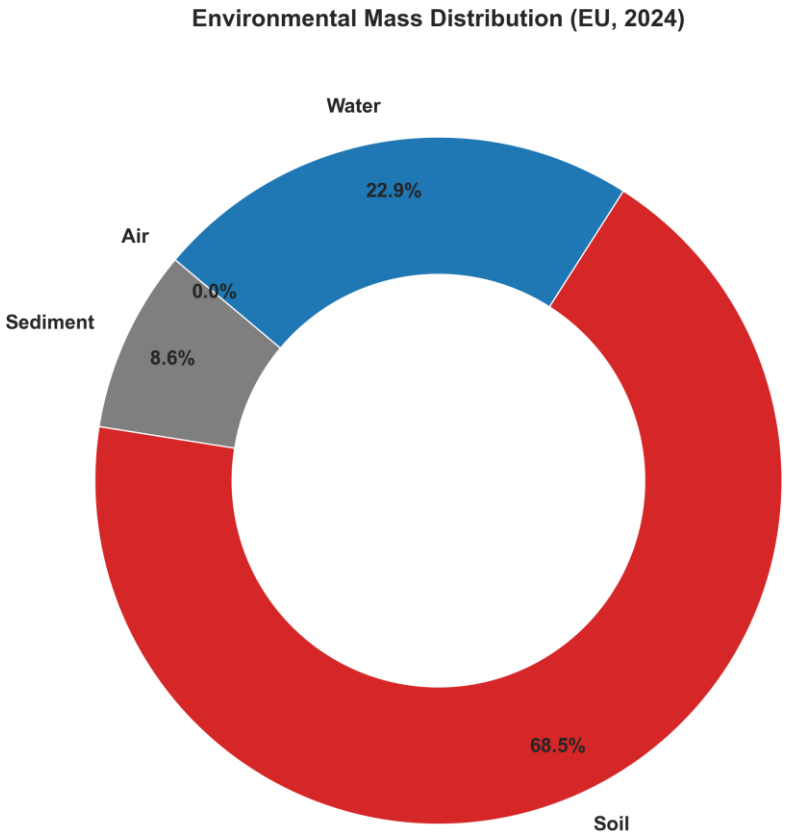


Figure 41. Relative multimedia mass distribution of amitriptyline in the European environment (Year 2024). The chart aggregates total mass inventory into four primary categories: Soil, Water, Sediment, and Air.

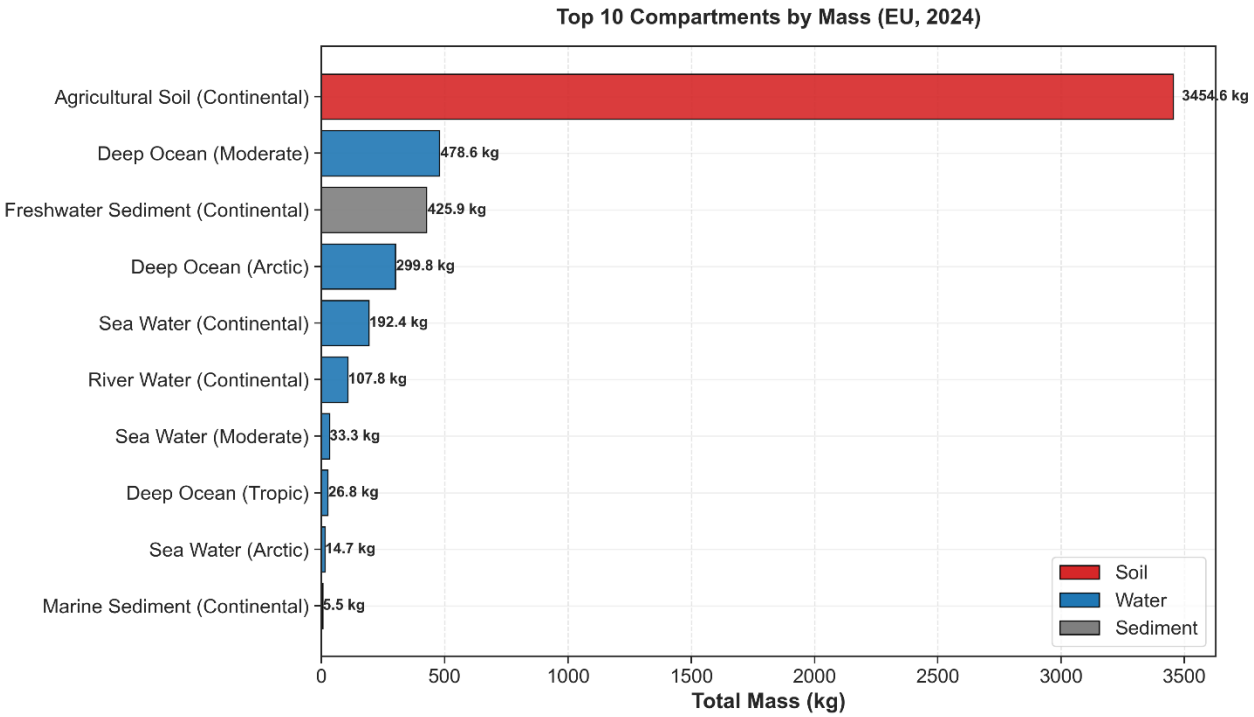


Figure 42. Top 10 environmental compartments by total stored mass of amitriptyline (steady-state, 2024). Bars are colour-coded by compartment type: Soil (Red), Water (Blue), and Sediment (Grey). Labels indicate the specific continental (C), regional (R), or global scale (A/M/T) compartments.

3.2.4.2 MULTIMEDIA FATE AND EXPOSURE ASSESSMENT OF DICLOFENAC

Emission Trends and Sources Annual EU-wide emissions of diclofenac between 2018 and 2024 are shown in Figure 43. Total emissions are dominated by wastewater treatment plant (WWTP) effluent discharges, which account for approximately 80–85% of the annual load, reflecting the predominantly urban and medical use of diclofenac and its limited association with sludge reuse pathways.

Soil emissions via biosolids application contribute a smaller but non-negligible fraction (~15–20%), remaining relatively stable over the study period.

A moderate increase in total emissions is observed after 2020, driven mainly by rising WWTP effluent loads. This trend is consistent with increased pharmaceutical consumption and aligns with reported EU-wide usage patterns for non-steroidal anti-inflammatory drugs. The comparatively small dip in 2020 likely reflects temporary changes in healthcare utilisation rather than structural shifts in emission pathways.

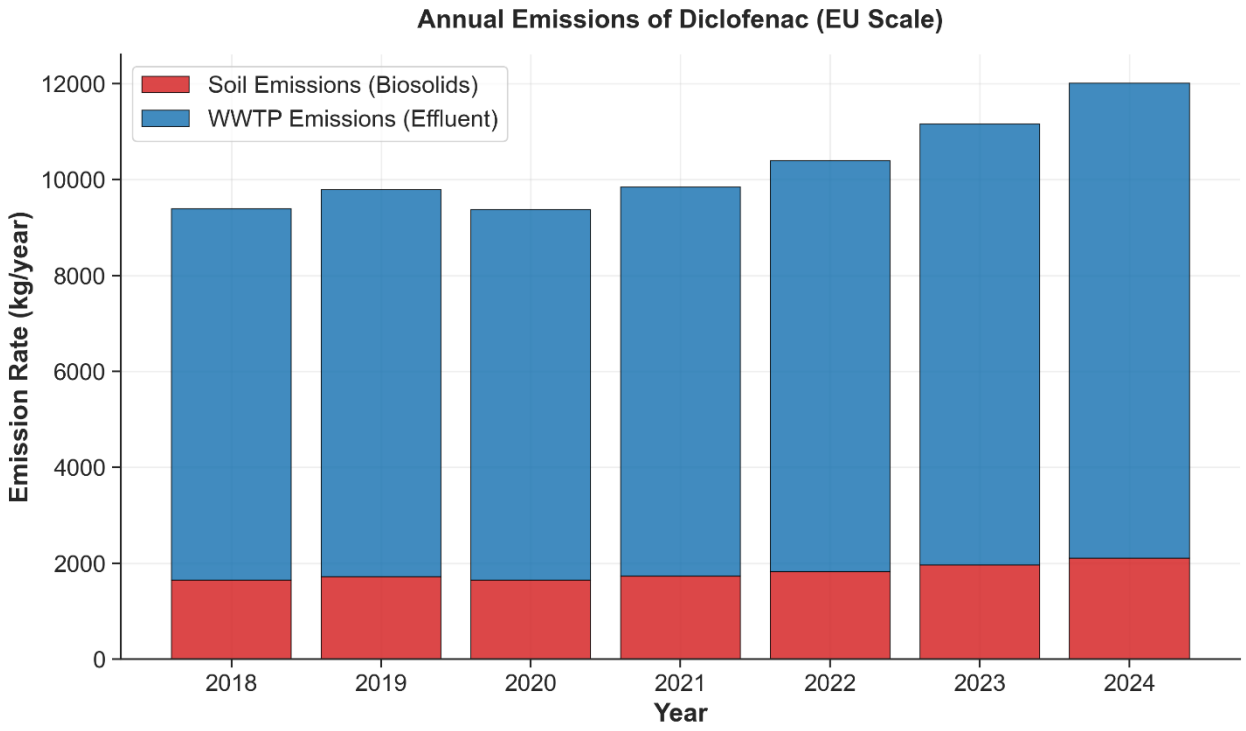


Figure 43. Annual aggregated emissions of diclofenac to the European continental environment (2018–2024). Stacked bars represent direct releases to agricultural soil via biosolids (red) and surface water via WWTP effluents (blue).

Predicted Environmental Concentrations (PEC) Steady-state predicted environmental concentrations (PECs) for continental river water (w1CU) and agricultural soil (s2CU) are presented in Figure 44. River water PECs range from approximately 2.1 to 2.7 ng/L, while soil concentrations remain lower, between 0.13 and 0.17 ng/kg.

The temporal pattern closely follows emission trends, with increasing PECs after 2021. River water concentrations are consistently higher than soil concentrations, reflecting both the dominant effluent-based emission pathway and the relatively low sorption affinity of diclofenac, which favours persistence in the aqueous phase. The tight correlation between emissions and concentrations indicates that the system is driven primarily by loading rates rather than accumulation, pointing to a pseudo-steady-state behaviour where output/degradation balances input relatively quickly. These modelled concentrations are within the range reported in European surface waters, supporting the plausibility of the SimpleBox predictions**.**

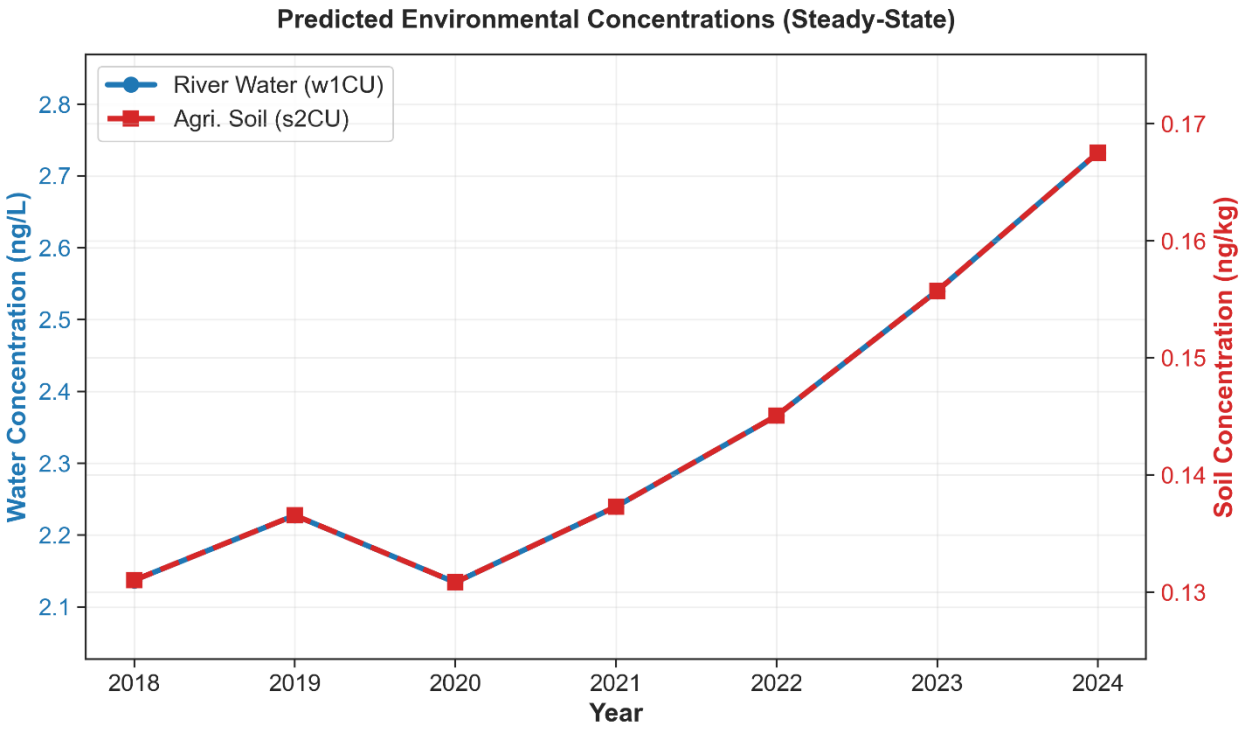


Figure 44. Trends in steady-state Predicted Environmental Concentrations (PEC) for diclofenac (2018–2024). Left axis (blue solid line): Concentration in continental river water (ng/L). Right axis (red dashed line): Concentration in continental agricultural soil (ng/kg dw).

Dynamic vs. Steady-State Behaviour The comparison between dynamic simulations and steady-state predictions is shown in Figure 45. For river water, dynamic mass trajectories rapidly converge toward steady-state values within the first simulation year, indicating that diclofenac reaches quasi-equilibrium quickly in aquatic compartments. This behaviour is consistent with its relatively short environmental half-lives in water and limited long-term storage capacity.
In contrast, soil compartments show slower accumulation and greater sensitivity to year-to-year emission changes. The steady-state prediction points (diamonds) align almost perfectly with the dynamic curves for both soil and water. This confirms that a steady-state Level III fugacity model is an appropriate tool for assessing Diclofenac in this regional context, as the chemical does not exhibit significant lag or "legacy" accumulation phases.

