Journal of Environmental Chemical Engineering 13 (2025) 119181

Contents lists available at ScienceDirect

Journal of Environmental Chemical Engineering

journal homepage: www.elsevier.com/locate/jece

Pharmaceuticals in the Douro basin: Occurrence, distribution, and ecological risk

Alena Voznakova [a], Ana María. Antao-Geraldes [b], Moisés Canle [a,*]

[a] React!, Departamento de Química, Facultade de Ciencias & CICA, Universidade da Coruña, A Coruña E-15071, Spain
[b] CIMO, LA SusTEC, Instituto Politécnico de Bragança, Campus de Santa Apolónia, Bragança 5300-253, Portugal

ARTICLE INFO

Keywords:
Pharmaceuticals
Surface water pollution
Ecological risk assessment
Emerging contaminants
Sediment contamination
One-health integrated approach

ABSTRACT

This study assesses water quality in the Portuguese section of the Douro River basin (Bragança region, NE Portugal) by evaluating the presence and potential impact of pharmaceutical contaminants (PhCs), classified as contaminants of emerging concern (CECs). A set of 65 pharmaceuticals was investigated for their occurrence and ecological and health impact. The extent of contamination by these compounds, and its possible effects on the aquatic ecosystem was analyzed and discussed. Additionally, the accumulation of these pharmaceuticals in sediments is investigated, providing a more comprehensive understanding of their distribution and persistence in the environment. Out of these 65 CECs, 23 were found in water and 10 in sediments. The most abundant correspond to acetaminophen, diclofenac and ibuprofen. The data obtained are used in this paper to develop an environmental indicator system, which serves as a valuable tool for assessing ecosystem health and water quality. This system provides key information to support decision-making regarding environmental management and conservation. Ultimately, this integrated approach aims to enhance the understanding and protection of water resources in the Bragança region and beyond.

1. Introduction

Water is used for very different purposes, including domestic, industrial and agricultural uses. Such diversity of uses has, over the last decades, resulted in the release of numerous unwanted compounds and pollutants into the environment, which not only negatively affect the water cycle, but also generate global concerns about their long-term effects on aquatic ecosystems, biodiversity and human health. The occurrence of these compounds, known as 'contaminants of emerging concern' (CECs), sometimes also referred to as micropollutants (MPs), in aquatic environments is increasingly recognized as a global environmental challenge due to their continuous input from municipal and industrial effluents, surface runoff from urban areas, and leachates from landfills, contributing to their persistence and bioaccumulation in aquatic systems[1,2] These substances, present at trace levels (pg, ng, and $\mu g \cdot L^{-1}$), persist in the environment despite conventional water and wastewater treatment processes and pose potential long-term risks to ecosystems and human health [3]. CECs include a wide range of substances such as pharmaceuticals, hormones, industrial chemicals, and pesticides, which enter aquatic systems through various pathways such as domestic and industrial discharges, agricultural runoff, and wastewater treatment plant effluents [4] in which conventional treatments are usually inefficient, leading to the release of these pollutants into the aquatic environment [5].

Pharmaceuticals (PhCs), in particular, have gained attention as one of the major categories of CECs, with residues from human and veterinary use frequently detected in surface water, sediments, and biota. The consumption of pharmaceuticals has significantly increased in recent decades due to population growth, technological advancements, and greater accessibility to prescription drugs. In Europe, its accessibility has risen considerably in just 15 years [6]. Recent studies suggest that the aquatic risk of pharmaceuticals, such as carbamazepine or ciprofloxacin, has risen 10–20 times over the past two decades, primarily due to the growing population in urban areas [7]. In particular, antibiotics have drawn significant attention over the past 20 years due to their widespread use, environmental persistence, and their role in the development and spread of antimicrobial resistance. The presence of pharmaceutical residues in water bodies is particularly concerning as they can induce chronic toxicity, endocrine disruption, and promote the development of resistant bacteria. This poses a severe threat to biodiversity, ecosystem stability, and public health on a global scale [8]. All of this must be viewed and analyzed in the framework of the one health

* Corresponding author.
E-mail addresses: mcanle@udc.es, moises.canle@udc.es (M. Canle).

https://doi.org/10.1016/j.jece.2025.119181
Received 31 March 2025; Received in revised form 13 August 2025; Accepted 6 September 2025
Available online 12 September 2025

integrated approach to balance and optimize the health of people, animals and ecosystems. The monitored compounds, originally developed to prevent and treat diseases and improve health of living beings, are biologically active substances that may persist in the environment due to their continuous input and limited degradation, a phenomenon known as pseudo-persistence [9], [10]. Following human or animal consumption, pharmaceuticals undergo partial metabolism, resulting in the excretion of various active chemical compounds through urine and feces. Depending on the pharmaceutical class, up to 90 % of the administered dose is excreted [11], [12] as the parent compound, which is subsequently released into the environment through animal manure or sewage, ultimately reaching wastewater treatment plants (WWTPs). Additionally, agricultural activities significantly contribute to water contamination, as processes such as soil erosion and leaching transport various pollutants, including pharmaceutical residues, into water bodies. Finally, the discharge of industrial waste, and inappropriate practices, such as self-medication and the disposal of unused pharmaceuticals in household garbage or down the drain, further worsen surface water pollution, disrupting the natural water cycle and raising global concerns about its long-term ecological consequences [13].

Freshwater ecosystems are particularly vulnerable to urban pollution, as they often flow through different cities and urban areas and serve multiple purposes, including water supply, irrigation, recreation, and wastewater treatment. As a result, they receive both diffuse and point-source contamination. The widespread use of pharmaceuticals, combined with inefficient or insufficient wastewater treatment, has significantly contributed to river pollution globally. Pharmaceutical residues have been detected worldwide in surface waters at concentrations ranging from $pg \cdot L^{-1}$ to $mg \cdot L^{-1}$ and in sediments from $\mu g \cdot kg^{-1}$ to $mg \cdot kg^{-1}$, highlighting their persistence and potential ecological impact. Sediments may act as reservoirs for certain pharmaceutical families, such as antibiotics, analgesics, and antidepressants, allowing these contaminants to persist in aquatic environments for extended periods. This accumulation can lead to their gradual release back into the water column, potentially affecting aquatic organisms and contributing to long-term pollution dynamics.

The accumulation of pharmaceuticals and other CECs in aquatic systems affects drinking water quality, agricultural irrigation, and overall water security, highlighting the urgent need for permanent and effective monitoring and mitigation strategies [14]. Regulatory efforts in Europe emphasize the need to monitor CECs, including pharmaceutical residues, to ensure the chemical and ecological integrity of surface waters. The Water Framework Directive established a framework for water conservation, later amended by Directive 2008/105/EC, which introduced a list of priority substances requiring monitoring. The Directive 2013/39/EU updated this list, expanding it to 45 substances and emphasizing the need for advanced water treatment technologies. Additionally, the EU Watch List under Decision 2015/495/EU was introduced to facilitate the collection of monitoring data on emerging pollutants to support future prioritization efforts. Member states of the EU are required to monitor the substances on the list at least once per year for up to four years. The Watch List was updated in 2018, 2020, 2022, and again in 2025 [15].

This study aims to monitor the occurrence of 65 pharmaceuticals (Table S1, Supplementary material), assess their ecological risks, and analyze their spatial and temporal distribution in water and sediment at 14 sampling sites over three campaigns in the upper Portuguese part of the river Douro basin (Bragança, NE Portugal). Its geography, with water bodies influenced by human activities and natural conditions, offers a unique opportunity to assess the spatial and seasonal distribution of these compounds. This region faces significant environmental pressures due to different land uses, which can introduce pollutants into aquatic ecosystems through urban runoff, agricultural practices, and sewage effluents.

The selection of target pharmaceuticals in this study was based on different criteria reflecting their regulatory relevance, environmental occurrence, and potential risks. Some of the selected pharmaceuticals are currently regulated in water quality guidelines due to their potential environmental and human health risks. Additionally, several compounds are included in the current EU Watch List for emerging pollutants or have been part of previous versions of this list, making their monitoring essential to assess persistence and potential regulatory needs. Moreover, certain substances were identified as candidates for inclusion in future EU Watch Lists because of their presence in aquatic environments and possible ecotoxicological effects.

The selection also prioritized compounds known or suspected to contribute to antimicrobial resistance, reflecting their potential human and ecological health effects. Furthermore, pharmaceuticals frequently detected in previous studies on surface water and sediment contamination (see supplementary data) were included to ensure a comprehensive assessment of their occurrence and distribution.

Since the majority of aquatic ecosystems evaluated in this study had not been previously surveyed for pharmaceutical compounds, low prevalence or rarely reported substances were also assessed. This decision aimed not only to address significant gaps in current knowledge regarding their environmental presence and distribution, but also to anticipate possible shifts in pharmaceutical usage and related ecological exposure scenarios.

Despite its environmental and socioeconomic relevance, the Portuguese section of the Douro River basin in Bragança region has been poorly studied in terms of the presence of emerging pollutants, such as pharmaceuticals, which can pose a significant threat to aquatic ecosystems and human health [16].

This study differs from previous research by developing environmental indicators to assess ecosystem health, thus providing essential insights into the environmental fate of pharmaceuticals and their impact on aquatic ecosystems. These indicators clarify pollution patterns and support informed decision-making for water management and conservation. To enhance their applicability, a four-color alert system has been incorporated, simplifying risk assessment based on pharmaceutical concentrations. Moreover, these indicators can be easily replicated in other freshwater ecosystems worldwide.

Furthermore, the results obtained in this study were compared with data from previous studies on these contaminants conducted in Portugal and other European countries. We emphasize the importance of this preliminary information for river basin managers and policymakers.

2. Methodology

2.1. Study site

The study was carried out in the Portuguese section of the Douro River basin, within the Bragança district - NE Portugal. The Douro River is an international river flowing through 897 km from Picos de Urbión (Soria, Spain) through Portugal into the Atlantic Ocean, with its mouth in Porto (Portugal). The sampling area is characterized by the strong seasonality, with periods of strong drought, and for constituting a highly diverse system of rivers and reservoirs, which play a key role in water supply, biodiversity, agricultural and recreational activities.

Fourteen sampling points strategically distributed in rivers and reservoirs of the region were selected. Most of the river points belong to the Sabor River basin, an important tributary of the Douro River. In addition, a sampling point was included directly in the Douro River, at Miranda do Douro (S14), where the river enters Portugal. Three sampling campaigns were conducted between mid-March and mid-April (campaign A), May (campaign B) and September (campaign C) 2024, covering wet (March/April and May) and dry (September) periods to assess the influence of flow and seasonal variations on the concentration of PhCs in different aquatic compartments.

The sampling points covered a wide range of environmental conditions and potential sources of contamination (Table 1, Figure S1).

These permanent rivers have a strong torrential hydrological regime,

Table 1
Sampling sites description.

Code	Sampling site	Characteristics	GPS Coordinates	
			North	West
S1	Serra Serrada Reservoir	Located in Montesinho National Park (altitude, 1200 m) urban water supply and hydroelectric power generation cause accentuated water level fluctuations. Although human influence on the reservoir seems to be negligible, extensive grazing on the reservoir shores, woodland and scrub, Mesotrophic reservoir	41.962211	−6.772782
S2	Castanheira Reservoir	Extensive agriculture and farming, woodland and scrub Mesotrophic to eutrophic	41.78658	−6.820871
S3	Fervença Riverupstream Bragança city	Rural area, extensive agriculture and grazing, woodland and scrub	41.794507	−6.800465
S4	Fervença River-IPB University Campus	Inside Bragança's urban area (22,685 inhabitants [17]). The river runs through the university campus	41.798257	−6.76437
S5	Fervença River-5 km downstream from Bragança WWTP	Extensive agriculture and grazing, runoff from a semi-intensive pig farm with around 300 animals, Eutrophication, strong odor, foam.	41.776104	−6.715371
S6	Sabor River-Camping	The river runs through a campsite (capacity of 200 persons); extensive agriculture, woodland and scrub	41.843795	−6.745939
S7	Sabor River-Coelhoso	Woodland and scrub, extensive agriculture	41.665534	−6.643853
S8	Azibo River Upstream	Upstream Azibo reservoir, highway runoff, Woodland and scrub, extensive agriculture	41.625731	−6.855616
S9	Azibeiro River (confluence Azibo reservoir)	Extensive water level fluctuation due to reservoir influence. Extensive agriculture, woodland, scrub	41.588806	−6.906762
S10	Azibo Reservoir	Urban and agriculture water supply, tourism (350,000 tourists/year), River beaches, small village, extensive agriculture, woodland and scrub Mesotrophic reservoir	41.575006	−6.897132
S11	Azibo River (downstream Azibo reservoir)	Extensive agriculture, woodland and scrub.	41.469622	−6.850333
S12	River Sabor Mouth	River beach at the confluence of the Sabor and Douro rivers. Small villages, agriculture, woodland and scrub	41.17719	−7.111157
S13	Angueira River-São Martinho	Urban area (239 inhabitants). The location where the Angueira River, an international river, enters Portuguese territory. Extensive agriculture, woodland and scrub	41.633947	−6.35144
S14	Douro River-Miranda Reservoir	The location where the Douro River enters Portuguese territory. Hydroelectric power generation, urban areas, Douro International Natural Park, extensive agriculture, woodland and scrub. Mesotrophic to eutrophic reservoir	41.492357	−6.26565

with large flow variations, in line with rainfall.

In addition, sampling was carried out at the Bragança Drinking Water Treatment Plant (DWTP) and the Bragança Wastewater Treatment Plant (WWTP), both at the inlet and outlet of the facilities. This approach allows us to evaluate not only the presence and distribution of pollutants in natural water bodies, but also the effectiveness of the treatment processes in removing these compounds.

2.2. Meteorological data

Meteorological data were obtained from the Portuguese Institute for Sea and Atmosphere (IPMA) [18]. Monthly average precipitation values were considered for March, April, May, August and September 2024, corresponding to the sampling campaigns. For the campaign a, carried out between mid-March and mid-April, precipitation data for both months were included to provide an accurate characterization of the hydrological conditions during the entire sampling period. Campaign C was conducted during the first days of September, in a period without rainfall. For this reason, the accumulated rainfall data for August are also included, since they reflect more accurately the conditions prior to sampling than the rainfall recorded in September. This approach was adopted to ensure that variability in precipitations, which can significantly influence the presence and concentration of contaminants in aquatic environments, was properly accounted for in the interpretation of the results.

Rainfall data are summarized in Table 2. These values were used to contextualize the observed pharmaceutical concentrations in water and sediments. Precipitation can affect the presence and distribution of PhCs through processes such as dilution, runoff from urban and agricultural areas, and particle resuspension. Therefore, considering these environmental conditions provides additional insight into the seasonal patterns and spatial variability of contaminant occurrence observed in this study.

Table 2
Average monthly rainfall in Bragança during monitoring campaigns.

Sampling campaign	Month	Average precipitation (mm)
Campaign A	March 2024	121.6
	April 2024	38.8
Campaign B	May 2024	48.3
Campaign C	August 2024	3.7
	September 2024	51.5

2.3. Water sampling and sediment collection

Water samples were collected from the surface and preserved in 125 mL glass bottles with Teflon caps, previously washed with sulfochromic mixture, followed by 1 % HCl aqueous solution and double distilled water. Samples were labeled, cooled, and subsequently frozen at −18 °C until analysis.

Sediment samples were obtained using a stainless-steel grab sampler and stored in the dark at 4 °C. In laboratory samples were labeled, cooled, and subsequently frozen at −18 °C until further analysis.

Physicochemical parameters, including pH, conductivity, and temperature, were measured *in situ* using portable multiparameter probes (HANNA HI98194) to provide contextual environmental data.

2.4. Contaminant analysis and sample processing

All contaminants were analyzed by HPLC/MS, and detection was performed by high-resolution mass spectrometry (HRMS).

As for the general method of sediment lixiviate preparation, four parts milli-Q water were mixed with one part of sediment, by volume. Then they were held in continuous stirring for 24 h. At the end of the mixing period, the mixture was left to decant for approximately 1 h. The supernatant liquid was filtered through filter paper with a pore size between 20 and 25 μm. These filters have been previously treated, washed with distilled water and dried. The first 10 mL of filtered supernatant liquid were discarded to obtain a sample with as few impurities as possible. Both water and sediment samples were stored in the dark in a refrigerated container and then frozen at −20 °C until analysis.

All compounds were analyzed by high-performance liquid chromatography (HPLC) using two different columns, depending on the target analytes. A Zorbax SB-Aq column (2.1 × 150 mm, 3.5 μm) and an XSelect HSS T3 column (3.0 × 150 mm, 2.5 μm) were used for separation. The column temperature was maintained at 40 °C, with an injection volume of 100 μL and a flow rate of 0.4 mL·min^{-1} .

Elution was performed in gradient mode with a binary mobile phase system: phase A consisted of water with 0.1 % acetic acid and 1 mM ammonium acetate, while phase B was acetonitrile with 0.1 % acetic acid. The gradient profile was as follows: 100 % A at 0.00 min, maintained until 2.00 min, then gradually decreasing to 2 % A and 98 % B at 14.00 min, held until 17.00 min, and returning to initial conditions at 19.00 min, with a post-run equilibration time of 3 min.

To ensure reproducibility and proper method validation, all relevant mass spectrometric parameters used in the analysis are provided in Supplementary material, Table S2. These include the ionization mode, precursor and product ions, fragmentor voltage, collision energy, and cell accelerator voltage for each compound analyzed using triple quadrupole MS under multiple reaction monitoring (MRM) mode.

2.5. Quality assurance/quality control

Calibration curves were built from each of the CECs, from solutions of the standard material (maximum purity commercially available). These calibrations exhibited excellent linearity over the working range (0.01–6.00 μg·L^{-1}), with correlation coefficients 0.9968–0.9999, showing the robustness of the quantification model. The sensitivity was confirmed, with a limit of quantification (LOQ) of 0.005 μg·L^{-1} . Method repeatability, assessed in terms of peak area and analyte concentration, yielded maximum relative standard deviations of 9.30 % and 9.85 %, respectively, indicating high consistency in measurements. Accuracy values ranged from 82.1 % to 116.6 %, reflecting the method's reliability in recovering target compounds.

For sediment samples, the analysis was performed on their leachates, which were treated following the same quality control procedures as for water samples. Matrix effect evaluation confirmed that, at the working dilutions, no significant matrix interference was observed. Therefore, the same calibration, sensitivity, repeatability, and accuracy parameters applied to water were considered valid for sediment leachates, ensuring consistent analytical performance across both matrices.

2.6. Environmental risk assessment

To assess the potential risk that the detected substances may cause to human health, the risk quotient (RQ) was calculated. This coefficient, applied to polar substances, is defined as the ratio of the measured environmental concentration (MEC) in the water column to the predicted no effect concentration (PNEC), which represents the concentration below which adverse effects are unlikely to occur during exposure, either in the short or long term. The PNEC value is determined from a reference concentration, selected as the lowest value from available experimental data for the organism of interest, and an assessment factor (AF), which can range from 10 to 1000, depending on whether it is derived from long-term (chronic) toxicity data for all trophic levels or from short-term (acute) toxicity data for at least one trophic level, respectively.

A comprehensive literature review was conducted to compile the lowest reported PNEC values available for freshwater organisms (Table S3). The PNEC value for each compound was consistently selected as the lowest available concentration reported in the reviewed literature, thereby maximizing environmental protection through a precautionary approach. Most of the selected values were derived from chronic toxicity data, which better reflect realistic environmental exposure scenarios and generally provide a more protective basis for risk assessment. However, in a few instances where chronic data were unavailable, acute toxicity data were used, and a higher assessment factor (AF=1000) was applied, following established ecotoxicological risk assessment guidelines.

The PNEC for sediments was calculated using the equilibrium partitioning method [19], expressed through the simplified formula

$$PNEC_{sediment} = PNEC_{water} \cdot (0.783 + 0.0217 \bullet K_{OC}) \quad (1)$$

Once the risk coefficient was determined, the values were ranked according to the estimated risk and a color-coded system was established. If the RQ value is ≤ 0.1, no adverse effects are expected, and the risk is classified as negligible (green). If the RQ value is between 0.1 and 1, the risk is low, but the possibility of adverse effects should be considered (yellow). If the RQ value ranges between 1.0 and 10, some adverse effects are likely to occur, and the risk is classified as moderate (orange). Finally, if the RQ value is ≥ 10, a high risk is expected (red) [20].

Toxic units (TUs) were calculated for each group of substances analyzed by adding the previously determined RQ values to assess the potential risk of toxicity due to the simultaneous presence of multiple substances.

2.7. Statistical analysis

The detection frequencies were calculated by counting the number of samples in which each pharmaceutical was detected and dividing this value by the total number of analyzed samples (n = 42), expressing the result as a percentage. Mean concentrations were calculated by applying the simple arithmetic mean, from all measured values.

To investigate potential relationships between the physicochemical properties of water and the presence of pharmaceuticals, a correlation matrix was constructed. The analysis included key parameters such as pH, conductivity, and temperature, along with the concentrations of detected pharmaceuticals.

Pearson's correlation coefficient (r) was used to quantify the strength and direction of the linear relationships between variables.

3. Results and discussion

3.1. Ocurrence and spatio-temporal variability in water

Out of the 65 pharmaceuticals monitored in the Bragança section of the Douro River basin, 23 were quantified in water samples (Table S4-S6). The occurrence of these contaminants varied significantly across sampling sites and campaigns. However, spatial differences suggest that specific anthropogenic influences may play a role in contamination distribution.

It is essential to note that all substances detected in the water column are present at very low concentrations, mostly in the ppb range, indicating good water quality in the region. However, their potential environmental risk could increase if their concentration rises. Therefore, continuous monitoring is essential to establish a record of their trends in time.

In the case of contaminants with measured concentrations below the quantification limit, *i.e.*, < 0.005, they have been considered as not detected for the purposes of this study, assuming that their concentration is insufficient for reliable quantification within the analytical method used.

Table 3 presents the detection frequencies, ranges, mean concentrations, and standard deviation of the quantified PhCs across all campaigns in water samples.

The pharmaceuticals identified in the water samples were classified into six distinct groups (Fig. 1). Cardiovascular drugs represented the largest category, comprising nine compounds (39.13 %). This was followed by anti-inflammatory drugs, with four compounds (17.39 %), and antibiotics, with four compounds (17.39 %). Analgesics accounted for three substances (13.04 %) and group of neurological/psychiatric drugs was represented by two compounds (8.70 %), while gastrointestinal drugs were the least represented, with a single compound (4.35 %). Anti-inflammatory drugs presented the highest detection frequency, 100 %. All samples were contaminated by at least one substance of this group, followed by analgesics (95.48 %), cardiovascular drugs (59.52 %), gastrointestinal drugs (42.86 %), antibiotics (21.43 %) and neurological and psychiatric drugs (4.76 %).