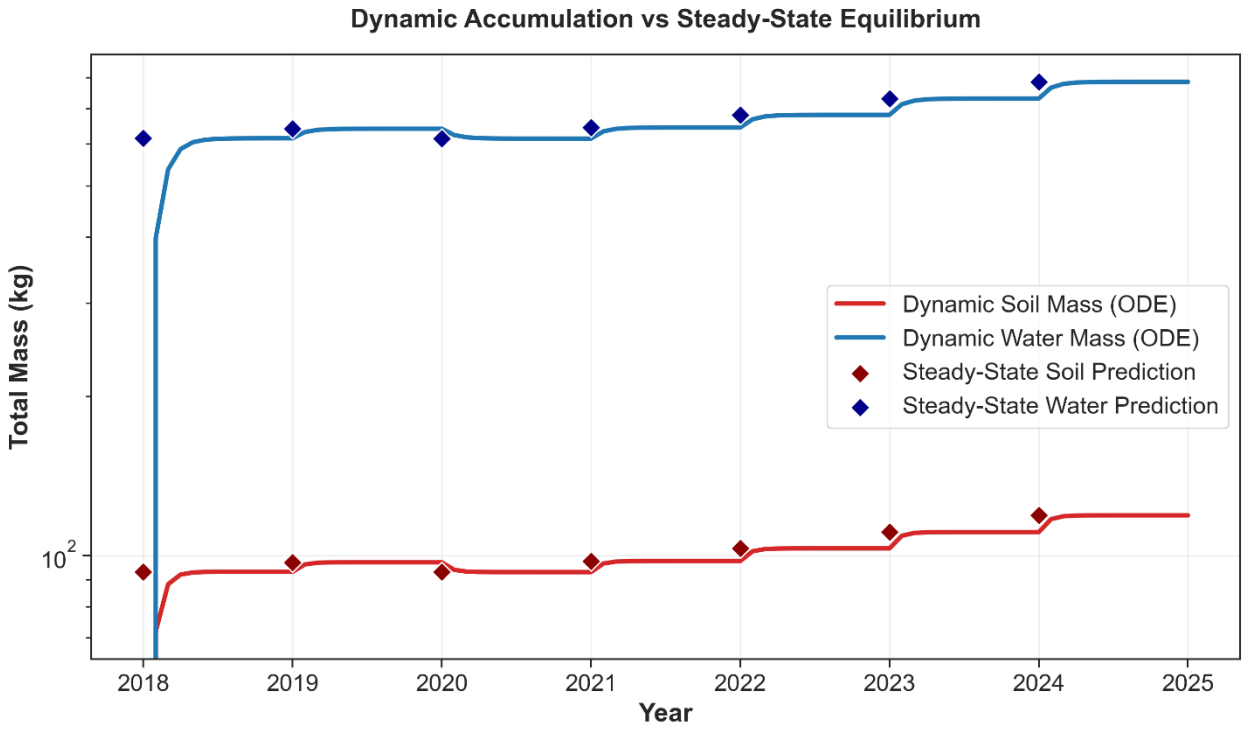


Figure 45. Comparison of dynamic (ODE) and steady-state mass simulations for diclofenac. Continuous lines represent the dynamic mass accumulation over time; discrete markers represent the steady-state equilibrium mass calculated for each specific year. Note the logarithmic scale on the y-axis.

Environmental Mass Distribution Across Compartments The partitioning of Diclofenac mass across environmental compartments (Figure 46 and Figure 47) highlights its physical-chemical affinity for the aqueous phase.

The EU-wide environmental mass distribution in 2024 is illustrated in Figure 46. Water compartments dominate the overall mass balance, accounting for approximately 87% of total environmental diclofenac mass. Continental river water is the single largest reservoir, followed by continental sea water.

Soil represents around 11%, while sediments and air together contribute less than 2%. Agricultural soil appears as the most important terrestrial compartment, but remains secondary to aquatic environments. Sediment compartments contribute only minor fractions, consistent with the compound's relatively low sediment–water partition coefficients. These results suggest that aquatic ecosystems, particularly rivers downstream of urban centres, are the primary exposure targets for diclofenac at the continental scale. While soil exposure is non-negligible, especially in regions with intensive sludge application, it is unlikely to dominate overall environmental risk compared to surface waters.

This strong dominance of aquatic compartments highlights diclofenac's hydrophilic behaviour and limited partitioning into soils and sediments. The negligible air fraction reflects both low volatility and rapid atmospheric degradation, confirming that atmospheric transport is not a relevant exposure pathway for this compound. This contrasts with more sorptive or persistent pharmaceuticals, emphasizing the importance of compound-specific properties when interpreting multimedia exposure predictions.

The close agreement between dynamic and steady-state results further supports the use of annual steady-state simulations for screening-level continental assessments of diclofenac, provided that emission inventories capture realistic temporal trends. However, for short-term scenarios or localised assessments, dynamic modelling remains essential to capture transient behaviour following emission fluctuations. Furthermore, the increasing trend suggests that without improvements in tertiary wastewater treatment technologies (e.g., ozonation or activated carbon), environmental loads will continue to scale with pharmaceutical consumption.

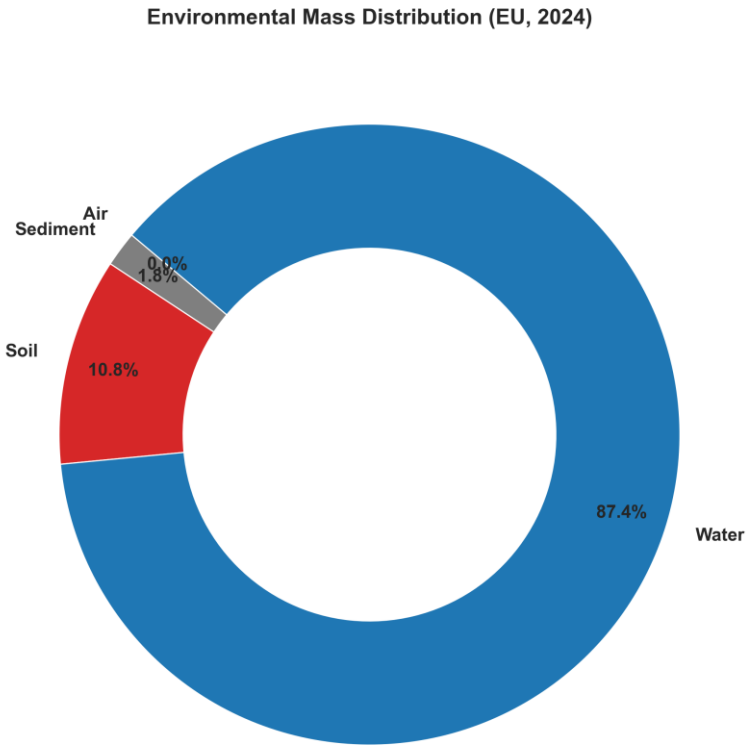


Figure 46. Relative multimedia mass distribution of diclofenac in the European environment (Year 2024). The chart aggregates total mass inventory into four primary categories: Soil, Water, Sediment, and Air.

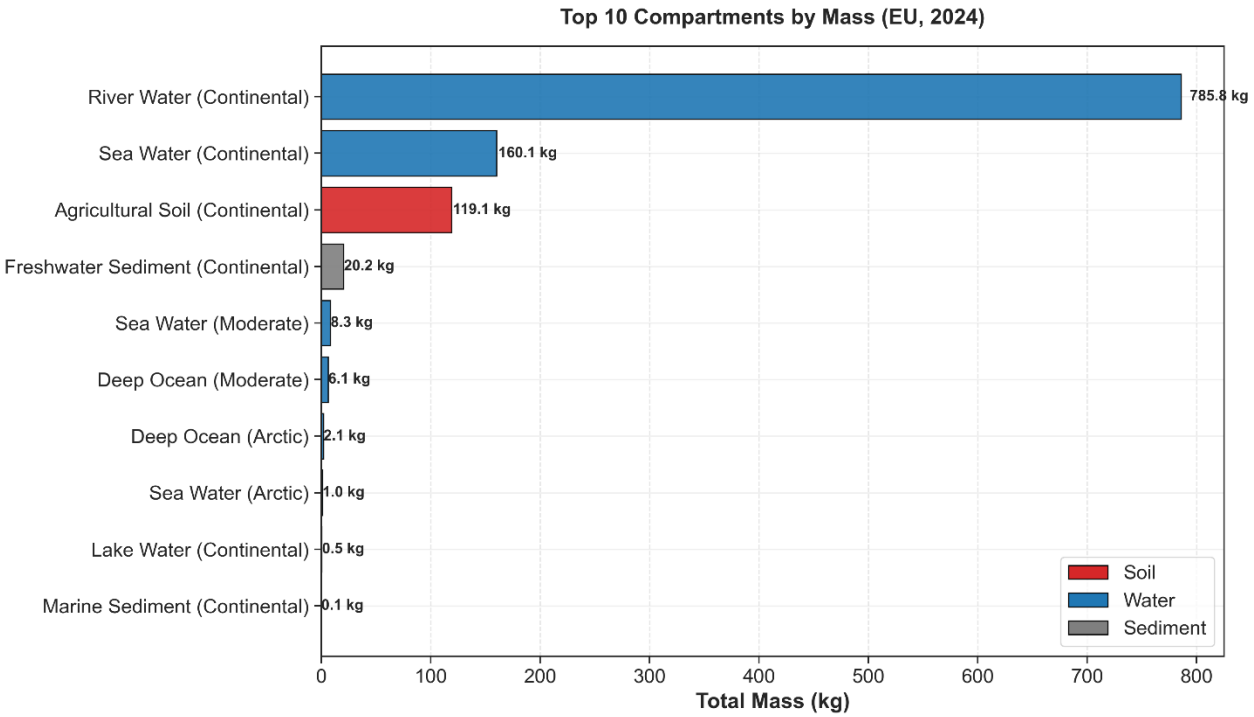


Figure 47. Top 10 environmental compartments by total stored mass of diclofenac (steady-state, 2024). Bars are colour-coded by compartment type: Soil (Red), Water (Blue), and Sediment (Grey). Labels indicate the specific continental (C), regional (R), or global scale (A/M/T) compartments.

3.2.4.3 MULTIMEDIA FATE AND EXPOSURE ASSESSMENT OF GLICLAZIDE

Emission Trends and Sources The annual aggregated emissions of gliclazide to the European continental environment are presented in Figure 48. Total emissions exhibit a gradual declining trend over the study period, driven primarily by decreasing emissions to agricultural soil, while wastewater treatment plant (WWTP) effluent emissions remain comparatively stable.

Soil emissions constitute the dominant pathway, contributing approximately 50–55 % of total releases across all years. This reflects the spatially distributed nature of diffuse pharmaceutical inputs to agricultural soils, for example via sewage sludge application or manure reuse. In contrast, WWTP emissions represent a more centralized but persistent source, contributing roughly 45–50 % of total emissions annually. The relative stability of WWTP emissions suggests that wastewater-based inputs are less sensitive to temporal changes in use or management practices than soil-related pathways.

Overall, the magnitude of gliclazide emissions (on the order of 10^3 kg yr^{-1} at the EU scale) is consistent with reported usage volumes and removal efficiencies for sulfonylurea antidiabetic drugs.

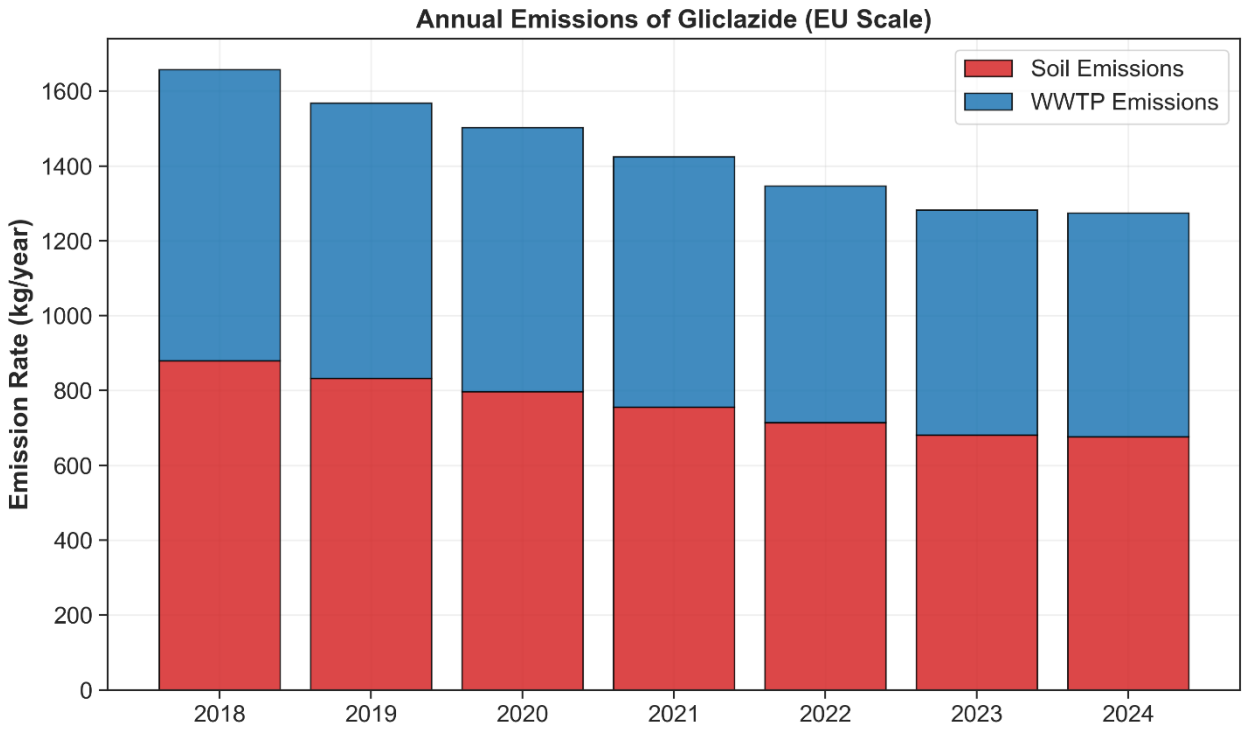


Figure 48. Annual aggregated emissions of gliclazide to the European continental environment (2018–2024). Stacked bars represent direct releases to agricultural soil via biosolids (red) and surface water via WWTP effluents (blue).

Predicted Environmental Concentrations (PEC) Steady-state predicted environmental concentrations (PECs) in continental river water (w1CU) and agricultural soil (s2CU) are presented in Figure 49. Both compartments show declining concentrations from 2018 to 2024, consistent with the observed reduction in total emissions.

River water PECs decrease from approximately 0.68 ng L^{-1} in 2018 to around 0.52 ng L^{-1} in 2024. Soil PECs follow a similar pattern, declining from about 0.70 ng kg^{-1} (dry weight) to approximately 0.54 ng kg^{-1} over the same period. The close correspondence between soil and water trends reflects the coupled nature of emissions and inter-compartmental transport in the SimpleBox framework.

These PEC values are within the lower ng L^{-1} and ng kg^{-1} range, which is consistent with reported environmental measurements for gliclazide and comparable pharmaceuticals in European surface waters and soils. Importantly, the steady-state assumption represents a long-term average exposure scenario, smoothing out short-term variability in emissions and hydrological conditions.

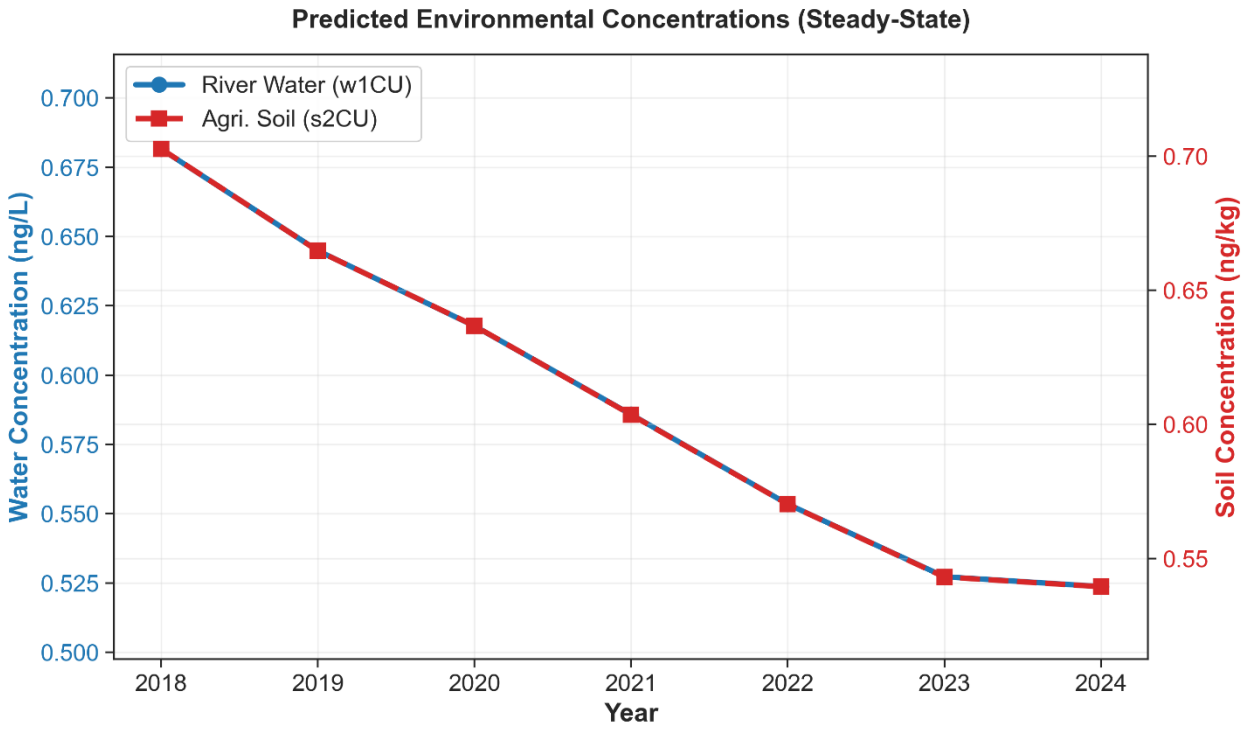


Figure 49. Trends in steady-state Predicted Environmental Concentrations (PEC) for gliclazide (2018–2024). Left axis (blue solid line): Concentration in continental river water (ng/L). Right axis (red dashed line): Concentration in continental agricultural soil (ng/kg dw).

Dynamic vs. Steady-State Behaviour The comparison between dynamic (time-varying ODE) and steady-state simulations (Figure 50) reveals distinct behaviours for the water and soil compartments. Following the onset of emissions in 2018, both compartments exhibit rapid accumulation during the initial years, approaching quasi-steady conditions within approximately 1–2 years.

The dynamic mass profile for river water closely tracks the steady-state predictions, indicating a rapid response time to changes in emission loads. The soil compartment exhibits a significant lag. While the steady-state model predicts an immediate equilibrium mass based on that year's emission, the dynamic model shows a gradual accumulation. The dynamic trajectories closely converge towards the steady-state solutions, indicating that the steady-state approximation is reasonable for multi-year exposure assessments of gliclazide at the continental scale.

However, small deviations between dynamic and steady-state masses persist, particularly during periods of declining emissions. This highlights the added value of dynamic simulations for capturing temporal lag effects and the inertia of environmental compartments with relatively slow degradation rates.

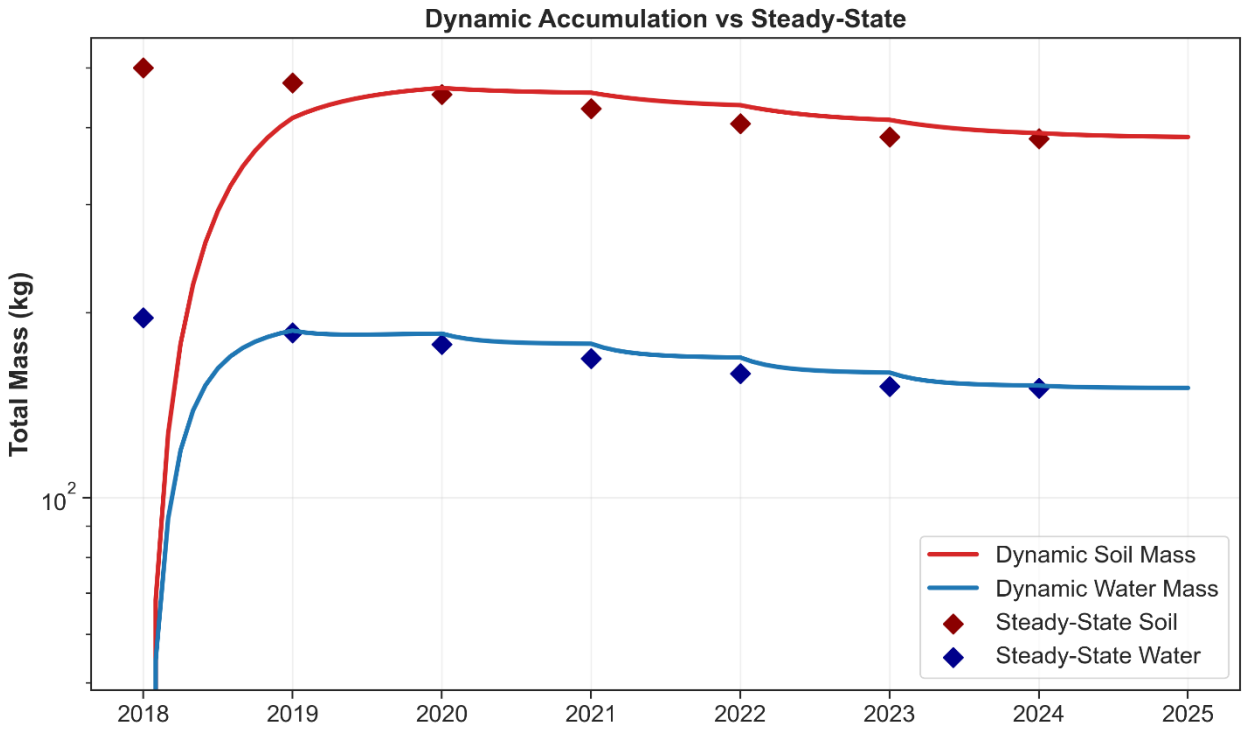


Figure 50. Comparison of dynamic (ODE) and steady-state mass simulations for gliclazide. Continuous lines represent the dynamic mass accumulation over time; discrete markers represent the steady-state equilibrium mass calculated for each specific year. Note the logarithmic scale on the y-axis.

Environmental Mass Distribution Across Compartments The steady-state mass distribution for the year 2024 is summarised in Figure 51 and Figure 52. The majority of the gliclazide mass in the system is retained in Agricultural Soil (383 kg), followed by River Water (151 kg) and Continental Sea Water (128 kg).

Marine compartments (seawater and deep ocean boxes) contain comparatively smaller fractions, reflecting both dilution and slower transport from continental sources. The negligible contribution of air is consistent with gliclazide's low volatility and low Henry's law constant, confirming that atmospheric transport is not a relevant pathway for this compound. The partitioning highlights the role of the soil compartment as a significant environmental sink, driven by the continuous application of biosolids and the substance's sorption characteristics.

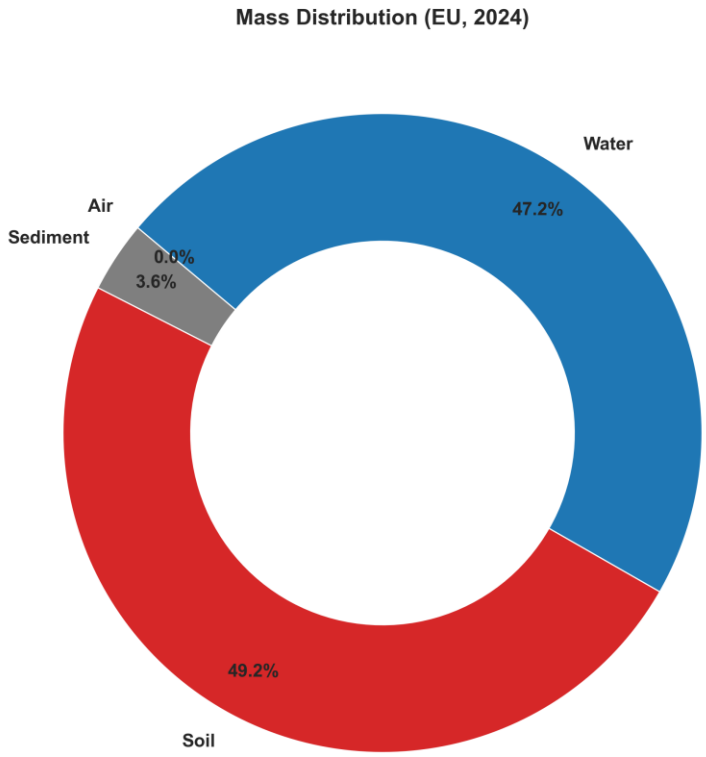


Figure 51. Relative multimedia mass distribution of gliclazide in the European environment (Year 2024). The chart aggregates total mass inventory into four primary categories: Soil, Water, Sediment, and Air.

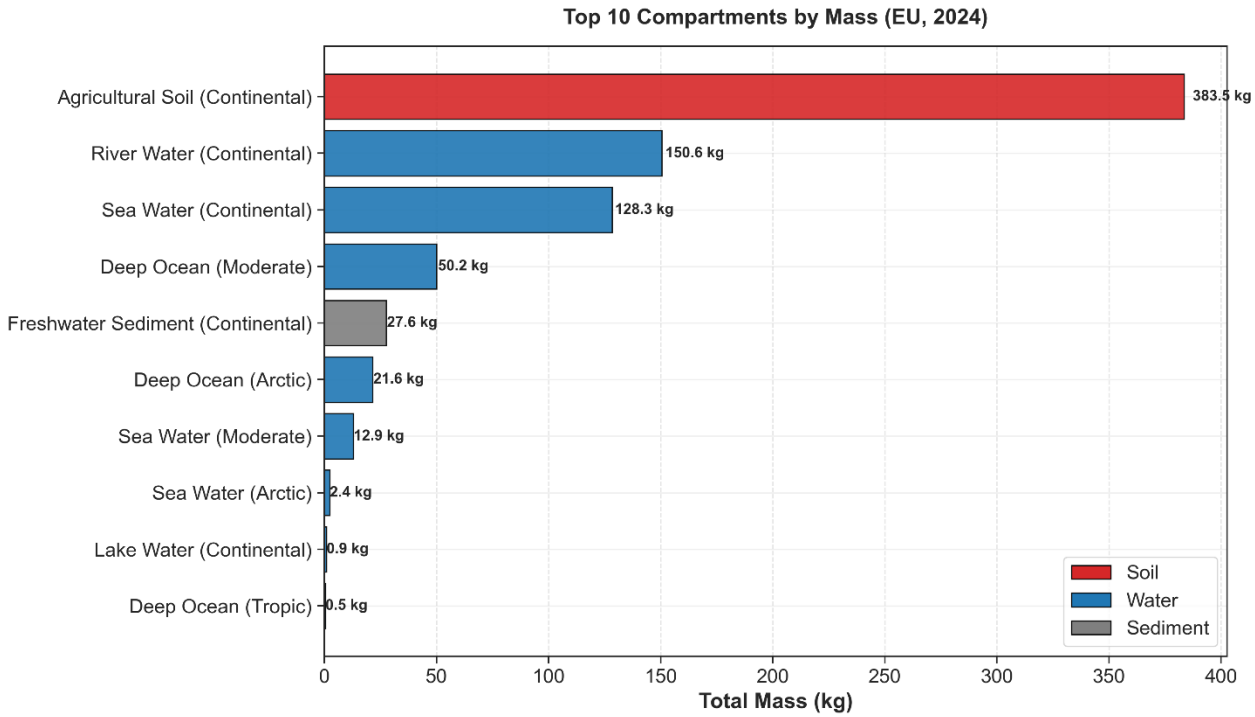


Figure 52. Top 10 environmental compartments by total stored mass of gliclazide (steady-state, 2024). Bars are colour-coded by compartment type: Soil (Red), Water (Blue), and Sediment (Grey). Labels indicate the specific continental (C), regional (R), or global scale (A/M/T) compartments.

Sensitivity Analysis A two-dimensional sensitivity analysis was conducted to assess the influence of degradation half-lives (DT_{50}) in water and sediment on the resulting PECs (Figure 53 and Figure 54) and was performed due to the limited availability of reliable literature values for the corresponding k_{deg} parameters.

PEC Sediment: The concentration in sediment was found to be highly sensitive to the sediment half-life ($DT_{50\_sediment}$), with PECs increasing by orders of magnitude as persistence increased from 1 to 1000 days. Cross-sensitivity to water persistence was visible, confirming that sediment exposure is driven by direct emissions and transfer rates from the river. The results emphasise the critical role of uncertainty in sediment degradation rates when assessing water exposure of gliclazide.

The concentration in river water showed strong sensitivity to water half-life (DT_{50_water}), with longer aquatic persistence leading to substantially higher concentrations. This suggests that remobilisation of gliclazide from soil to water (e.g., via runoff) is a minor pathway compared to direct WWTP discharges.

Taken together, these results demonstrate that gliclazide exhibits persistent, low-level exposure in both sediment and freshwater compartments at the European scale. While predicted concentrations are low, their widespread spatial distribution and continuous input pathways warrant consideration in mixture risk assessments and long-term monitoring strategies.