Regarding mean concentration, the results do not follow the same pattern, the highest one was observed in the antibiotic group (2.242 $\mu g \cdot L^{-1}$), followed by gastrointestinal (1.022 $\mu g \cdot L^{-1}$), analgesics (1.252 $\mu g \cdot L^{-1}$) and cardiovascular drugs (0.910 $\mu g \cdot L^{-1}$). The highest individual concentration was found for antibiotics (amoxicillin, 15.382 $\mu g \cdot L^{-1}$) and anti-inflammatory drugs (acetaminophen, 10.587 $\mu g \cdot L^{-1}$).

As for the most quantified substances out of a total of 42 samples taken, diclofenac appeared in 100 % of them, followed by acetaminophen, which appeared in 38 samples (90.48 %), ibuprofen appeared in 35 samples (83.33 %) and omeprazole was quantified in 19 samples (45.24 %).

The highest frequency of detection is for anti-inflammatory and analgesic drugs, especially acetaminophen, which is not surprising, since most of these substances are among the most prescribed drugs worldwide and are sold over the counter in Portugal. On the other hand, the frequencies of detection of cardiovascular drugs could be related to the demographic characteristics of the studied area, with aging demography [21], which likely contributes to the higher consumption of cardiovascular pharmaceuticals and their subsequent detection in the aquatic environment. The same is true in relation with the detection of omeprazole, widely used to treat gastrointestinal problems, that also tend to be more prevalent in older patients.

Interestingly, the low concentrations and limited detection frequencies of antidepressant venlafaxine and carbamazepine, used as anticonvulsant in epilepsy treatment and also in patients with bipolar disorder, observed in our study could reflect several factors. First, it may indicate a relatively low consumption of these substances, possibly suggesting a lower prevalence or underdiagnosis of mental health problems in the studied area. In addition, antidepressants are usually prescription drugs whose distribution is more controlled than that of common analgesics or anti-inflammatories. On the other hand, these substances show a metabolic prevalence (Table S7) which leads to very small amounts being excreted as the parent compound, which may also contribute to their scarcity in the environment.

PhCs overall concentrations detected in water samples from the three sampling campaigns are shown in Fig. 2. The boxplot illustrate the

Table 3
Occurrence of the pharmaceutical residues quantified in this study in water samples.

Pharmaceutical group	Frequency (%)	Minimum ($\mu g \cdot L^{-1}$)	Mean ($\mu g \cdot L^{-1}$)	Maximum ($\mu g \cdot L^{-1}$)	SD (%)
Anti-inflammatory drugs	100	0.018	0.418	3.744	0.641
Diclofenac	100.00	0.118	0.273	3.165	0.464
Ibuprofen	83.33	0.147	0.569	3.744	0.780
Ketoprofen	4.76	0.170	0.403	0.635	0.233
Naproxen	2.38	1.266	1.266	1.266	0.000
Analgesics	95.48	0.087	1.252	10.587	1.821
Acetaminophen	90.48	0.087	1.450	10.587	1.971
Codeine	4.76	0.015	0.018	0.021	0.003
Tramadol	19.05	0.087	0.618	1.988	0.686
Antibiotics	21.43	0.018	2.242	15.382	4.416
Amoxicillin	16.67	0.592	3.809	15.382	5.247
Clarithromycin	2.38	0.018	0.018	0.018	0.000
Isoniazid	4.76	0.033	0.059	0.084	0.026
Sulfadimethoxine	4.76	0.021	0.053	0.084	0.032
Cardiovascular drugs	59.52	0.022	0.910	8.216	1.426
Atenolol	11.90	0.034	0.894	2.370	0.882
Atorvastatin	7.14	0.121	0.349	0.684	0.242
Bisoprolol	19.05	0.045	1.199	2.360	0.691
Clofibric acid	9.52	0.089	0.361	1.165	0.464
Furosemide	9.52	0.667	3.315	8.216	2.994
Propranolol	11.90	0.045	0.346	1.159	0.413
Ramipril	16.67	0.027	0.775	2.659	0.978
Sotalol	9.52	0.052	0.081	0.115	0.023
Warfarin	2.38	0.022	0.022	0.022	0.000
Neurological and psychiatric drugs	4.76	0.033	0.274	0.611	0.246
Carbamazepine	2.38	0.180	0.180	0.180	0.000
Venlafaxine	4.76	0.033	0.322	0.611	0.289
Gastrointestinal drugs	45.24	0.111	1.403	8.255	1.998
Omeprazole	45.24	0.111	1.403	8.255	1.998

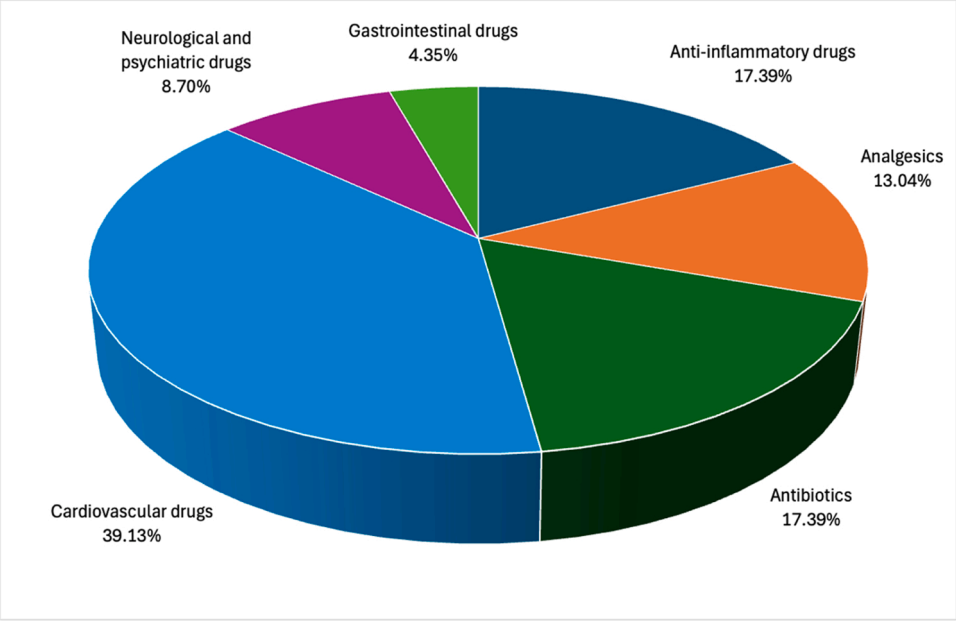

Fig. 1. Pharmaceuticals by groups quantified in water samples.

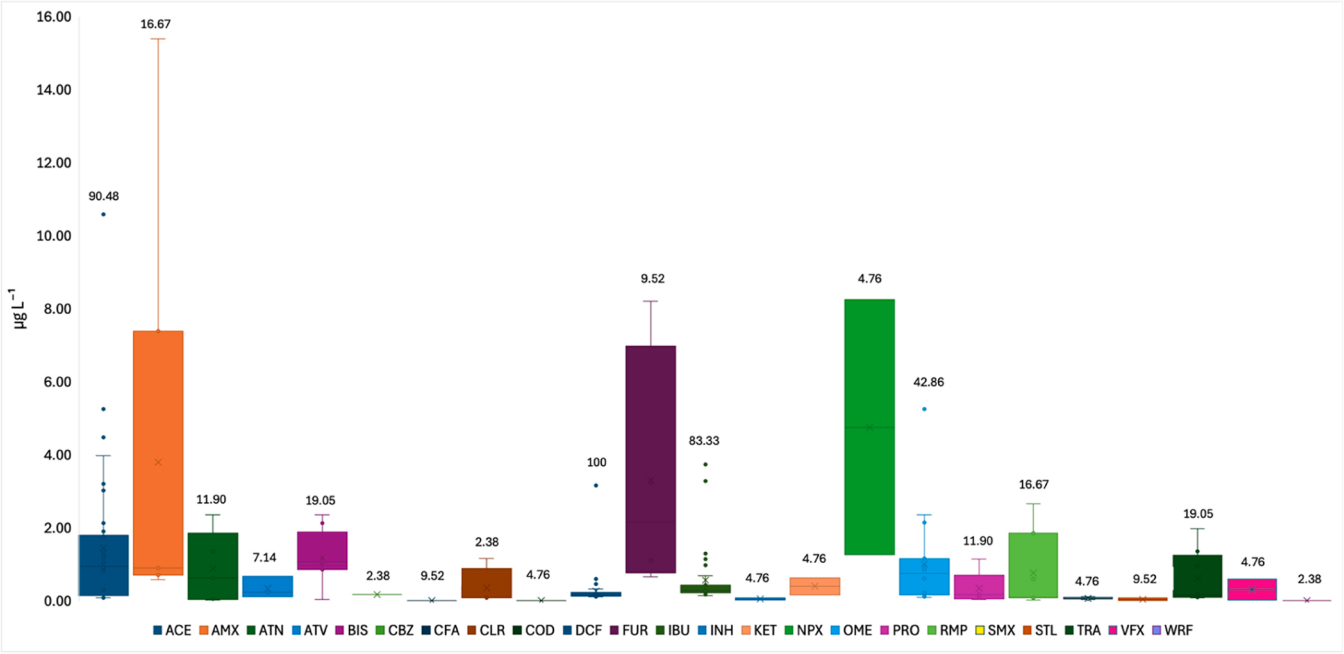

Fig. 2. Overall concentrations of PhCs detected in water samples in Douro River basin (numbers in the figure indicate the frequencies (%) of detection in 42 samples collected during the three sampling campaigns). ACE-acetaminophen, AMX-amoxicillin, ATN-atenolol, ATV-atorvastatin, BIS-bisoprolol, CBZ-carbamazepine, CFA-clofibric acid, CLR-clarithromycin, COD-codeine, DCF-diclofenac, FUR-furosemide, IBU-ibuprofen, INH-isoniazid, KET-ketoprofen, NPX-naproxen, OME-omeprazole, PRO-propranolol, RMP-ramipril, SMX-sulfadimethoxine, STL-sotalol, TRA-tramadol, VFX-venlafaxine, WRF-warfarin.

distribution and variability of the compounds across the 14 sampling sites. A wide range of concentrations was observed, with some compounds showing notable dispersion, as outliers, but generally concentration levels were relatively low. Amoxicillin and furosemide presented the highest variability, indicating sporadic peaks of contamination. In contrast diclofenac and ibuprofen presented lower concentration and narrower distribution ranges, suggesting continuous release to the environment across sampling sites and time.

The greatest diversity of compounds in water samples was found in campaign A, in March, with 17 substances detected. The highest occurrence was observed at site S13 (Table 1), where 11 different pharmaceuticals were quantified on the Angueira River. During this campaign, the highest accumulated concentrations of substances were observed at sites S1 (9.293 $\mu g \cdot L^{-1}$) and S5 (17.540 $\mu g \cdot L^{-1}$). On the other hand, the substance for which the highest concentrations were observed was amoxicillin at the same points, S1 and S5 (Table 1), achieving 7.387 $\mu g \cdot L^{-1}$ and 15.382 $\mu g \cdot L^{-1}$, respectively.

A high presence of amoxicillin at S1 is an observation of great concern since the water from the Serra Serrada reservoir is intended to be used for drinking water for the city of Bragança and is one of the most

remote sampling points, located within a protected natural park, far from villages, at high altitude (1200 m). The observed values can only be associated with the presence of livestock grazing in the surrounding area, to which veterinary pharmaceuticals may have been administered. In addition, the site is subjected to accentuated water level fluctuations [22], which may enhance the mobilization and dispersion of pollutants from diffuse sources, contributing to the presence of amoxicillin in surface waters despite the isolated nature of the site. All the drugs observed at this site omeprazole, acetaminophen and ibuprofen are of veterinary use.

In sampling campaign B, 14 PhCs were quantified, with the highest occurrence at sites S7 (Table 1) (7), followed by S5, S10 and S14 (Table 1) (6 at all of them), while the highest accumulated concentration was measured at site S9 (19.616 $\mu g \cdot L^{-1}$). The substances for which the highest concentrations were observed were acetaminophen reaching 10.587 $\mu g \cdot L^{-1}$ on the Azibeiro River at S9 and omeprazole on the Sabor River at S6 sampling point, achieving 8.255 $\mu g \cdot L^{-1}$.

Campaign C resulted in the detection of 14 substances, with site S7 exhibiting the highest number of PhCs (7), whereas the highest accumulated concentration was again recorded at site S5 (12.371 $\mu g \cdot L^{-1}$). Finally, the substance with the highest measured concentration was acetaminophen with 4.491 $\mu g \cdot L^{-1}$ at site S5.

Across all campaigns, campaign A presented the highest diversity of quantified substances in water. However, the sites associated with the highest cumulative concentrations varied depending on the sampling period, with S5 showing elevated levels in campaign A and campaign C, while S9 had the highest concentrations in May (Fig. 3). Notably, site S5 is located immediately downstream of a wastewater treatment plant (WWTP) and near a pig farm, which may contribute to the elevated pharmaceutical concentrations recorded in this area. Moreover, it is worth highlighting that, in the campaign A, at site S13, four antibiotics were simultaneously detected, representing the highest number of antibiotics found at a single sampling point in this study.

To compare the pharmaceutical profiles between campaigns, cumulative concentrations were converted into relative abundances (Fig. 4). This approach allows highlighting the contribution of each pharmaceutical to the total contamination load, independently of the absolute concentration differences between sampling campaigns, allowing a clearer visualization of compositional differences over time.

Some seasonal differences were observed, with certain contaminants, such as amoxicillin, appearing predominantly in campaign A, while others, such as acetaminophen, bisoprolol and furosemide were more prevalent in campaigns B and C. These trends may reflect changes in contaminant input, environmental conditions, or degradation rates over time.

Dissipation half-life (DT_{50}), defined as the time required for 50 % of a compound's initial concentration to dissipate from the environmental compartment, is a standard indicator of environmental persistence. DT_{50} values reported in the literature were consulted for both surface waters and sediments to better interpret the persistence and pseudo-persistence of the detected pharmaceuticals (Supplementary material, Table S8). In surface waters, acetaminophen typically shows a short half-life of about 3 days, while diclofenac has DT_{50} values around 5 days, depending on light exposure and microbial activity. Amoxicillin presents an intermediate degradation profile, with DT_{50} values of approximately 35.5 days. Carbamazepine stands out for its high persistence, with reported DT_{50}

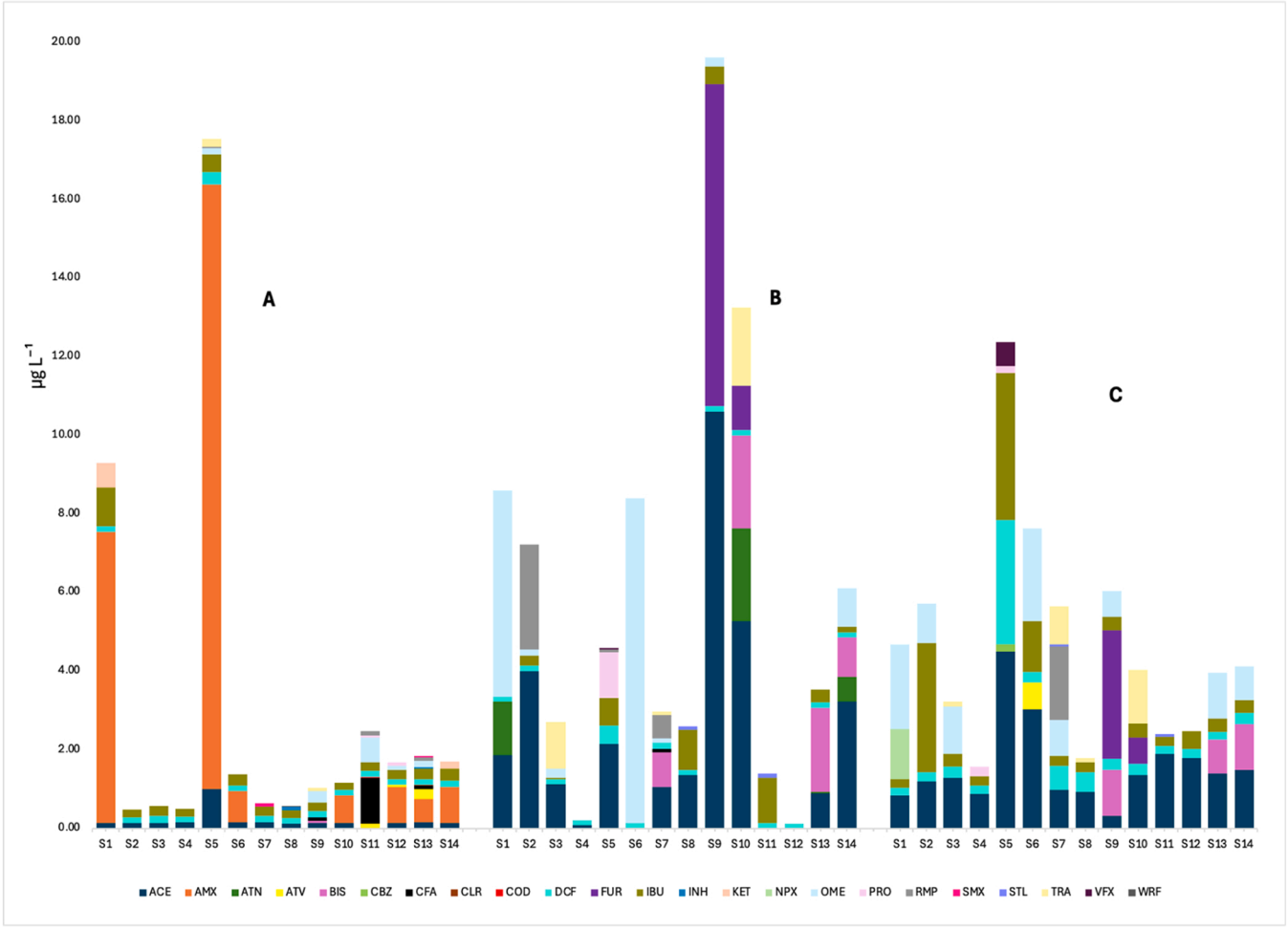

Fig. 3. Cumulative concentrations at different sampling points for the pharmaceutical residues found in water, across the three sampling campaigns.

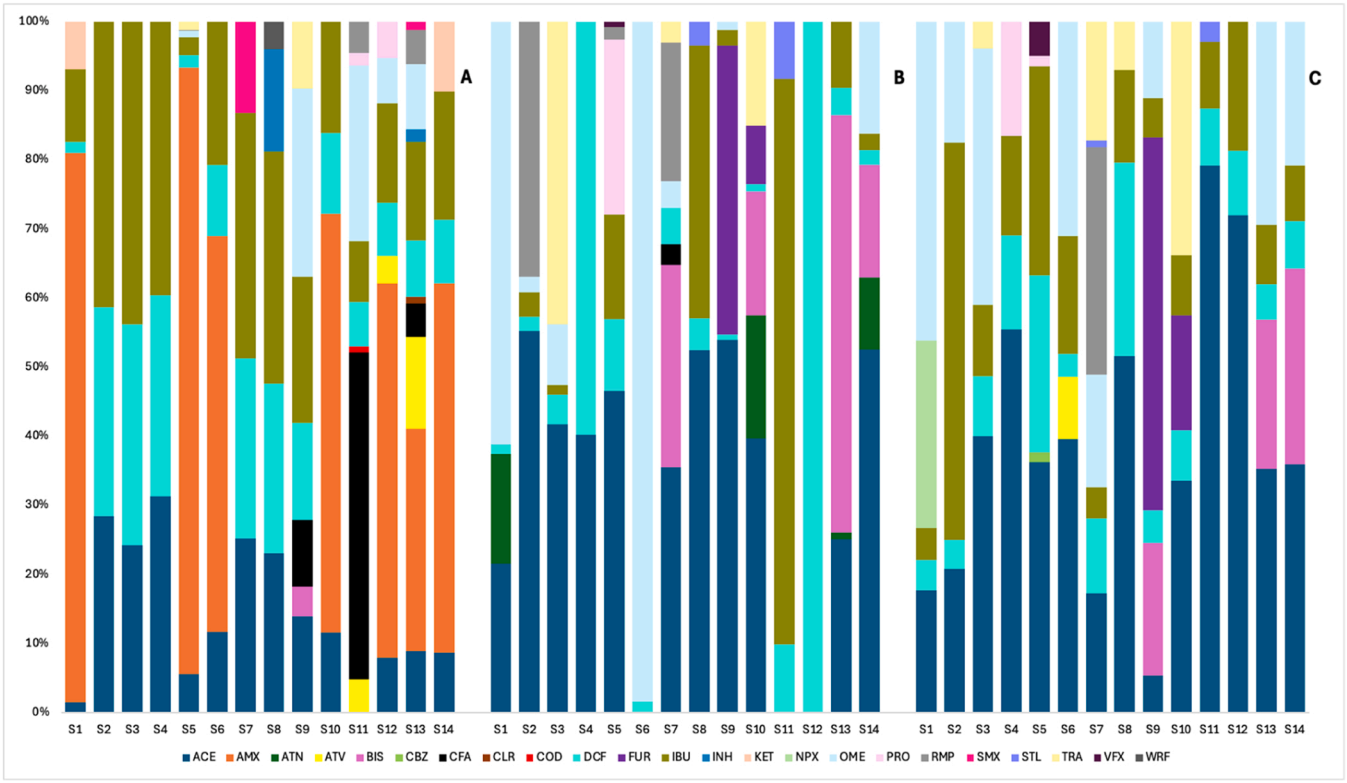

Fig. 4. Relative abundance at different sampling points for the pharmaceutical residues found in water, across the three sampling campaigns.

values often exceeding 328 days in aquatic systems.

In sediments, available data are more limited, but they reinforce the persistence classification of some compounds. Acetaminophen again shows a short half-life (~3 days), and ibuprofen degrades relatively quickly (~10 days), indicating low persistence. In contrast, carbamazepine shows notable stability in sediments, with DT_{50} values close to 47 days, supporting its classification as a pseudo-persistent compound. Venlafaxine displays intermediate behavior, with sediment DT_{50} values around 17 days. Overall, these degradation patterns help explain the frequent or continuous detection of certain pharmaceuticals across sampling campaigns and support their identification as pseudo-persistent pollutants.