The sensitivity analysis further indicates that uncertainties in degradation rates, particularly in water for aquatic exposure, can substantially influence PEC estimates.

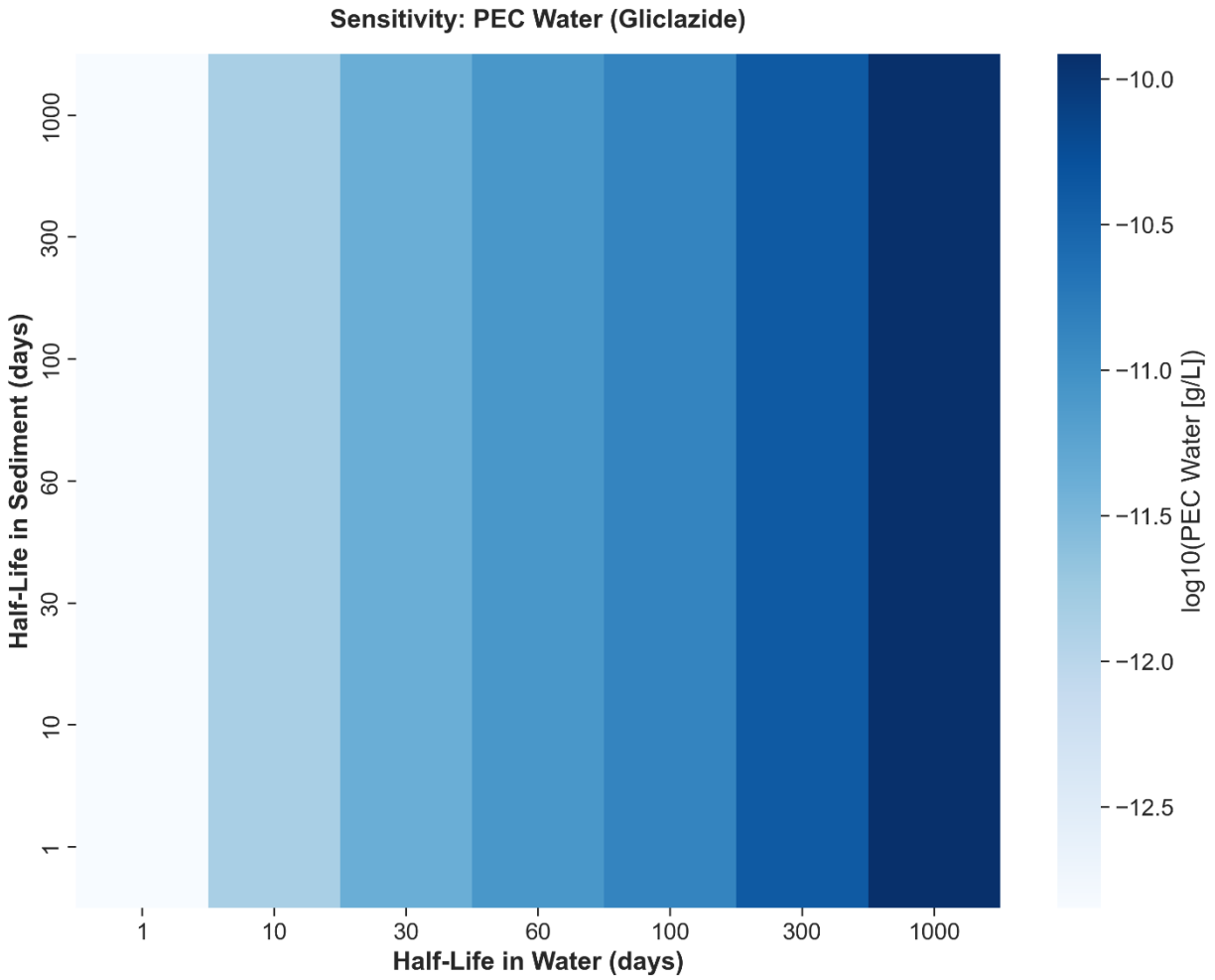


Figure 53. Sensitivity analysis of Predicted Environmental Concentration in River Water (PEC_{water}) to variations in degradation half-lives (DT_{50}). The heatmap displays log_{10} values, with darker blue intensities indicating higher concentrations.

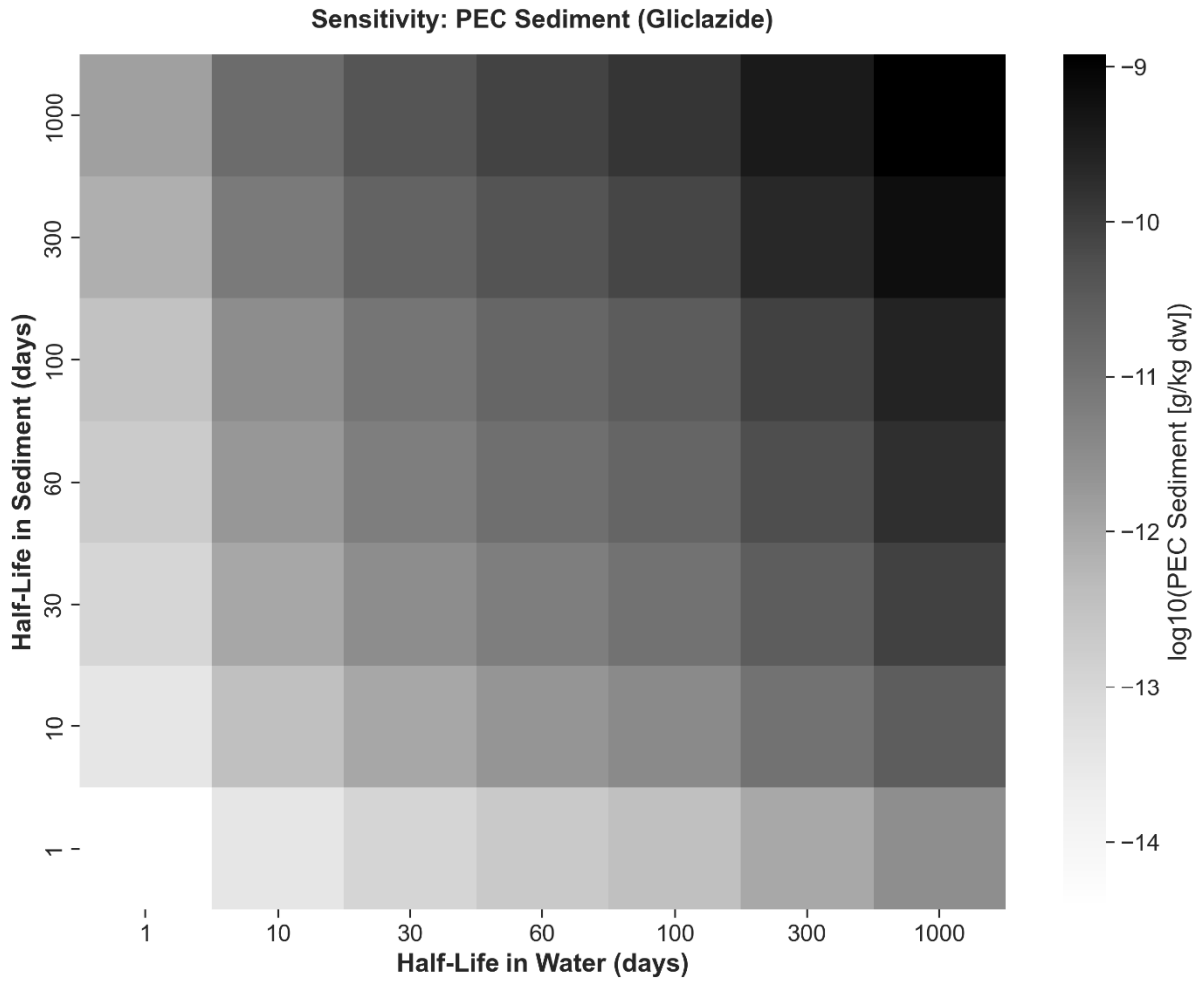


Figure 54. Sensitivity analysis of Predicted Environmental Concentration in River Sediment (PECsediment) to variations in degradation half-lives (DT50). The heatmap displays log10(PEC) values, with darker grey intensities indicating higher concentrations. Axes represent the range of half-lives tested (1 to 1000 days) for sediment and water compartments.

3.2.4.4 Multimedia Fate and Exposure Assessment of Ibuprofen

Emission Trends and Sources Annual emissions of ibuprofen at the European scale show a clear dominance of soil-related inputs via biosolid application, with comparatively minor contributions from wastewater treatment plant (WWTP) effluents (Figure 55). Between 2018 and 2024, total emissions declined substantially, driven primarily by decreasing biosolid-related releases. Soil emissions decreased from approximately 140,000 kg yr^{-1} in 2018 to about 84,000 kg yr^{-1} in 2024, reflecting reduced usage or improved waste management practices over time. In contrast, WWTP effluent emissions remain several orders of magnitude lower and contribute negligibly to the overall emission budget.

This emission structure reflects the widespread terrestrial use and disposal pathways of ibuprofen and highlights the importance of land-based compartments in determining environmental exposure. While ibuprofen may be effectively removed from the aqueous phase during wastewater treatment (low effluent emissions), a significant fraction is partitioned into the sludge, which is subsequently applied to agricultural land.

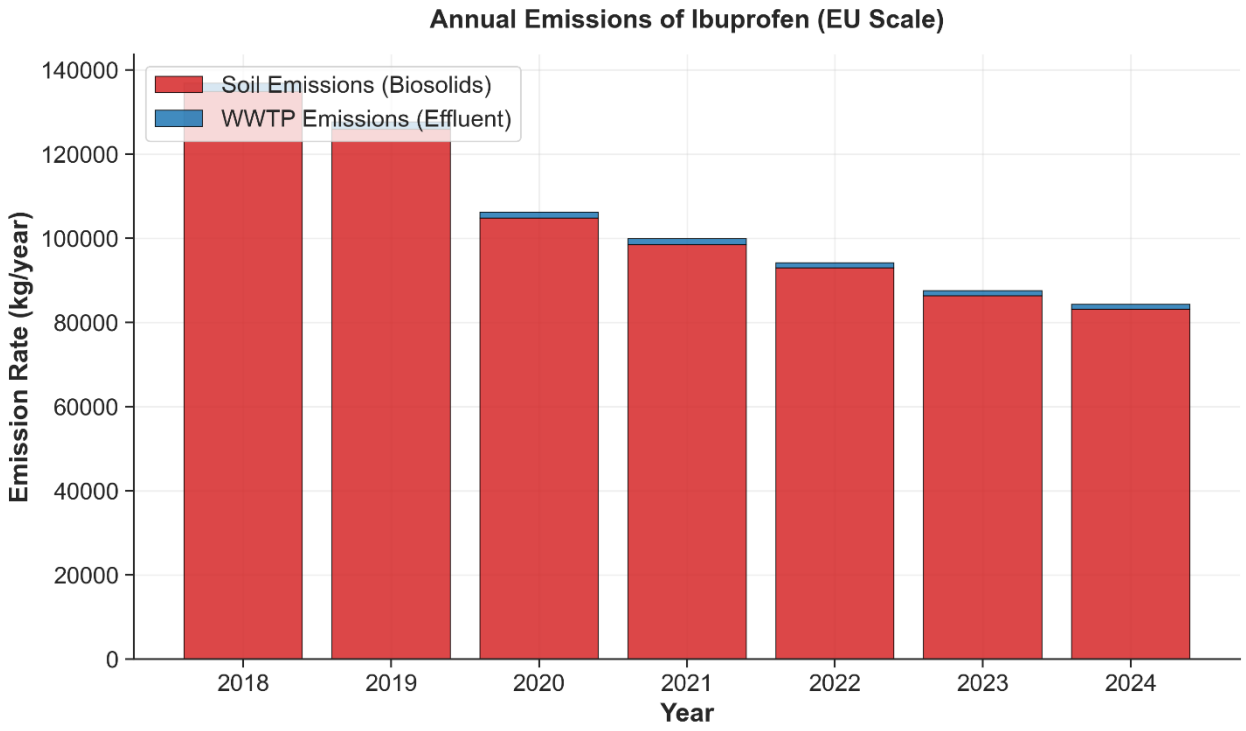


Figure 55. Annual aggregated emissions of ibuprofen to the European continental environment (2018–2024). Stacked bars represent direct releases to agricultural soil via biosolids (red) and surface water via WWTP effluents (blue).

Predicted Environmental Concentrations (PEC) Steady-state SimpleBox predictions indicate a consistent decline in environmental concentrations of ibuprofen over the study period, in line with decreasing emissions (Figure 56). River water concentrations (w1CU) decrease from approximately 6.1 ng L^{-1} in 2018 to around 3.7 ng L^{-1} in 2024, while agricultural soil concentrations (s2CU) decline from about 50 ng kg^{-1} to 30 ng kg^{-1} over the same period.

The parallel temporal trends in water and soil PECs reflect the strong coupling between emission magnitudes and equilibrium concentrations within the SimpleBox framework. Despite its relatively rapid degradation compared to more persistent pharmaceuticals, ibuprofen remains detectable across multiple environmental media due to sustained emissions and large compartment volumes.