The decrease in the concentration of amoxicillin in water between March and May may also be associated with its seasonal use, as this antibiotic is commonly prescribed for respiratory and urinary infections [23], which tend to occur more often during specific periods of the year.

The spatial and seasonal variations observed in the concentrations of PhCs in water samples appear to be influenced not only by anthropogenic sources but also by hydrological conditions. March, the campaign with the greatest diversity of compounds (17 substances) and notably high concentrations at sites S1 and S5, coincided with the highest recorded precipitation (121.6 mm). This precipitation probably contributed to the mobilization of pollutants through increased surface runoff, which could explain the high diversity of substances detected in this campaign and generally lower loads observed, due to dilution processes. In contrast, May, with lower precipitation values (48.3 mm), showed slightly reduced diversity and changes in pollution patterns, with points S2, S6, S9 and S10 having the highest cumulative concentrations, possibly reflecting areas with increased human presence and potential tourism activity. In the case of the campaign C, although climate records indicate a higher amount of accumulated precipitation (51.5 mm) compared to May, the samples were collected during the first days of September, in a period without rainfall. For this reason, precipitation data from August have also been considered (3.7 mm), as they better reflect the conditions prior to sampling. The decrease observed in the occurrence and concentrations of some compounds does not seem to be due to direct dilution, but rather to desorption processes promoted by solar radiation and higher temperatures [24], [25].

Physicochemical parameters showed seasonal variations across the three sampling campaigns. Water temperature increased significantly in September (16.57–24.76 ºC) compared to March (9.81–16.11 ºC) and May (11.05–18.70 ºC), reflecting the expected seasonal trends. Conductivity and total dissolved solids (TDS) showed a marked rise in September, reaching maximum values of 1382 $\mu S \cdot cm^{-1}$ and 690 $mg \cdot L^{-1}$, respectively, particularly downstream of the WWTP. In contrast, March and May displayed lower and more stable conductivity (8–354 $\mu S \cdot cm^{-1}$) and TDS (4–177 $mg \cdot L^{-1}$). pH values remained relatively stable throughout the campaigns (6.05–9.26), with localized alkalinity variations in certain sites, such as Azibo Reservoir (S6) and Sabor River in Coelhoso (S7). Tables and graphics with detailed data on pH, temperature, conductivity and TDS are available in the supplementary information (Tables S9-S12 and Figures S2-S5).

A correlation matrix (Table S13) was carried out to assess whether physicochemical properties, specifically pH, conductivity and temperature, influence the distribution of PhCs in the water column. This analysis aimed to identify possible relationships between these parameters and the presence of pharmaceuticals in surface waters. The results revealed correlations for certain compounds. For example, tramadol showed a positive correlation with pH, suggesting that its persistence in the water column may be influenced by pH-dependent processes such as ionization or solubility changes. Ibuprofen and diclofenac showed a weak positive correlation with conductivity, which could indicate a relationship between their presence and variations in ionic content, possibly due to wastewater inputs. In contrast, atenolol and sotalol showed negative correlations with both conductivity and temperature, suggesting a different environmental behavior, possibly degrading faster or being transported to areas with less anthropogenic impact.

However, it is important to remark that not all pharmaceuticals were consistently detected in all locations and campaigns, which may limit the strength of these correlations and indicate other underlying factors,

such as local sources of contamination, degradation rates, or hydrodynamic conditions. These results suggest that physicochemical parameters may play a role in the distribution and fate of pharmaceuticals in aquatic environments, although further research, is needed to confirm these patterns and identify the dominant processes driving the distribution of pharmaceuticals in the study area.

The presence of PhCs in surface waters has been widely reported worldwide, reflecting their widespread use and continuous discharge into aquatic environments. Abundant information is available for PhCs in water in Europe, though a bit less for Portugal (Table S14). In this study, the concentrations detected are slightly higher as those previously reported in other Portuguese water bodies. Specally higher concentrations were observed for compounds, such as acetaminophen (0.087–10.587 $\mu g \cdot L^{-1}$) or amoxicillin (0.592–15.382 $\mu g \cdot L^{-1}$), suggesting a point contamination issue. However, if average concentrations are considered, the results are fully comparable to those described in similar studies carried out in Portugal. The presence of diclofenac, detected in 100 % of the samples, is a matter of concern. Nevertheless, these results are in line with findings from other studies conducted in Portuguese river systems, where diclofenac has also been reported as one of the most prevalent pharmaceuticals [16], [26].

In addition, the results obtained for sampling points S4, S5, and S6 (Fervença River) were compared with data collected at the same locations in February 2018 by Canle and Antão-Geraldes [16]. Although not all the compounds analyzed in the present study were included in the previous monitoring campaign, a clear increase in the concentrations of all pharmaceuticals that were common to both studies (acetaminophen, carbamazepine, clofibric acid, diclofenac and ibuprofen) was observed (Table S15). Several factors may explain these differences. Firstly, seasonal variation plays a crucial role in the presence of pharmaceuticals in surface waters, as lower river flows during certain periods can lead to higher concentrations due to reduced dilution capacity. Additionally, is also important to consider the performance of wastewater treatment plants, which can vary seasonally or due to operational factors, affecting the load of contaminants reaching receiving water bodies. Lastly, methodological improvements in analytical sensitivity between both sampling campaigns could also partly explain the detection of higher concentrations in the current study.

Compared with data reported for other European rivers (Table S16), the concentrations observed in this study are also within range. Although variations between regions are to be expected, due to differences in consumption patterns, wastewater treatment performance and environmental conditions, the levels detected in the studied area are consistent with those reported in European monitoring studies. These results confirm that the presence of pharmaceuticals in surface waters of the Bragança region is in line with national and European trends, highlighting the diffuse and persistent nature of pharmaceutical pollution.

High detection frequencies of anti-inflammatory drugs were observed, with concentration ranges aligning with previous data from Portuguese and European rivers. However, the distribution of drugs by therapeutic class did not follow patterns reported in other studies [27]. While anti-inflammatory and analgesic drugs were predominant, a notable proportion of the samples also contained cardiovascular compounds. This may reflect local demographics, as cardiovascular disease prevalence tends to increase in aging populations.

Among the detected pharmaceuticals, three compounds are currently included in the EU Watch List: amoxicillin, propranolol and venlafaxine. Additionally, diclofenac, which was part of the EU Watch List until 2018, when it was removed due to the availability of sufficiently high-quality monitoring data [28], was detected in 100 % of the water samples analyzed in this study. This consistent presence underlines that diclofenac remains as a compound of great environmental concern and should not be overlooked in future monitoring programs. In addition, it is important to highlight that during the sampling campaign A at site S13, all four antibiotics detected in this study were present simultaneously. This finding along with the high concentration of amoxicillin at S1 and S5 in the same campaign reinforces concerns about the continued entry of antibiotics into the aquatic environment and suggests the existence of local sources of contamination, such as untreated discharges or inappropriate treatment at the WWTP. The simultaneous presence of multiple antibiotics at a single site may contribute to development and spread of antibiotic-resistant bacteria and resistance genes, underscoring the need for continued monitoring and stricter control measures [29].

3.2. Occurrence and spatio-temporal variability in sediments

Out of the 65 pharmaceuticals monitored, 10 were quantified in sediment samples (Table S17-S19). Table 4 presents the detection frequencies, ranges, mean concentrations, and standard deviation of the quantified pharmaceutical residues across all campaigns in sediment samples. The PhCs detected in sediment samples were classified into five distinct therapeutic groups (Fig. 5). Anti-inflammatory drugs constituted the largest category, comprising four compounds (40 %), followed by cardiovascular drugs, with three compounds (30 %). Analgesics, neurological and gastrointestinal drugs were represented by one compound each (10 %). As well as in water samples, anti-inflammatory drugs presented the highest detection frequency, 100 %. All 42 samples were contaminated by at least one substance of this group, followed by analgesics (90.48 %), cardiovascular drugs (47.62 %), gastrointestinal drugs (42.86 %) and neurological and psychiatric drugs (4.76 %). As for the most quantified substances out of a total of 42 samples taken, diclofenac was present in 100 % of samples of sediments, as in water samples, followed by acetaminophen, which appeared in 38 samples (90.50 %), ibuprofen appeared in 34 samples (80.95 %) and Ketoprofen was quantified in 29 samples (69.05 %). The frequent detection of these PhCs in the samples is not surprising, as these are among the most prescribed anti-inflammatory and analgesic drugs, and in many cases, they are taken by patients without medical prescription.

Fig. 6 shows the overall concentrations of PhCs detected in sediment samples collected during the three sampling campaigns. In general, the concentrations in sediments were considerably lower than those observed in water. However, same as in water samples, some substances showed a high dispersion in their concentrations, as in the case of omeprazole, acetaminophen and ketoprofen, highlighting the presence of outlier values. On the contrary, diclofenac, similarly as in water samples, showed lower and homogeneously distributed concentrations, suggesting a continuous release into the environment.

In campaign A sediments, six pharmaceutical residues, acetaminophen, bisoprolol, diclofenac, ibuprofen, ketoprofen, and omeprazole, were quantified across six sampling points (S4, S5, S7, S8, S9 and S11). The highest cumulative concentration was recorded at S4 (6.408 $\mu g \cdot L^{-1}$), while the highest individual concentration was observed for omeprazole at S5 (4.647 $\mu g \cdot L^{-1}$).

Similarly, in campaign B, the same six substances were detected at six sampling sites (S1, S3, S4, S5, S6 and S13). The highest cumulative concentration was found at S6 (9.406 $\mu g \cdot L^{-1}$), whereas acetaminophen exhibited the highest individual concentration at S7 (5.987 $\mu g \cdot L^{-1}$).

Campaign C had the highest occurrence, with a total of nine PhCs identified. The greatest number of substances (6) was found at S4, where acetaminophen, diclofenac, ibuprofen, ketoprofen, and ramipril were present. The site with the highest cumulative concentration was S14 (6.999 $\mu g \cdot L^{-1}$), while the highest individual concentration was recorded for acetaminophen at S5 (3.452 $\mu g \cdot L^{-1}$).

Fig. 7 represents the cumulative concentrations found in the sediment in the three sampling campaigns. Generally, the highest cumulative concentrations were recorded at sampling points S5, S6, S7 and S14, although the dominant locations varied between campaigns. In campaign C, a clear decrease in concentrations can be observed, probably due to increased exposure of sediments to solar radiation and consequent desorption processes [30].

Table 4
Occurrence of the pharmaceutical residues quantified in this study in sediment samples.

Pharmaceutical group	Frequency (%)	Minimum (μg·L^{-1})	Mean (μg·L^{-1})	Maximum (μg·L^{-1})	SD (%)
Anti-inflammatory drugs	100	0.062	0.512	3.193	0.519
Diclofenac	100	0.165	0.285	0.421	0.043
Ibuprofen	80.95	0.062	0.491	2.303	0.480
Ketoprofen	69.05	0.114	0.791	3.193	0.632
Naproxen	2.38	2.658	2.658	2.658	0.000
Analgesics	90.48	0.129	1.693	5.987	1.226
Acetaminophen	90.48	0.129	1.693	5.987	1.226
Cardiovascular drugs	47.62	0.014	0.324	3.270	0.692
Bisoprolol	38.10	0.014	0.152	0.608	0.157
Propranolol	4.76	0.240	1.755	3.270	1.515
Ramipril	4.76	0.166	0.266	0.365	0.100
Neurological and psychiatric drugs	4.76	0.032	0.600	0.032	0.568
Venlafaxine	4.76	0.032	0.600	0.032	0.568
Gastrointestinal drugs	42.86	0.166	2.535	0.166	1.474
Omeprazole	42.86	0.166	2.535	0.166	1.474

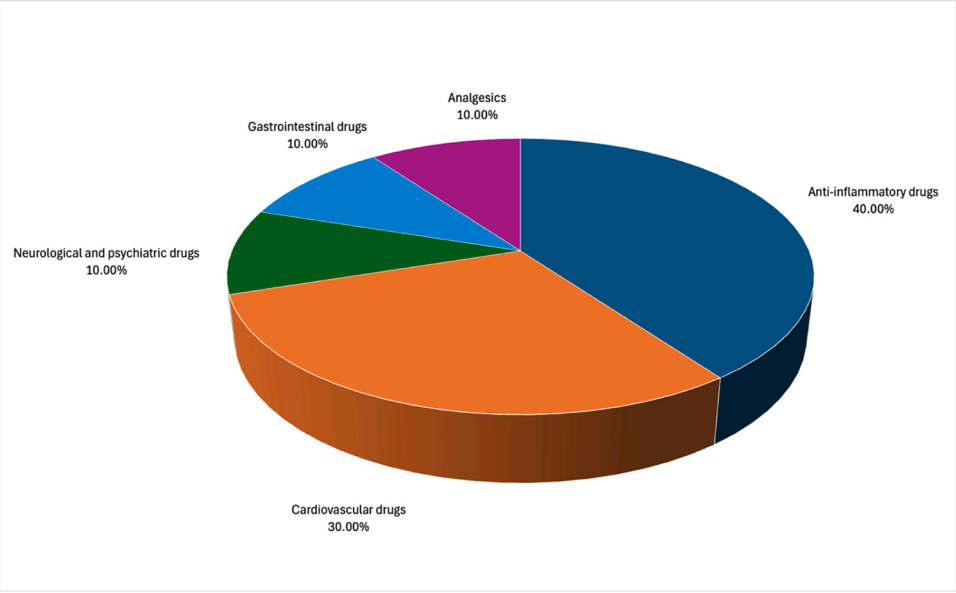

Fig. 5. Pharmaceuticals by groups quantified in sediment samples.

Similarly, as for water samples cumulative concentrations were converted into relative abundances to see the contribution to the contamination of the sediment leachate samples (Fig. 8).

The relative abundance profiles in sediments shows that in campaign A, acetaminophen, ramipril, ketoprofen and omeprazole were predominant. In campaign B, contamination was marked by a higher proportion of acetaminophen and ketoprofen. In contrast, campaign C showed almost total disappearance of ketoprofen and omeprazole in the samples, with acetaminophen and ibuprofen emerging as the main contributors to the overall pharmaceutical load. The absence of omeprazole in the September samples could be attributed to its sensitivity to light and heat [31]. An important role in the distribution process of PhCs in the environment play physical and chemical properties of these substances such as water solubility, adsorption coefficient (K_{OC}), octanol-water partitioning coefficient (*log* K_{OW}), distribution coefficient (*log* D) and Henry's law constant (Table S3). While *log* K_{OW} has traditionally been used to estimate hydrophobicity, it only reflects the neutral form of a compound. In contrast, *log* D accounts for all ionization states present at a given pH, offering a more realistic indicator of environmental behavior for ionizable compounds, including many pharmaceuticals[32]. Given the range of pH values recorded during the sampling campaigns (6.05–9.26), *log* D is especially relevant to describe partitioning processes (Table S20-S22).

The higher the K_{OC}, log K_{OW}, or *log* D coefficients, the greater the affinity of the substance for the organic matter in the sediment, leading to its accumulation and retention there. Nevertheless, this correlation does not always align with the concentrations observed in sediments for all detected compounds. Sometimes the measured concentration ratio between water and sediment is influenced also by the polar and ionic nature of the compound [33]. Additionally, this ratio is affected by local factors, including: the mineral composition and grain size of sediments, temporal variations in contamination levels, riverbed morphology, the degree of shading provided by riparian vegetation, which can affect the photodegradation rates of many PhCs [34–37].

An example of this complexity is the presence of acetaminophen in sediments, despite its relatively low K_{OC} and *log* D values (0.82–0.91), which would theoretically indicate limited sorption potential compared to other compounds such as ibuprofen, omeprazole, or diclofenac. This apparent contradiction can be explained by several factors meant before: local environmental conditions (such as pH and sediment composition), its high water solubility and continuous input into the environment (being among the most prescribed analgesics worldwide) ensure its omnipresence and facilitate its eventual deposition and accumulation in sediments. These findings highlight that simple partitioning constants alone, particularly *log* K_{OW}, are insufficient to explain sediment concentrations [38], as they are influenced by a complex interaction of

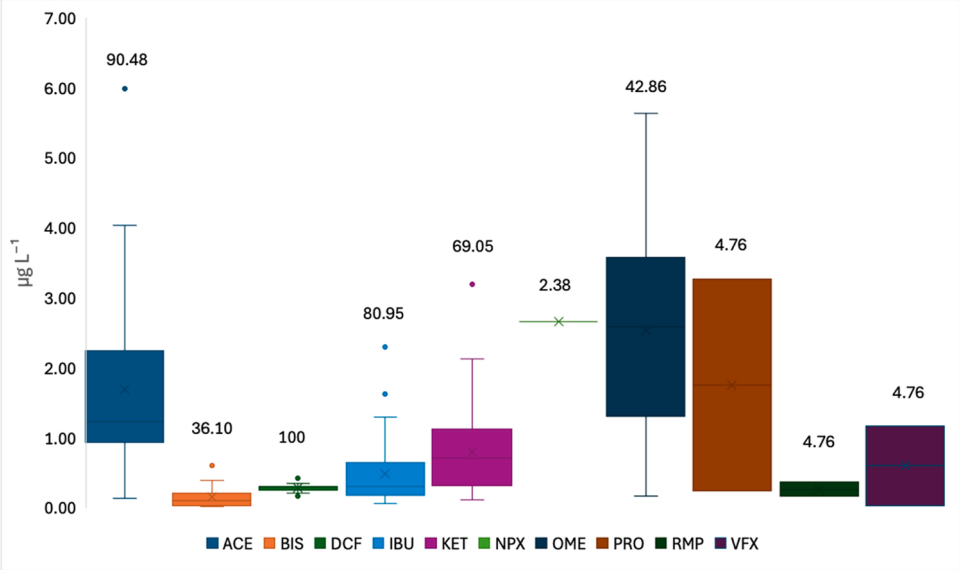

Fig. 6. Overall concentrations of PhCs detected in sediment samples in Douro River basin (numbers in the figure indicate the frequencies (%) of detection in 42 samples collected during the three sampling campaigns).

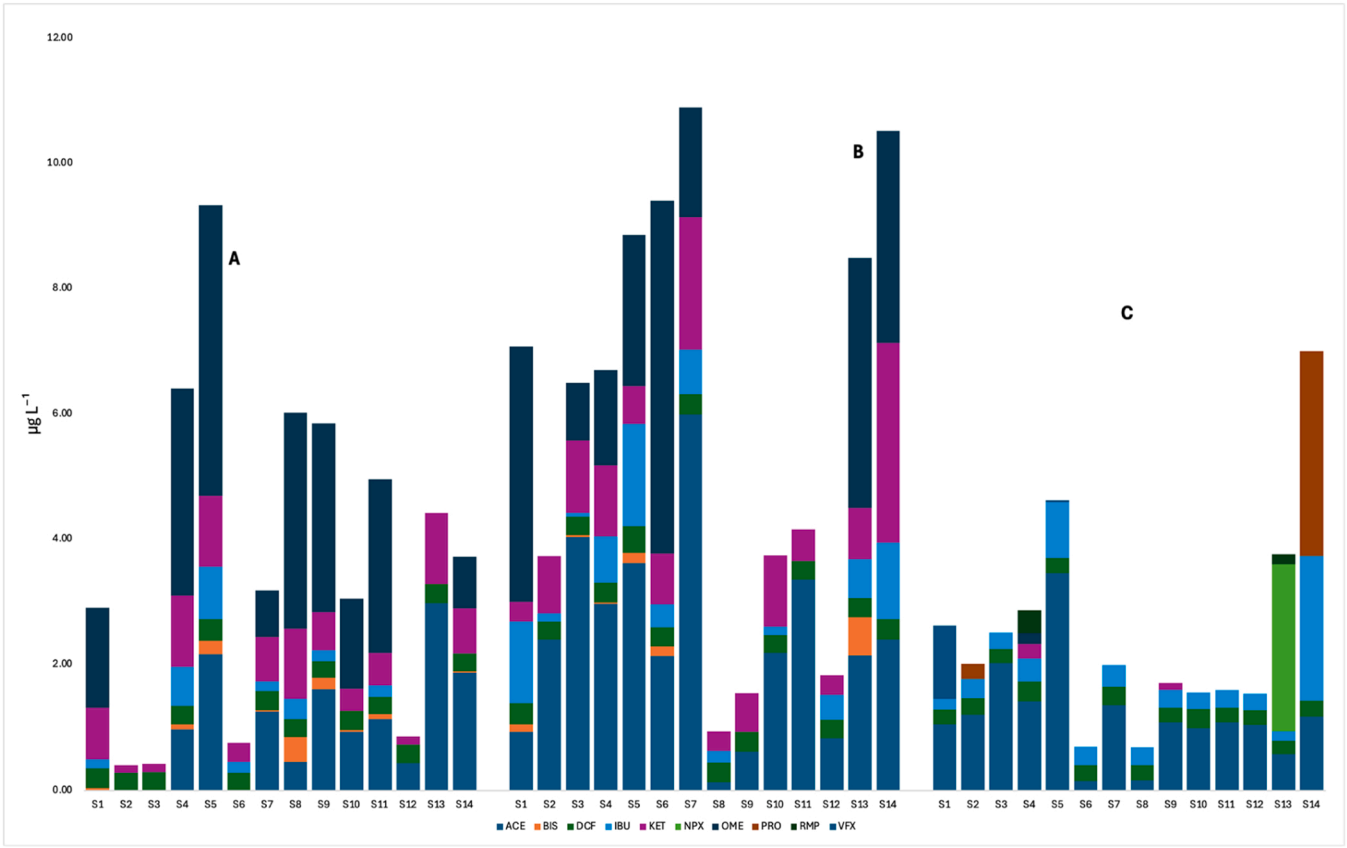

Fig. 7. Cumulative concentrations at different sampling points for the pharmaceutical residues found in sediments, across the three sampling campaigns.

chemical properties, environmental dynamics, and anthropogenic pressure.

Pharmaceutical concentrations in sediment lixiviates were expressed in $\mu g \cdot L^{-1}$, reflecting the fraction potentially mobilized into the aqueous phase under the applied extraction conditions (1:4 sediment-to-water volume ratio). Since all the substances analyzed in this study are polar, attention was paid only to sediment leaching.

Similarly, as in the case of the water samples, a correlation matrix (Table S23) was performed to evaluate whether physicochemical properties, pH, conductivity and temperature, influence the distribution of pharmaceutical residues between water and sediments, however no significant correlation was demonstrated.