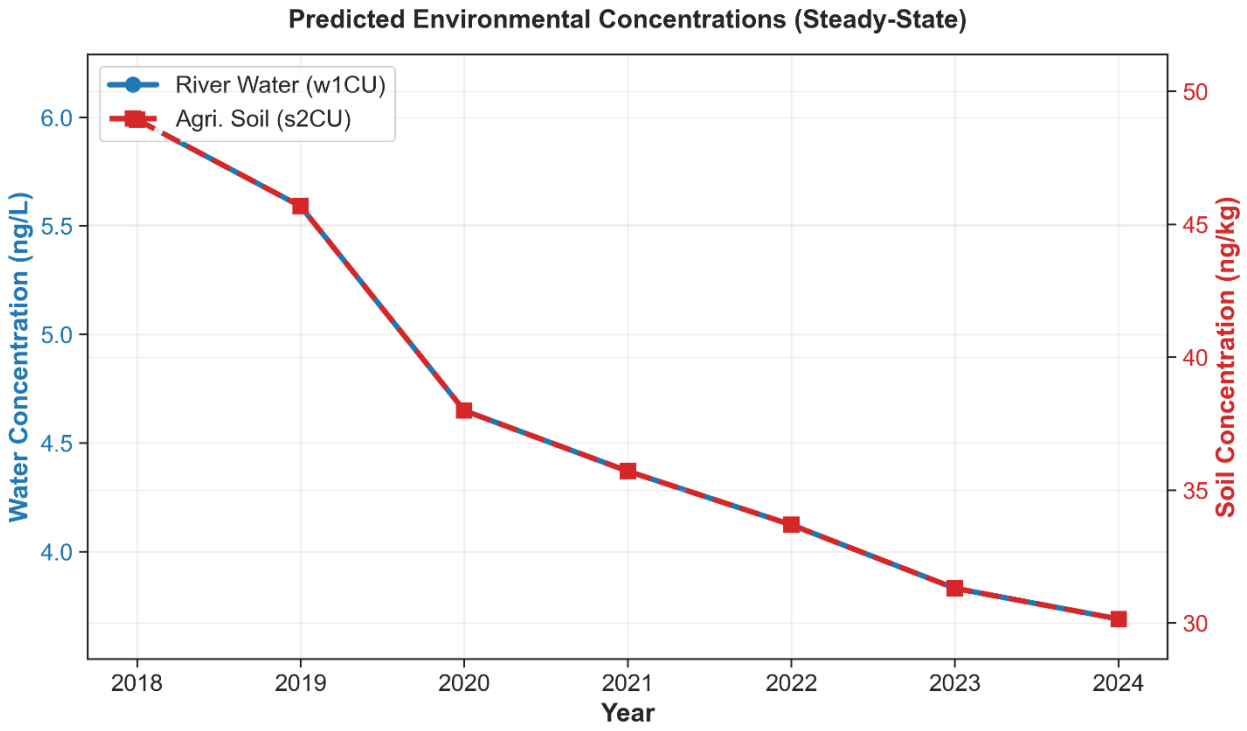


Figure 56. Trends in steady-state Predicted Environmental Concentrations (PEC) for ibuprofen (2018–2024). Left axis (blue solid line): Concentration in continental river water (ng/L). Right axis (red dashed line): Concentration in continental agricultural soil (ng/kg dw).

Dynamic vs. Steady-State Behaviour Dynamic simulations reveal a rapid initial accumulation of ibuprofen in both soil and water compartments, followed by gradual adjustment toward declining steady-state masses as emissions decrease (Figure 57). Soil compartments show the highest absolute masses, reaching >10^4 kg shortly after model initialisation, before slowly declining toward lower steady-state values in later years. Water compartments exhibit lower overall masses (on the order of 10^3 kg) but respond more quickly to emission changes due to faster turnover rates.

The close agreement between dynamic trajectories and annual steady-state predictions demonstrates that, for ibuprofen, the system approaches quasi-steady conditions on relatively short timescales, particularly in aquatic compartments. This indicates limited long-term accumulation and a strong control of degradation and advective losses.

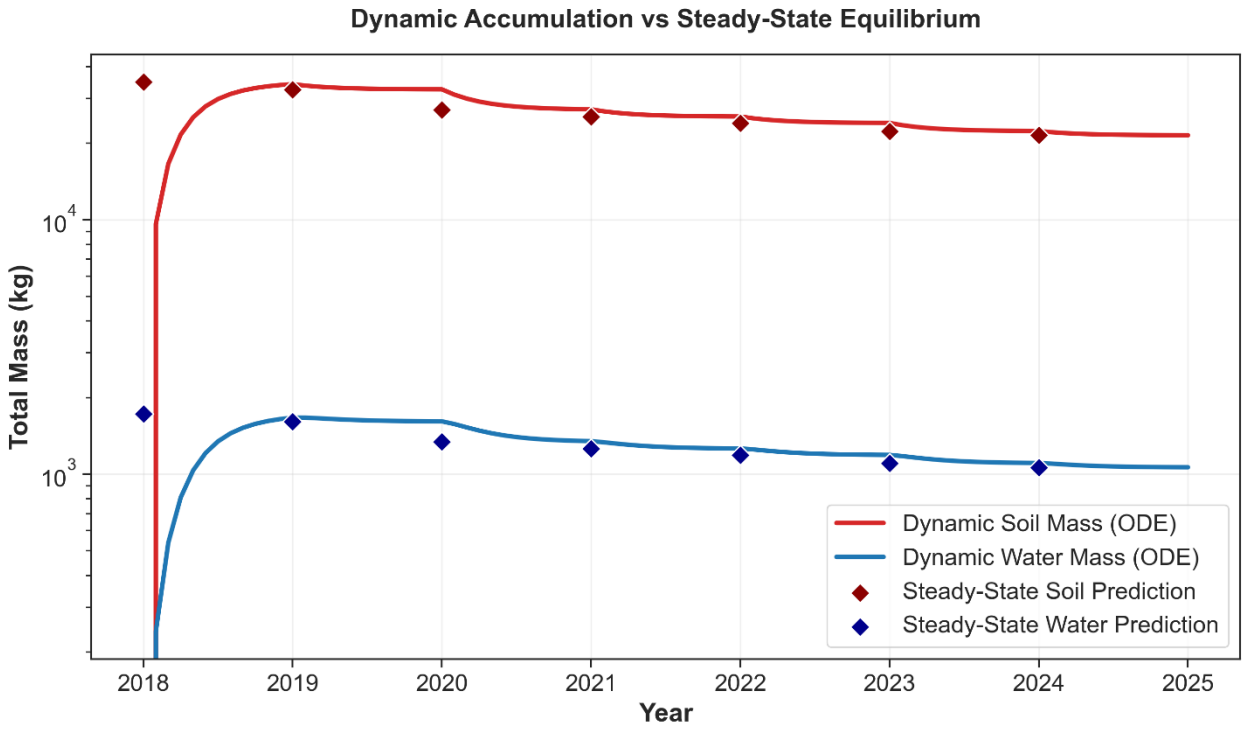


Figure 57. Comparison of dynamic (ODE) and steady-state mass simulations for ibuprofen. Continuous lines represent the dynamic mass accumulation over time; discrete markers represent the steady-state equilibrium mass calculated for each specific year. Note the logarithmic scale on the y-axis.

Environmental Mass Distribution Across Compartments The multimedia mass distribution in 2024 is strongly dominated by soil compartments, which account for approximately 93% of the total environmental mass of ibuprofen (Figure 58). Water compartments contribute around 6–7%, while sediment and air together represent less than 1% of the total mass. This pronounced soil dominance is consistent with the emission profile and with ibuprofen's physicochemical properties, which favour sorption to soils and repeated terrestrial inputs via biosolids. The negligible contribution of air reflects low volatility and limited atmospheric transport.

An analysis of the top ten compartments by mass in 2024 confirms that agricultural soil (continental scale) is by far the most important environmental reservoir for ibuprofen, containing more than 21,000 kg (Figure 59). River water, sea water, and lake water follow at much lower masses, while sediment and deep ocean compartments contribute marginally.

This distribution is driven by the emission vector (biosolids application) rather than chemical hydrophobicity alone. While Ibuprofen is relatively mobile and has low sorption coefficients (K_d) in many soils, the massive direct loading of sludge onto agricultural land forces the mass balance heavily toward the soil compartment. These results highlight that ibuprofen exposure assessments should prioritise terrestrial systems and freshwater environments, as they represent both the largest mass reservoirs and the most relevant pathways for ecological exposure.

Overall, ibuprofen exhibits a declining exposure profile across all environmental media over the 2018–2024 period, driven by decreasing emissions. However, the rapid equilibrium shown in Figure 57 suggests that if biosolids application were to cease, soil concentrations would likely deplete relatively quickly due to the compound's biodegradability.

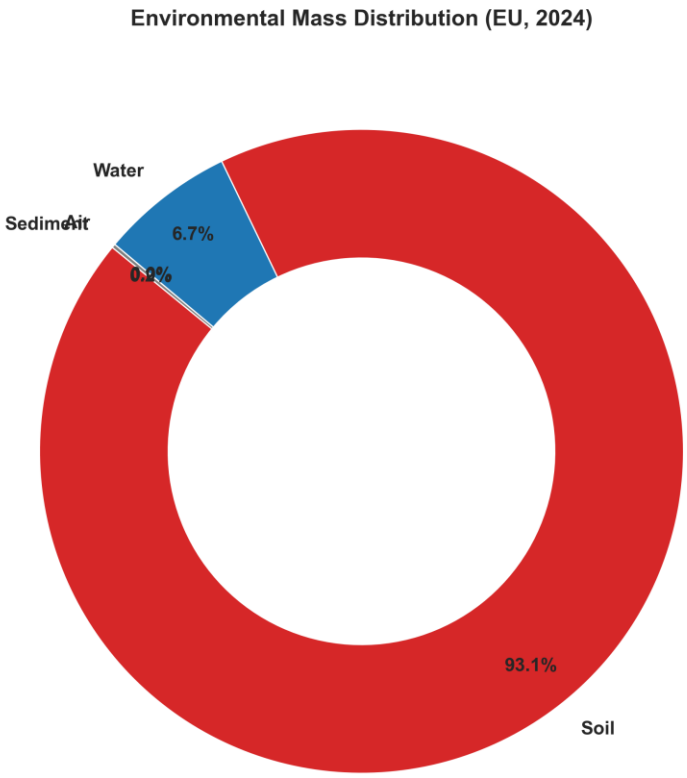


Figure 58. Relative multimedia mass distribution of ibuprofen in the European environment (Year 2024). The chart aggregates total mass inventory into four primary categories: Soil, Water, Sediment, and Air.

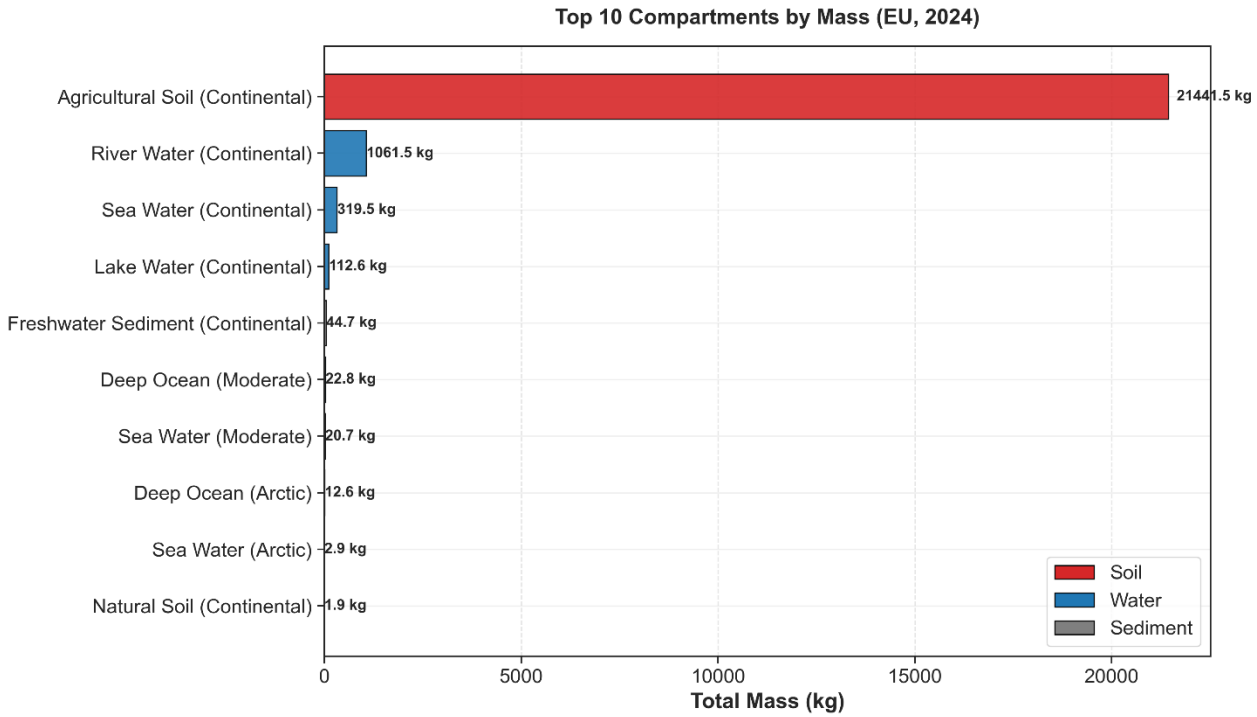


Figure 59. Top 10 environmental compartments by total stored mass of ibuprofen (steady-state, 2024). Bars are colour-coded by compartment type: Soil (Red), Water (Blue), and Sediment (Grey). Labels indicate the specific continental (C), regional (R), or global scale (A/M/T) compartments.

3.2.4.4 MULTIMEDIA FATE AND EXPOSURE ASSESSMENT OF RIFAXIMIN

Emission Trends and Sources Rifaximin emissions to the environment were assumed to occur exclusively via wastewater treatment plant (WWTP) effluents, reflecting its negligible systemic absorption in humans and limited likelihood of direct release to agricultural soils. Consequently, no direct soil emissions were included in the model, and atmospheric emissions were not considered. Annual WWTP emissions increased steadily over the period 2018–2024, rising from approximately 1.3×10^4 kg·year^{-1} in 2018 to about 2.5×10^4 kg·year^{-1} in 2024 (Figure 60). This temporal trend reflects increasing pharmaceutical usage and wastewater loading across the European Union.

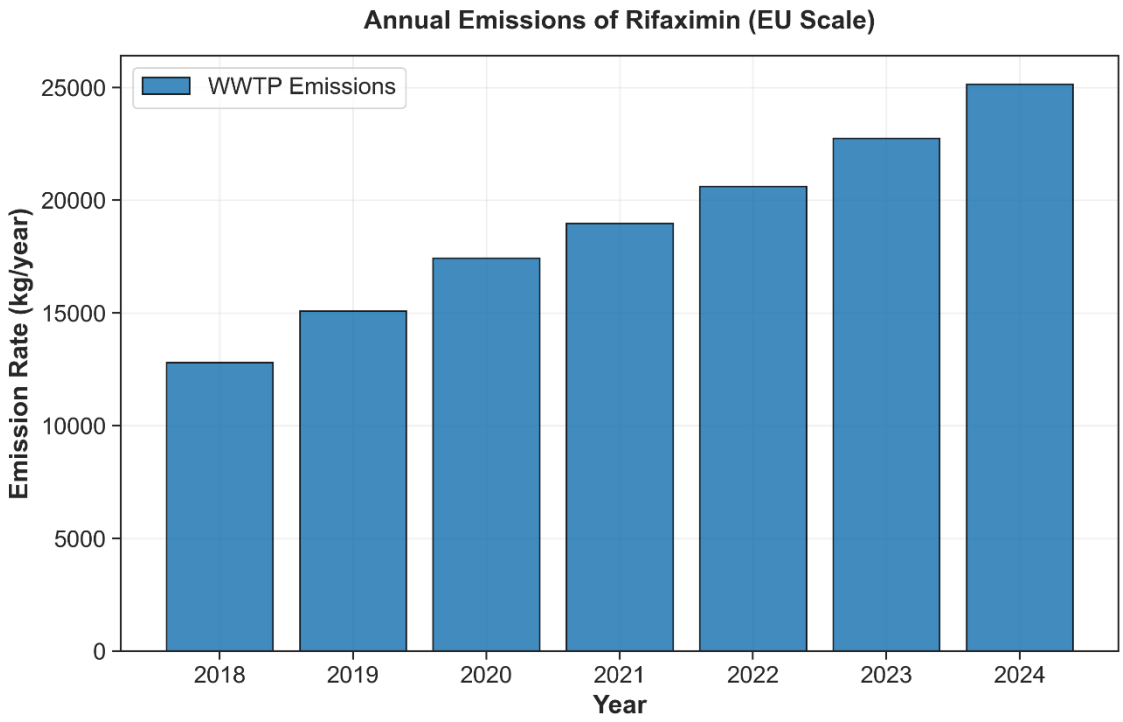


Figure 60. Annual aggregated emissions of rifaximin to the European continental environment (2018–2024). Stacked bars represent direct releases to surface water via WWTP effluents (blue).

Predicted Environmental Concentrations (PEC) Steady-state SimpleBox simulations indicate that rifaximin remains almost entirely confined to aquatic compartments, with predicted environmental concentrations (PECs) in continental river water increasing gradually over time (Figure 61). Modelled PECs in river water rose from approximately 0.67 ng·L^{-1} in 2018 to about 1.32 ng·L^{-1} in 2024.

Despite the absence of direct soil emissions, very small concentrations were predicted in agricultural soils due to indirect inter-media transfers within the multimedia framework. However, these soil PECs remained orders of magnitude lower than aquatic concentrations (≈10^{-15} ng·kg^{-1}), indicating negligible terrestrial exposure under the modelled assumptions.

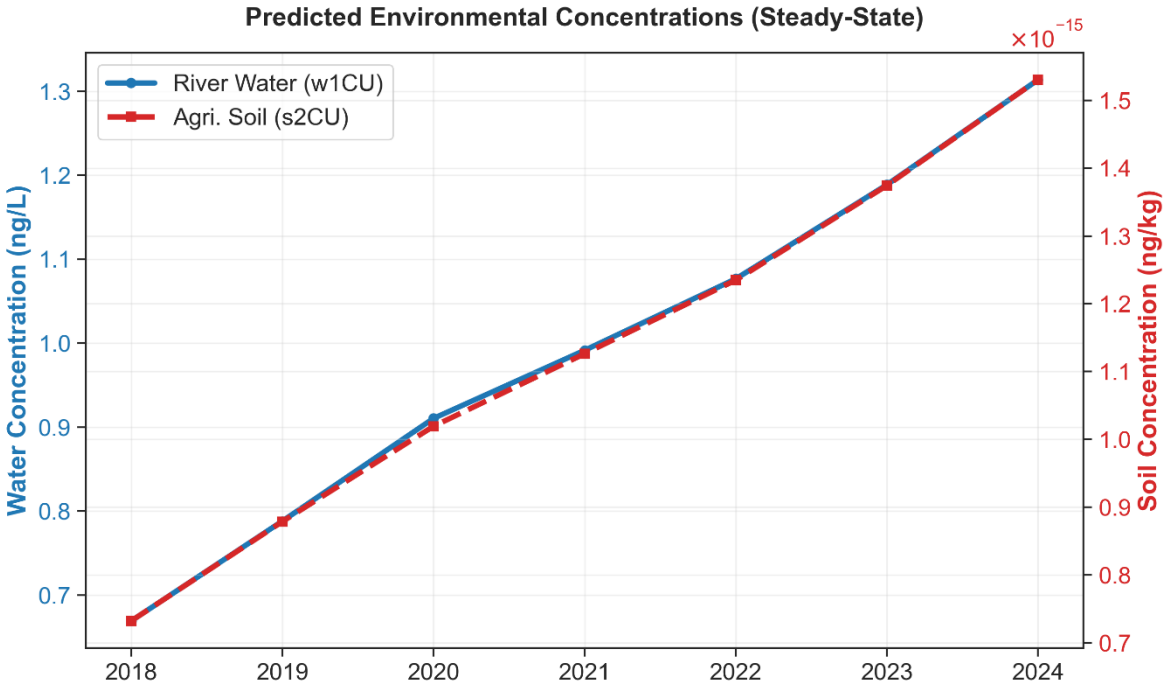


Figure 61. Trends in steady-state Predicted Environmental Concentrations (PEC) for rifaximin (2018–2024). Left axis (blue solid line): Concentration in continental river water (ng/L). Right axis (red dashed line): Concentration in continental agricultural soil (ng/kg dw).

Dynamic vs. Steady-State Behaviour The comparison between dynamic mass accumulation and steady-state predictions for rifaximin is shown in Figure 62. The dynamic simulation illustrates a rapid initial accumulation of rifaximin in surface waters, followed by stepwise increases that closely track the annual emission inputs. Within each simulation year, the dynamic water mass converges quickly toward the corresponding steady-state prediction, indicating that characteristic equilibration times in the aquatic compartment are short relative to the annual emission time step.

Across the entire 2018–2024 period, steady-state water masses slightly exceed the dynamically simulated end-of-year values, reflecting the assumption of continuous emissions and constant environmental conditions inherent to the steady-state formulation. Nevertheless, the close agreement between the two approaches demonstrates that steady-state PECs provide a robust approximation of long-term average water concentrations for rifaximin under gradually increasing emission scenarios.

In contrast, both dynamic and steady-state soil masses remain effectively zero throughout the simulation period. This behaviour is consistent with the model configuration, in which no direct soil emissions were included and degradation in soil was set to zero, preventing accumulation via intermedia transfer. The absence of soil accumulation further confirms that rifaximin exposure is dominated by aquatic pathways.

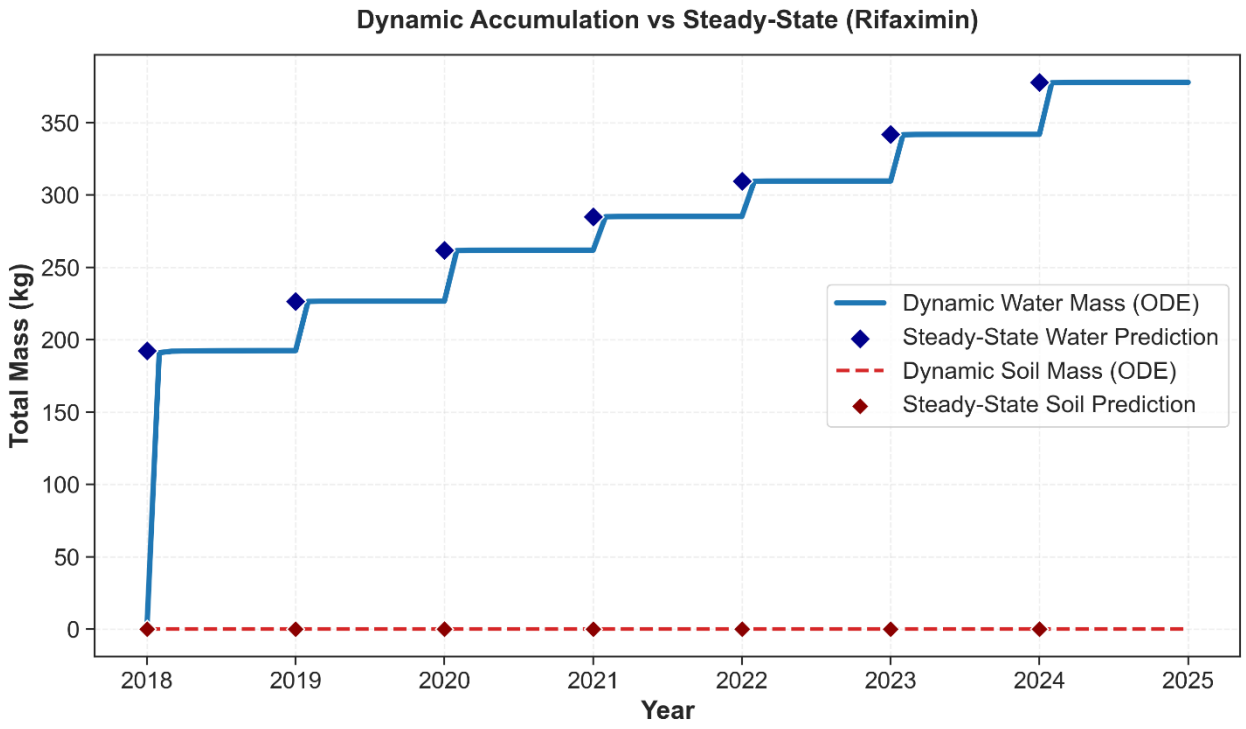


Figure 62. Comparison of dynamic (ODE) and steady-state mass simulations for rifaximin. Continuous lines represent the dynamic mass accumulation over time; discrete markers represent the steady-state equilibrium mass calculated for each specific year. Note the logarithmic scale on the y-axis.

Environmental Mass Distribution Across Compartments The steady-state mass distribution for 2024 shows a strong dominance of the aquatic environment, with approximately 91% of the total environmental mass residing in water compartments and about 9% associated with sediments (Figure 63). Contributions from soil and air compartments were effectively zero.

This pattern is consistent with rifaximin's physicochemical properties and the imposed degradation settings, where degradation in air and soil was set to zero ($k_{deg,air} = 0$; $k_{deg,soil} = 0$) and removal processes were controlled exclusively by aquatic and sediment degradation and inter-media transport.

A more detailed breakdown of the top compartments in 2024 (Figure 64) reveals that continental river water accounted for the largest share of rifaximin mass (~3.8×10^2 kg), followed by continental freshwater sediments (~3.9×10^1 kg). Minor contributions were predicted for continental seawater and moderate marine water compartments, while deeper oceanic and regional compartments contained negligible masses. This distribution highlights the strong coupling between surface waters and sediments for rifaximin once released via WWTP effluents.

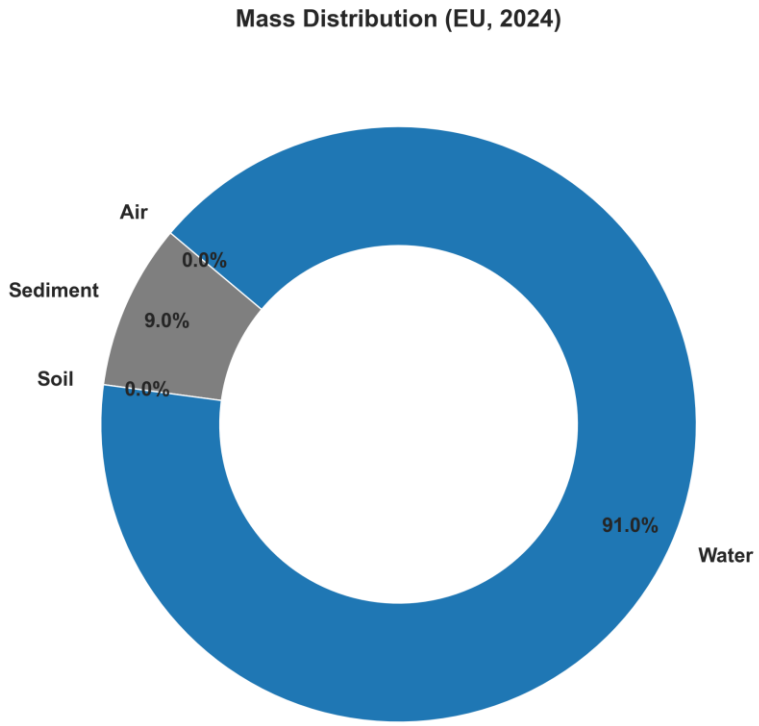


Figure 63. Relative multimedia mass distribution of rifaximin in the European environment (Year 2024). The chart aggregates total mass inventory into four primary categories: Soil, Water, Sediment, and Air.

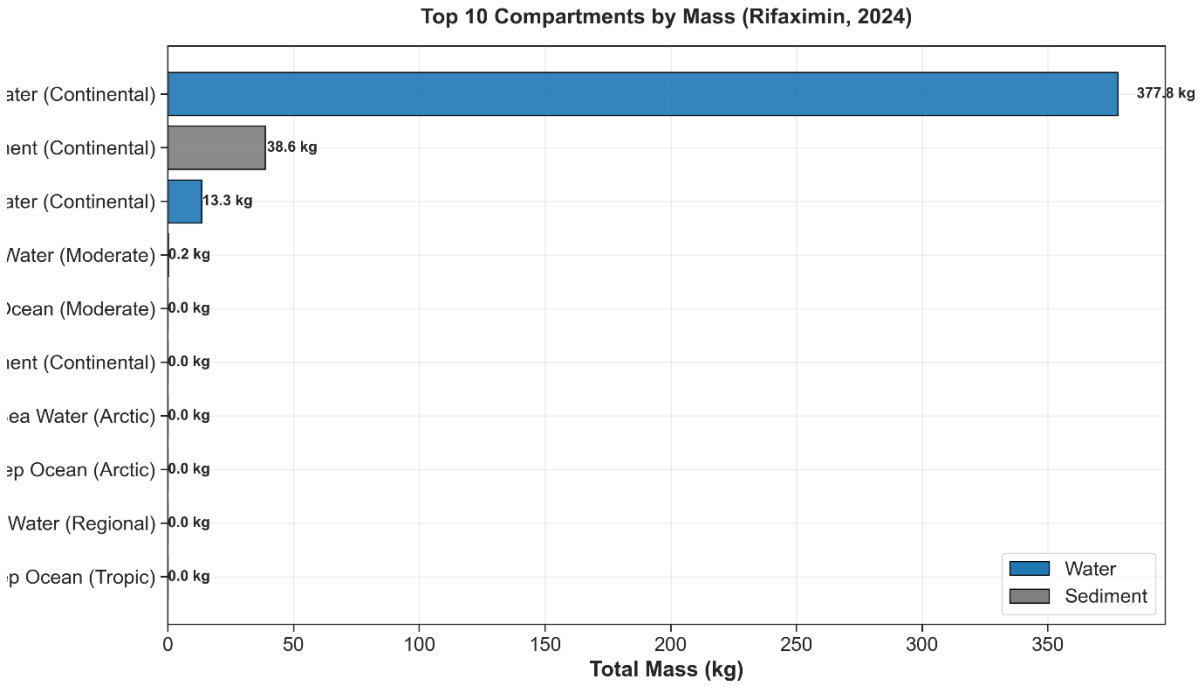


Figure 64. Top 10 environmental compartments by total stored mass of rifaximin (steady-state, 2024). Bars are colour-coded by compartment type: Water (Blue), and Sediment (Grey). Labels indicate the specific continental (C), regional (R), or global scale (A/M/T) compartments.