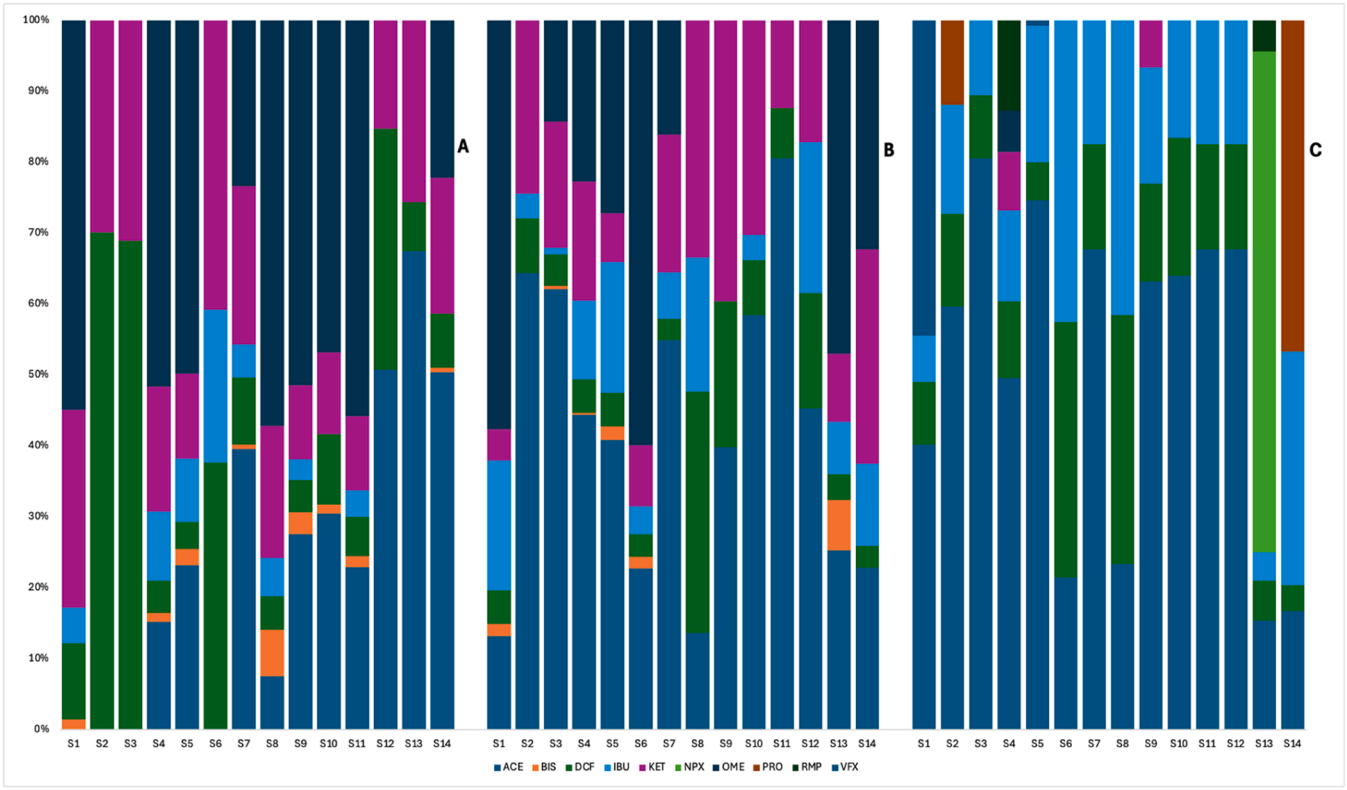

Fig. 8. Relative abundance at different sampling points for the pharmaceutical residues found in sediment samples, across the three sampling campaigns.

3.3. *Ecological risk assessment*

The following heatmaps illustrate the potential ecological risk of detected pharmaceuticals at 14 sampling sites. Each cell corresponds to a specific substance at a particular site, with darker shades indicating higher potential impact on aquatic organisms. This visual summary aids in identifying sites and substances that may require closer monitoring and management to protect water quality. Particularly concerning are the concentrations of ibuprofen, amoxicillin, and diclofenac, which pose significant risks to aquatic ecosystems and also to avians or mammals [39], [40].

The Ecological Risk Assessment was conducted in accordance with the Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use, issued by the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) [41]. The ratio of MEC to PNEC was calculated to determine the potential risk for each contaminant, expressed as Toxic Units (TUs). Sites with higher TUs indicate greater ecological risk. To provide a comprehensive overview, the TUs for all substances at each site were summed, resulting in Total Toxic Units (TTUs), which reflect the combined risk posed by the contaminants detected (Fig. 9). In water samples RQ higher than 10 was found for 5 pharmaceuticals (amoxicillin, carbamazepine, diclofenac, ibuprofen, and venlafaxine). Additionally, 15 out of 23 quantified pharmaceuticals would present RQs higher than 0.1 at least at one of the sampling points. Furthermore, Total Toxic Units exceeded an RQ greater than 1 at all sampling sites and across all three campaigns. This finding is particularly concerning at site S1, where the water serves as the primary source of drinking water for the city of Bragança. An RQ above 1 suggests a potential risk to human health, highlighting the need for further monitoring [42], [43].

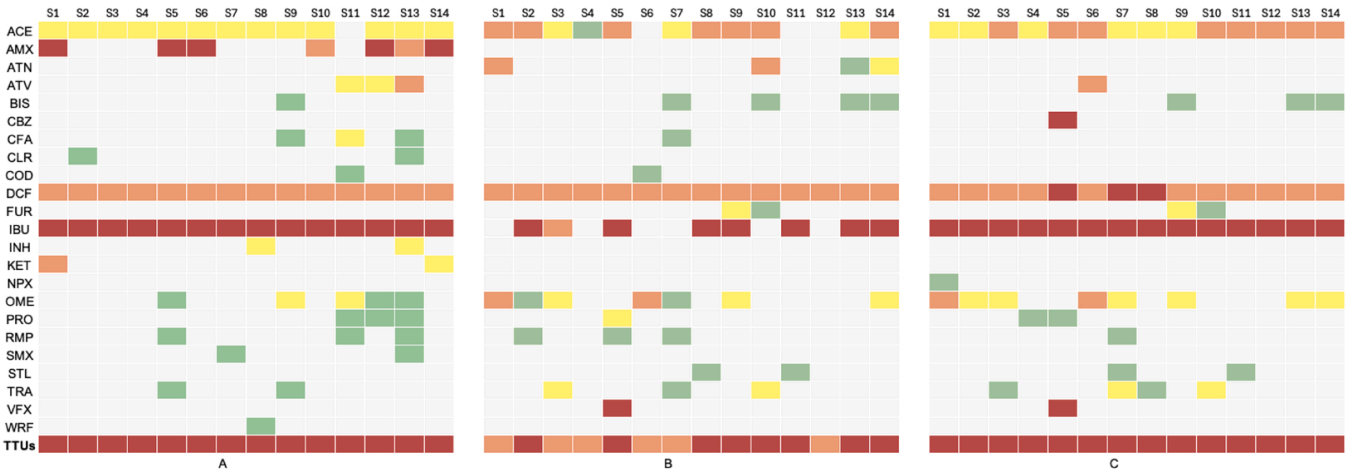

Fig. 9. Environmental risk heat maps for PhCs found in water samples: a) Campaign A, b) Campaign B, c) Campaign C.

Fig. 10 shows a RQ in sediment leachate samples. A worrying RQ higher than 10 was found in one case (at S1 in sampling campaign C for venlafaxine). Further, RQs higher than 1 were observed for five compounds: acetaminophen, ibuprofen, diclofenac, ketoprofen, and venlafaxine. Considering the use of the water from this site, this issue would need close monitoring and control by the relevant authorities.

The heat maps showed significant differences between water and sediment contamination patterns, pointing to an accumulation of PhCs in sediments. In water, contaminants exhibited more variety of quantified substances and a broader distribution with noticeable variability between sampling sites and campaigns, likely influenced by dilution, degradation, and hydrological factors. In contrast, sediments act as long-term reservoirs, displaying more stable contamination patterns over time [44]. Anti-inflammatory drugs such as ibuprofen, acetaminophen, and diclofenac were detected in both matrices, while ketoprofen was prevalent in sediments, suggesting a higher tendency for retention.

During the September campaign, a decrease in potential environmental risk was observed for several compounds (acetaminophen, ibuprofen, diclofenac, and ketoprofen), likely due to desorption processes during the warmer season [45].

3.4. Monitoring pharmaceutical residues in water treatment facilities

WWTPs represent significant sources of aquatic contamination, as many PhCs are not fully removed by conventional treatment processes and persist in the environment as organic MPs. The assessment of PhCs residues at critical points along the water treatment process provides valuable information about their persistence and the effectiveness of removal technologies [46]. In this study, concentrations were measured at both the influent and effluent of the DWTP and wastewater treatment plant, enabling the evaluation of removal efficiencies and the identification of the most persistent compounds.

In this study, at the DWTP influent, a total of 11 pharmaceutical residues were quantified (Table S24), with concentration ranges varying from 0.010 to 4.687 $\mu g \cdot L^{-1}$. The total concentration of detected PhCs ranged from 1.540 $\mu g \cdot L^{-1}$ in campaign B to 8.455 $\mu g \cdot L^{-1}$ in campaign C. The most frequently detected compounds were diclofenac and ibuprofen, both quantified in all sampling campaigns, with maximum concentration reaching 0.838 and 0.281 $\mu g \cdot L^{-1}$ respectively. The PhC with the highest individual concentration was ketoprofen in campaign C, reaching 4.687 $\mu g \cdot L^{-1}$.

After treatment, in the DWTP effluent, seven PhCs remain detectable, with concentration levels ranging between 0.010 and 1.62 $\mu g \cdot L^{-1}$, with total concentration ranged from 0.195 $\mu g \cdot L^{-1}$ to 2.416 $\mu g \cdot L^{-1}$. The removal efficiency varied depending on the compound, with an overall elimination percentage ranging from negative values to 99.89 %. The most efficiently removed substances were tramadol, amoxicillin and isoniazid (reaching 99 %), while ibuprofen and acetaminophen showed lower removal rates, and carbamazepine and venlafaxine showed zero removal rates, suggesting persistence through conventional treatment processes (Table S24). It is important to emphasize that only three sampling campaigns were conducted, therefore, these calculations are based on a highly limited dataset of three measurements. Additionally, not all pharmaceuticals were detected in all three campaigns, which should be considered when interpreting the results. Moreover, complex hydrodynamic processes, as well as adsorption onto biofilm and sediment, occur within the DWTP. Therefore, these results should be interpreted with caution.

Potabilization treatment not only makes the water safe from a disinfection point of view but also has some effect on the concentrations of PhCs. In this context, the comparison of the concentrations found in the influent of the DWTP with those measured at the nearest upstream sampling point provides valuable information on the influence of anthropogenic pressure and the fate of the pollutants. This comparison is essential to identify potential local inputs of contaminants near the intake, assess the accumulation of pollutants before treatment, and evaluate whether the influent concentrations are affected by additional point or diffuse sources.

At the sampling point closest to the DWTP influent (point S1), eight different pharmaceuticals were quantified across the three sampling campaigns, fewer than those detected at the DWTP inlet. However, concentration ranges at S1 (0.118–7.387 $\mu g \cdot L^{-1}$) were notably higher than those measured at the DWTP influent. This discrepancy may be explained by hydrodynamic processes occurring within the water transport system, including sediment resuspension, and desorption of pharmaceuticals residues from pipe walls and biofilms accumulated on them over time [47]. These processes can lead to the release of previously deposited compounds, increasing concentrations at the DWTP intake. Furthermore, the lower diversity of substances at S1 compared to the plant influent could suggest intermittent discharges or transient pollution sources upstream of the intake point.