Sensitivity Analysis A two-dimensional sensitivity analysis was performed to evaluate the influence of first-order degradation rate constants in water (k_{deg_water}) and sediment ($k_{deg\_sediment}$) on steady-state PECs. Degradation in air and soil was excluded from the sensitivity analysis, consistent with the baseline model assumptions.

The sensitivity heatmaps (Figure 65 and Figure 66) show that predicted PECs in both water and sediment are highly sensitive to the magnitude of k_{deg} in the respective receiving compartments. Increasing k_{deg_water} resulted in a systematic reduction of aquatic PECs by nearly one order of magnitude across the explored parameter space, indicating that aquatic persistence is a key determinant of exposure levels.

Similarly, sediment PECs exhibited strong sensitivity to $k_{deg\_sediment}$, with lower degradation rates leading to pronounced accumulation in sediments. Cross-compartment interactions were evident but secondary, confirming that compartment-specific degradation dominates rifaximin fate under the modelled emission scenario.

Overall, the SimpleBox results indicate that rifaximin exposure in the European environment is predominantly aquatic, driven by WWTP effluent emissions and controlled by degradation processes in water and sediments. The absence of direct soil emissions and negligible atmospheric involvement result in minimal terrestrial exposure. These findings suggest that environmental risk assessments for rifaximin should prioritize surface water and sediment compartments, while soil exposure pathways are likely of limited relevance under current usage patterns

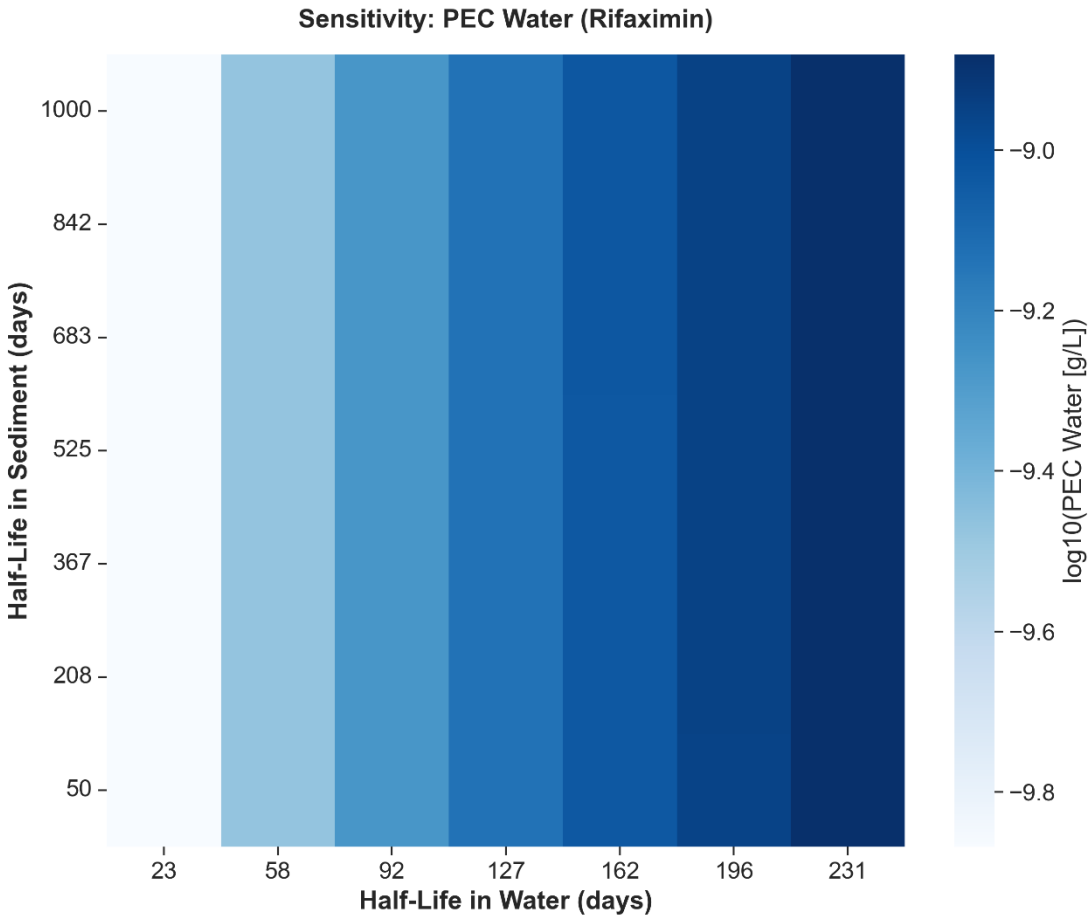


Figure 65. Sensitivity analysis of Predicted Environmental Concentration in River Water (PEC_{water}) to variations in degradation half-lives (DT_{50}). The heatmap displays log_{10} values, with darker blue intensities indicating higher concentrations.

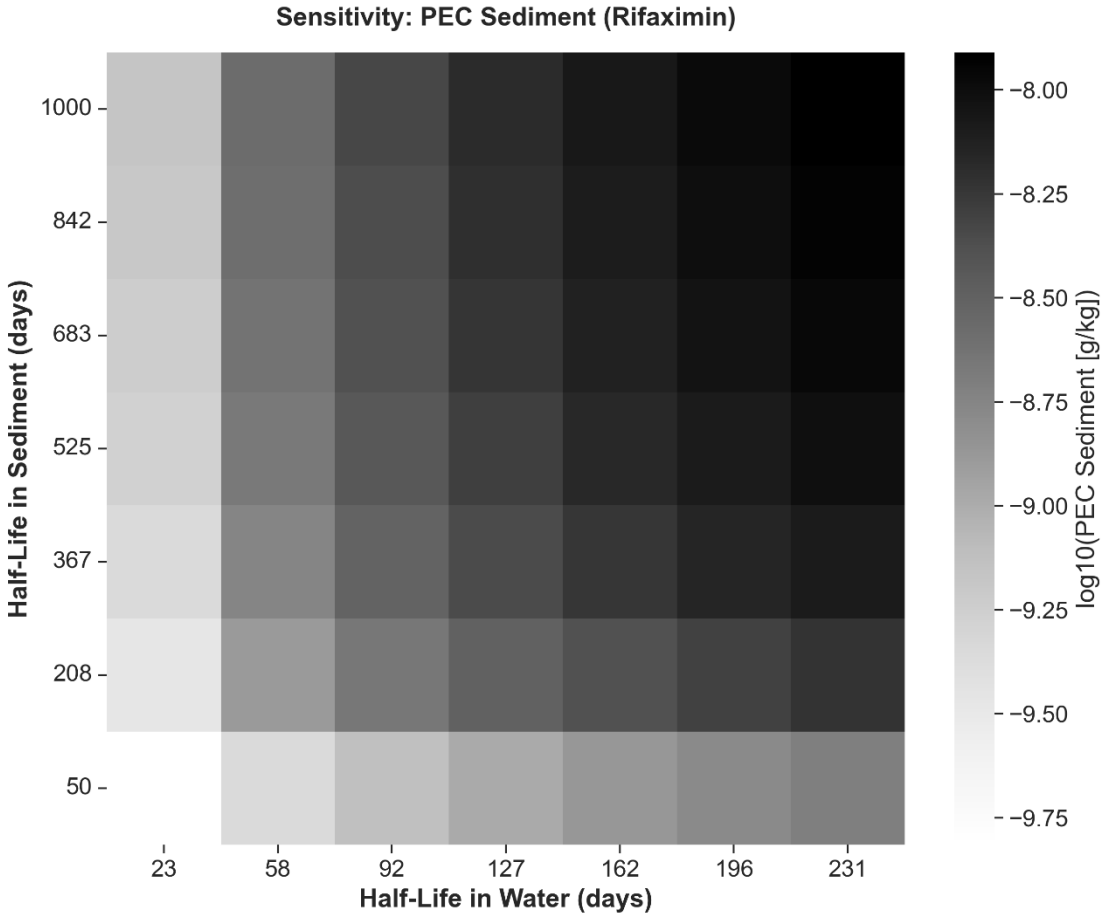


Figure 66. Sensitivity analysis of Predicted Environmental Concentration in Sediment (PEC_{soil}) to variations in degradation half-lives (DT_{50}). The heatmap displays log_{10}(PEC) values, with darker grey intensities indicating higher concentrations. Axes represent the range of half-lives tested (1 to 1000 days) for sediment and water compartments.

4 Environmental risk assessment

4.1 Environmental risk predicted from monitoring and hazard data

A risk ranking approach was applied to the collated freshwater and soil monitoring and hazard data to assess which in-use APIs are posing the greatest risk to aquatic and terrestrial species.

4.1.1 Freshwaters

A total of 464 APIs had both available freshwater exposure data and freshwater community-based SSDs and their risk to freshwater species were analysed using the worst-case risk ranking approach from Spurgeon et al (2022). This approach uses 95th percentile concentrations for APIs in freshwaters and the hazardous concentration to 50% of aquatic species (HC_{50}) derived from SSDs (Posthuma et al., 2019). The 95th percentile concentrations were chosen rather than the mean or

median due to many chemical measurements being below the detection limit. The HC_{50} concentrations were chosen rather than a lower effect threshold as they are the most robust values in the middle of the distribution. Furthermore, SSDs were chosen to obtain the hazard values from as these represent the sensitivity at a community level rather than at an individual species level. Only the APIs that are detected often (≥10 times) are included, resulting in a total of 194 APIs in the risk ranking. This ensures that the risk ranking only includes those APIs that are likely found in the environment, eliminating those APIs rarely detected. In the Spurgeon et al (2022) risk ranking approach, the detection frequency for each chemical is included, which bases the overall risk rank for each API on both the hazard and the probability of occurrence in the environment. The hazard quotient (HQ) rank (HQ=95^{th} %ile concentration/SSD HC_{50} concentration) and detection frequency are calculated to establish both the HQ rank and DF rank for each API, and the overall risk rank using the equation below.

Risk rank = HQ rank * DF rank

Results show that all 194 APIs have HQ values < 1 indicating that concentrations are below hazard thresholds for affecting 50% of aquatic species (Figure 67). Among the relative risk of 194 APIs, the top 30 APIs include analgesic, antibiotic, anticonvulsant, antidepressant/anxiolytic, antihistamine, diuretic, oestrogen and veterinary insecticide medications and caffeine. The top 5 APIs posing greatest risk to aquatic species are cetirizine, imidacloprid (veterinary insecticide), furosemide, cotinine and crotamiton (antipruritic) (Table 13).

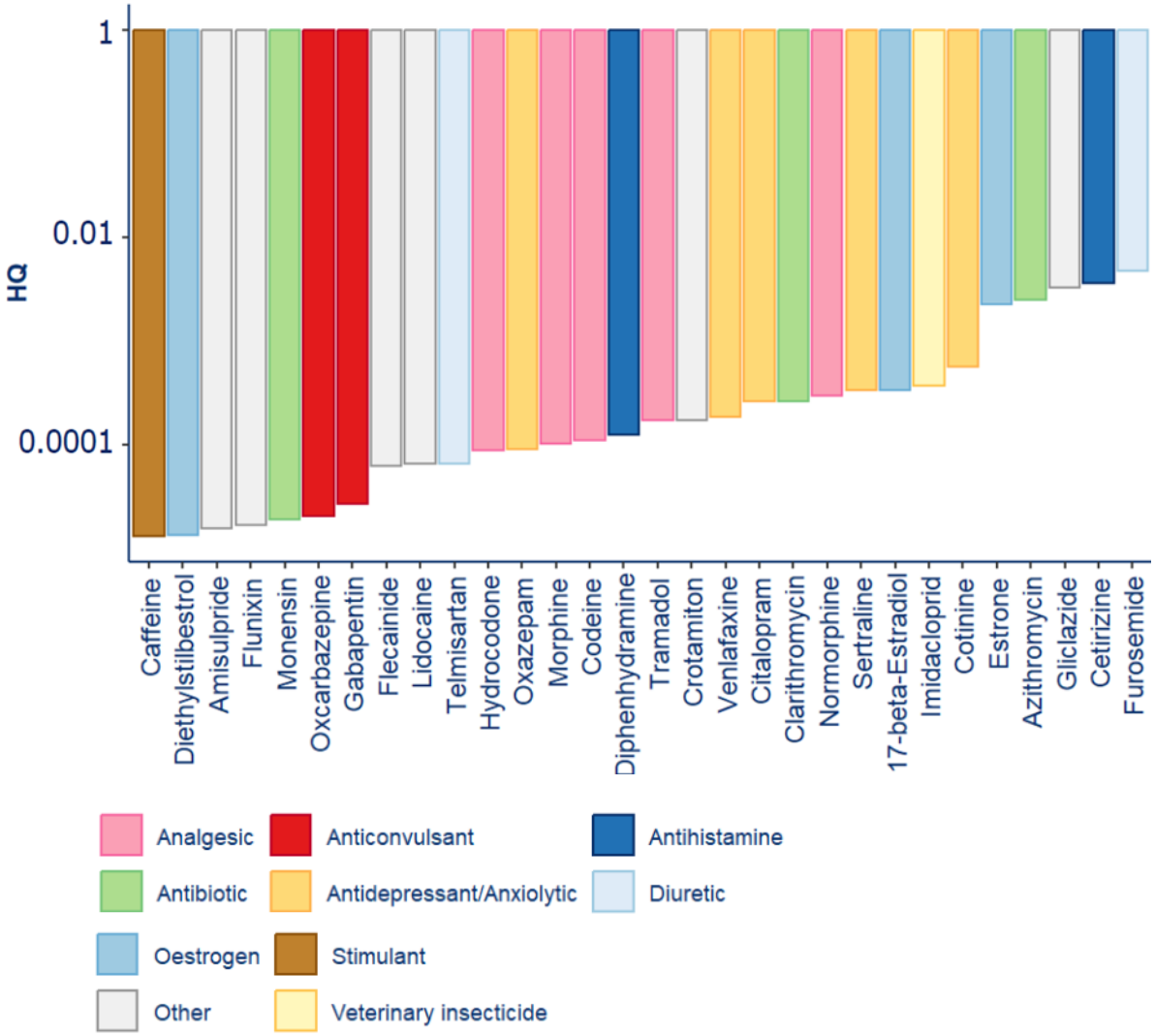


Figure 67. Hazard quotient of top 30 APIs detected in freshwaters.

Table 13. Hazard quotient and risk rank of top 30 APIs detected in freshwaters. * API transformation products, ‡ APIs for human & veterinary use and † APIs for veterinary use.

HQ Rank	API	Therapeutic group	Risk Rank	API	Therapeutic group
1	Furosemide‡	Diuretic	1	Cetirizine‡	Antihistamine
2	Cetirizine‡	Antihistamine	2	Imidacloprid†	Veterinary insecticide
3	Gliclazide	Antidiabetic	3	Furosemide‡	Diuretic
4	Azithromycin‡	Antibiotic	4	Cotinine*	Nicotine metabolite
5	Estrone	Oestrogen	5	Crotamiton‡	Antipruritic
6	Cotinine*	Nicotine metabolite	6	Gliclazide	Antidiabetic
7	Imidacloprid†	Veterinary insecticide	7	Codeine	Analgesic
8	17-beta-Estradiol	Oestrogen	8	Tramadol‡	Analgesic
9	Sertraline‡	Antidepressant/Anxiolytic	9	Venlafaxine‡	Antidepressant/Anxiolytic
10	Normorphine*	Morphine metabolite	10	Hydrocodone‡	Analgesic
11	Clarithromycin‡	Antibiotic	11	Azithromycin‡	Antibiotic
12	Citalopram‡	Antidepressant/Anxiolytic	12	Monensin†	Antibiotic
13	Venlafaxine‡	Antidepressant/Anxiolytic	13	Citalopram‡	Antidepressant/Anxiolytic
14	Crotamiton‡	Antipruritic	14	Estrone	Oestrogen
15	Tramadol‡	Analgesic	15	Caffeine	Stimulant
16	Diphenhydramine‡	Antihistamine	16	Gabapentin‡	Anticonvulsant
17	Codeine	Analgesic	17	17-beta-Estradiol	Oestrogen
18	Morphine‡	Analgesic	19	Clarithromycin‡	Antibiotic
19	Oxazepam‡	Antidepressant/Anxiolytic	19	Diethylstilbestrol‡	Oestrogen
20	Hydrocodone‡	Analgesic	20	Oxazepam‡	Antidepressant/Anxiolytic
21	Telmisartan	Diuretic	21	Telmisartan	Diuretic
22	Lidocaine‡	Anaesthetic	22	Flecainide‡	Antiarrhythmic
23	Flecainide‡	Antiarrhythmic	23	Lidocaine‡	Anaesthetic
24	Gabapentin‡	Anticonvulsant	24	Morphine‡	Analgesic
25	Oxcarbazepine‡	Anticonvulsant	25	Flunixin†	Antiinflammatory
26	Monensin†	Antibiotic	26	Sertraline‡	Antidepressant/Anxiolytic
27	Flunixin†	Antiinflammatory	27	Normorphine*	Morphine metabolite
28	Amisulpride‡	Psychotropic	28	Oxcarbazepine‡	Anticonvulsant
29	Diethylstilbestrol‡	Oestrogen	29	Diphenhydramine‡	Antihistamine
30	Caffeine	Stimulant	30	Amisulpride‡	Psychotropic

4.1.2 Soils

Results show that all 13 APIs have HQ values < 1 indicating concentrations are below hazard thresholds for affecting 50% of soil species (Figure 68). From the relative risk of the 13 APIs, the top 5 APIs include chlortetracycline, salicylic acid (analgesic), atenolol, gemfibrozil and bezafibrate (lipid-lowering drugs) (Table 14). Overall, there are substantially fewer APIs with soil monitoring and ecotoxicological data available in comparison to freshwaters, and from the available data and risk ranking approach the API compounds posing the greatest potential risk to soil communities are largely antibiotics and antiparasitic medications (Ivermectin).

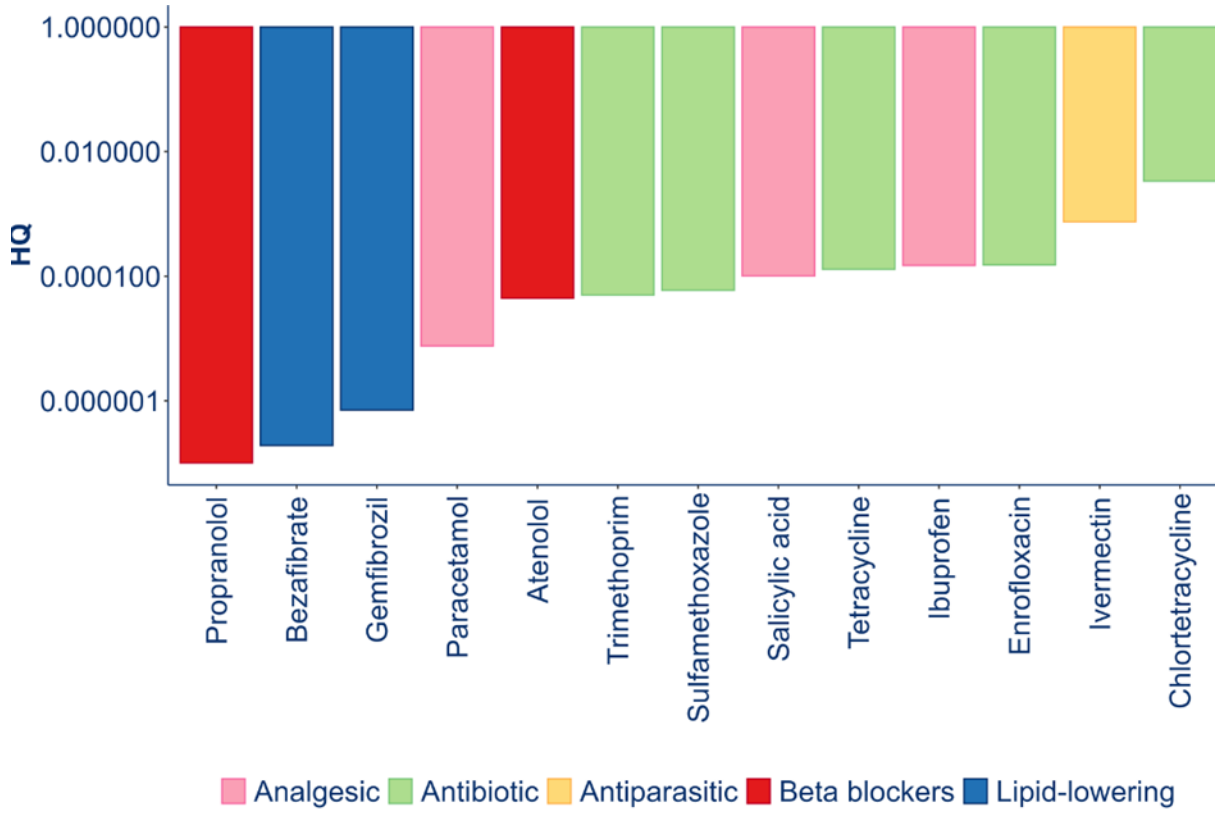


Figure 68. Hazard quotient of all APIs detected in soils with hazard data.

Table 14. Hazard rank, exposure rank, detection frequency (DF) rank and risk rank (HQ rank * DF rank) of all APIs detected in soils. Note: 1 = highest exposure, highest detection frequency and most toxic.

API	Therapeutic group	Hazard rank	Exposure rank	DF rank	Risk rank
Chlortetracycline	Antibiotic	3	2	5	1
Salicylic acid	Analgesic	5	8	1	2
Atenolol	β-blockers	11	5	1	3
Gemfibrozil	Lipid-lowering	4	13	1	4
Bezafibrate	Lipid-lowering	11	11	1	5
Ivermectin	Antiparasitic	2	7	10	6
Ibuprofen	Analgesic	1	9	6	7
Enrofloxacin	Antibiotic	13	1	10	8
Tetracycline	Antibiotic	11	3	7	9
Trimethoprim	Antibiotic	11	4	8	10
Paracetamol	Analgesic	6	10	9	11
Sulfamethoxazole	Antibiotic	7	6	13	12
Propranolol	β-blockers	12	12	10	13

5 Discussion

Based on observed concentrations of a broad selection of pharmaceutical compounds in the environment, we have been able to predict those which are most likely to pose a risk. In freshwater environments, our assessment showed cetirizine, imidacloprid and furosemide as being the top three risks. In soils, chlortetracycline, salicylic acid and atenolol where the highest ranked. Compared to other assessments of aquatic systems (e.g. Spilsbury et al 2024), our risk ranking is comparable in terms of the presence of similar APIs near the top of the ranking, though there are notable differences. These differences are mostly due to the fact that Spilsbury only included 27 APIs in their assessment, while we extended this to 464 APIs. Other differences can be attributed to our assessment correcting for detection frequency, a broader selection of data used in our assessment, and use of different metrics (90%-file vs median; HC50 vs PNEC). This underscores the fact that, though our understanding of pharmaceutical exposures, hazard and risk is relatively high (particularly compared to other chemicals), we still face difficulties in prioritising which APIs cause the most risk.

This is particularly true for terrestrial systems, where a very limited amount of data makes the assessment even more difficult. There is a clear need for future work that prioritises the collection and generation of such data.

Another notable observation is that risk is not driven solely by emissions, exposure or hazard, and using one of these as a proxy for risk may lead to incorrect conclusions. For example, the diuretic furosemide only just appears in the top 50 APIs in terms of 90%-file exposure concentration, but due to its hazard, appears third in the risk ranking.

Overall, emissions predictions were comparative with measured effluent concentrations from wastewater treatment plants, giving confidence that our emissions model is comprehensive enough to cover all major uses and emissions pathways. To predict exposures, we used the screening level multimedia exposure model SimpleBox, which aims to give "background" concentrations of emitted compounds (rather than predict hotspots). For the five APIs we performed this exposure assessment for, PECs were significantly lower than median and 90%-ile measured concentrations (Figure 69).

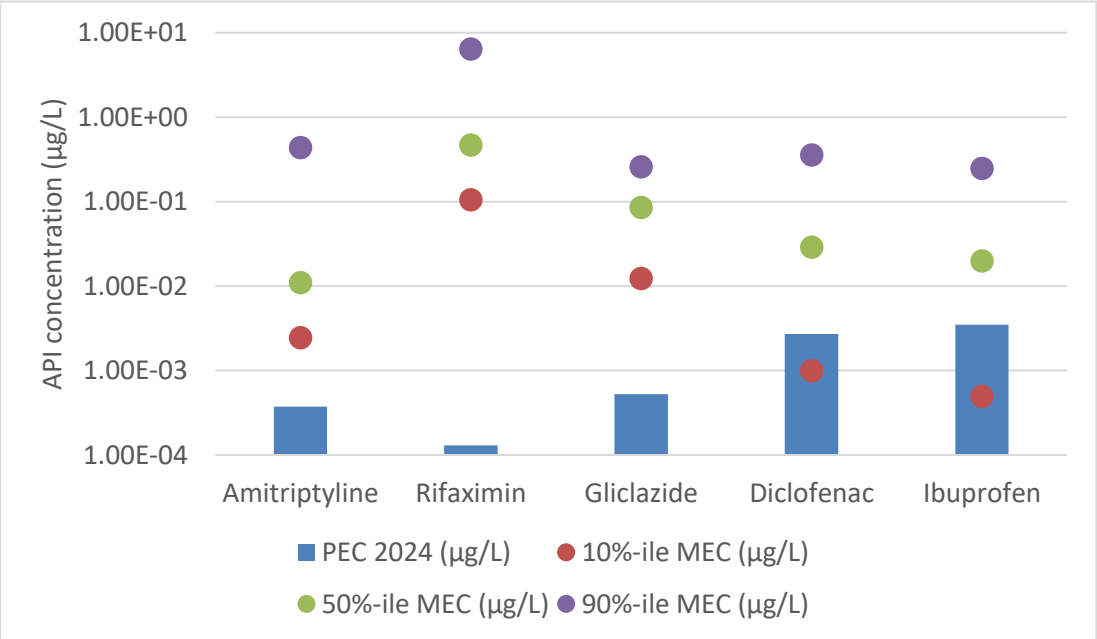


Figure 69. Comparison between surface water measured environmental concentrations (MECs; markers) and predicted environmental concentrations (PECs; bars) in 2024.

There could be several reasons for this. Real-word concentrations are a function of historic emissions of these APIs, meaning that there might be baseline exposure that our predictions (which begin in 2018) are not factoring in. However, the strong agreement between steady state and dynamic predictions indicates that steady state is reached relatively quickly in surface waters, meaning historic model runs before 2018 are unlikely to significantly raise concentrations. Another factor could be the values used to define the size of the surface water compartment in SimpleBox. Here, we use the default European continental parameters. Further work should validate these against national or local scenarios – for example, modelling exposure specifically in the UK. Finally, the speed at which the results reach steady state is strongly dependent on degradation dynamics. If degradation parameters are over-estimated, this could lead to the exposure model predicting removal at a rate that exceeds reality. In general, there are limited data on such parameters, making this a key area for future work. It is notable that the model predictions are better for the "better-studied" APIs ibuprofen and diclofenac (and comparable with other model predictions, e.g. Austin et al., 2022), hinting that this data availability issue could be an important factor.

It is worth noting that Spilsbury et al. (2024) compared their database of MECs against worst-case PECs predicted by a much simpler model, as recommended by the EMA for regulatory assessments:

$$PEC = \frac{DDD \times F_{PEN}}{DIL \times WW_{INH}}$$

where DDD is the defined daily dose (maximum recommended adult dose), F_{PEN} is the penetration factor (by default 1% of the population), DIL is the dilution factor (by default 10) and WW_{INH} is the daily wastewater produced per inhabitant (by default 200 L/inh/day). Their results showed these worst-case PECs systematically exceeded median MECs.

These results highlight that model choice and formulation require careful consideration when assessing the environmental exposure of pharmaceuticals, and that comparison with measured data (where available) is critical to ensure trust in results. For our work, the next logical step is to explore different scenarios (such as national or local scales) or move to a spatiotemporal modelling framework that is able to predict hotspots and temporal dynamics with much higher resolution. Future work should also prioritise providing more data on the terrestrial environment, and better data on model parameters such as degradation rates. This could be experimental or explore the use of quantitative tools to predict relationships between molecular structures and physicochemical properties.

6 Conclusions

In the deliverable, we have presented an environmental risk assessment of existing pharmaceutical compounds. In freshwater environments, our assessment showed cetirizine, imidacloprid and furosemide as being the top three risks. In soils, chlortetracycline, salicylic acid and atenolol where the highest ranked. We revealed a lack of data particularly for terrestrial environments, and uncertainties in exposure modelling parameters that lead to differences between measured and predicted API concentrations. Future work should focus on collating or generating more data for terrestrial environments, better understanding of uncertain but important parameters like degradation rates, and further exploration of exposure predictions using spatially and temporally resolved models.