In the influent of the WWTP, 20 pharmaceuticals were detected, with concentration ranges from 0.006 to 110.019 $\mu g \cdot L^{-1}$ (Table S25). The most abundant substances included amoxicillin, acetaminophen, omeprazole, ibuprofen and tramadol with peak concentrations reaching 110.019 $\mu g \cdot L^{-1}$ in the case of amoxicillin.

The treatment processes at the WWTP achieved removal efficiencies between negative values and 99.94 %, resulting in 18 pharmaceuticals being still detectable in the effluent. The remaining pharmaceutical concentration in the treated wastewater ranged from 0.010 to 15.438 $\mu g \cdot L^{-1}$. Compounds such as amoxicillin, bisoprolol, ramipril and tramadol exhibited high removal rates, whereas acetaminophen, diclofenac, ibuprofen, ketoprofen and pantoprazole persisted, indicating limited degradation.

In some cases, in both facilities, negative removal percentages were observed, indicating that higher concentrations of PhCs were detected at the plant outlet compared to the inlet. This phenomenon can be attributed to several factors, such as hydrodynamic processes within the treatment facilities, which cause mixing and recirculation, delaying the release of previously accumulated compounds. In addition, desorption of PhCs from suspended solids or biofilms may contribute to these increases. These results highlight the complexity of removal processes and

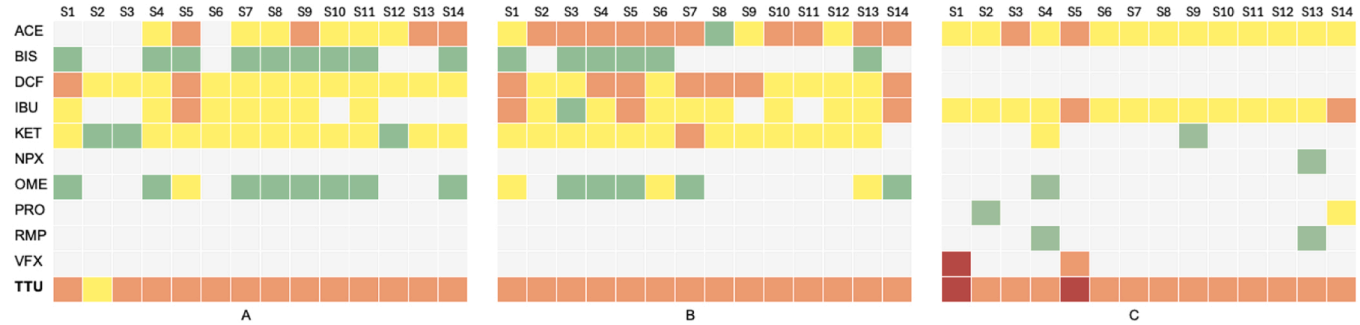

Fig. 10. Environmental risk heat maps for PhCs found in sediments samples: a) Sampling campaign A, b) Sampling campaign B, c) Sampling campaign C.

the need to interpret removal efficiencies with caution, especially for compounds with low biodegradability or high persistence.

The analysis of the WWTP effluent and the closest downstream sampling point (S5) allows for the evaluation of the impact of treated wastewater discharges on the river. At the WWTP effluent, a total of 16 different pharmaceuticals were detected, while at point S5, located downstream, 10 substances were quantified. This reduction in the number of detected compounds may be attributed to dilution processes, degradation, and possible sorption onto sediments or suspended particles [48], [25]. Overall, the concentrations found downstream of the WWTP were lower than those measured at the WWTP effluent, except during campaign A, when higher concentrations of amoxicillin and acetaminophen were detected at point S5 compared to the WWTP outlet. This is most likely attributable to rainfall events, which may have carried these pharmaceuticals, also commonly used in veterinary treatments [49], [50], from the nearby pig farm into the river at this location.

The occurrence of PhCs in drinking water has been reported worldwide, with concentrations generally varying between parts per trillion ($ng \cdot L^{-1}$) to parts per billion ($\mu g \cdot L^{-1}$) level [51], according to geographic region, water source, and treatment process. There is large amount of data available in the literature from numerous studies and reviews, reflecting increasing concern regarding the presence of these substances in water intended for human consumption (Table S26). The most frequently detected therapeutic groups are anti-inflammatory and analgesic drugs [52], consistent with their widespread consumption and persistence in the aquatic environment.

In this study, the concentrations of pharmaceuticals detected in tap water were low, far below the corresponding therapeutic daily doses (Table S7), suggesting that their presence does not pose, currently, a direct risk to human health based on current toxicological thresholds. However, it is noteworthy that the concentrations observed here are slightly higher than those reported in other European studies.

WWTPs are widely recognized as one of the most significant sources of pharmaceutical contamination in aquatic environments [53]. The concentration range of pharmaceuticals detected in WWTP effluents generally vary from a few $ng \cdot L^{-1}$ to several $\mu g \cdot L^{-1}$. In this study, the concentrations observed fall within the ranges reported in other European WWTPs (Table S27), confirming that this is not an isolated situation but rather a widespread issue.

Conventional wastewater treatment processes are inappropriate [54] to completely remove many pharmaceutical compounds. This limitation is particularly worrying for antibiotics, as their continuous release into aquatic environments contributes to the spread of antibiotic resistance genes (ARGs), posing a serious threat to ecosystems and public health. Recent studies have shown seasonal variations in the presence of sulfonamides and tetracyclines [55], along with their resistance genes, in urban reservoirs, highlighting agriculture and wastewater discharge as major pollution sources and underlining the environment's role in the proliferation and transmission of resistance. The proliferation of ARGs in the environment contributes to the development of antimicrobial resistance, which in turn places additional pressure on healthcare systems by leading to longer hospital stays, higher mortality rates, and the need for more complex and costly treatments [56].

Furthermore, it is also worrying the case of substances that, despite not being inherently persistent, are continuously introduced into the environment in low concentrations, leading to a phenomenon known as pseudo-persistence. An example is diclofenac, which in this study was detected in 100 % of the samples across both matrices analyzed.

In an attempt to mitigate / solve persistent water pollution, advanced treatment technologies are being developed and tested. For example, some studies have explored the use of heterogeneous photocatalysis for diclofenac removal [57]. This process involves the degradation of diclofenac under UV irradiation using nanostructured materials such as synthesized TiO_2 and functionalized multi-walled carbon nanotubes as catalysts. Under optimal conditions, complete removal of diclofenac was achieved, with high degradation rates. The process offers a promising solution for a compound that would otherwise be difficult to remove. Similarly, the removal of amoxicillin from contaminated water has been successfully achieved through adsorption onto modified bentonite [58], offering an efficient and targeted solution for this antibiotic.

These are just two examples of advanced technologies targeting PhCs that, in this study, were identified as particularly concerning. Nevertheless, numerous other innovative methods have been developed for a broader range of substances. However, the implementation of these advanced technologies, including ozonation, membrane filtration, advanced adsorption processes, and photocatalytic degradation methods, such as the ones described here, represents a significant financial challenge for wastewater treatment facilities.

4. Conclusions

A monitoring study of 65 target pharmaceuticals was conducted, resulting in the detection of 23 compounds in water and 10 in sediment samples. The results showed a widespread presence of pharmaceutical contaminants, with anti-inflammatory drugs being the most dominant group in both matrices. Diclofenac, ibuprofen, and acetaminophen were consistently detected, underscoring their continuous release into the environment. Additionally, the detection of higher concentrations of antibiotics in water highlights their potential environmental risks. The study also showed variability in contaminant concentrations between sites and sampling campaigns. Seasonal patterns were observed, with amoxicillin appearing predominantly in March, while acetaminophen and omeprazole were more prevalent in May. These trends may reflect variations in contaminant input, environmental conditions, or degradation rates over time. The fluctuation in the number and concentration of contaminants across sites and campaigns underscores the complexity of managing both diffuse and point sources of pollution. The predominance of cardiovascular drugs, anti-inflammatories, and antibiotics, along with their associated ecological risks, emphasizes the need for improved wastewater treatment processes and stricter environmental regulations.

The presence of pharmaceuticals in freshwater ecosystems, often as complex mixtures at low concentrations, raises concerns about their long-term environmental impact. Although many studies have focused on the occurrence of individual compounds, the combined effects of multiple pharmaceuticals, especially with continuous exposure, remain unknown. This highlights the urgent need to expand monitoring efforts, both spatially and temporally, to better understand the prevalence and behavior of these contaminants in freshwater bodies. Future research should prioritize the study of mixture toxicity and the potential effects of chronic exposure on aquatic organisms, including subtle impacts on behavior, reproduction, and the development of antimicrobial resistance. In addition, public education on the responsible use and disposal of pharmaceuticals is crucial to reducing environmental pollution. Regulatory frameworks also need to evolve, establishing consistent water quality standards for emerging contaminants and promoting the implementation of advanced treatment technologies. Lastly, large-scale, coordinated monitoring programs would be essential to inform decision-makers and guide effective environmental management strategies, ensuring the protection of aquatic ecosystems and the services they provide.

CRediT authorship contribution statement

Canle Moisés: Writing – review & editing, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Antao-Geraldes Ana María:** Writing – review & editing, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation. **Alena Voznakova:** Writing – review & editing, Writing – original draft, Visualization, Validation,

Methodology, Investigation, Formal analysis, Data curation.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Moises Canle Lopez reports financial support, article publishing charges, equipment, drugs, or supplies, and travel were provided by University of A Coruña. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

Financial support for this research was obtained through project PID2021–127898OB-I00 (WAntRed), funded by MICIU//AEI (Spain) and ERDF: A way of Making Europe. Xunta de Galicia (Spain) also provided financial support through project GRC/ED431C 2023/33. AV acknowledges grants for research stays at IPB from IACOBUS (GNP-AECT) and from the ERASMUS+ program. AMAG is grateful to the Foundation for Science and Technology (FCT, Portugal) for financial support by national funds FCT//MCTES (PIDDAC) to CIMO (UIDB/00690/2020 and UIDP/00690/2020), SusTEC (LA/P/0007/2020). Funding for open access for this article was made available by: Universidade da Coruña / CISUG. Authors are also grateful to Gracinda Rodrigues (Be Water, S.A.) and Isabel Lopes (AdNorte-Águas do Norte, S.A) for the logistical support in the water sampling at the DWTP and WWTP. The constructive input of two anonymous reviewers is also highly appreciated for their unvaluable contribution to the manuscript.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jece.2025.119181.

Data availability

Data will be made available on request.

References

[1] M.Y. Nanusha, E.E. Frøkjær, H. Rüsz Hansen, S. Bonde Rasmussen, J. Bruun Nicolaisen, M. Hansen, Explorative quantitative nontarget analysis reveals micropollutants in danish groundwater, ACS EST Water 3 (12) (Dec. 2023) 3992–4003, https://doi.org/10.1021/acsestwater.3c00403.
[2] E. Nilsen, et al., Critical review: grand challenges in assessing the adverse effects of contaminants of emerging concern on aquatic food webs, Environ. Toxicol. Chem. 38 (1) (Oct. 2018) 46–60, https://doi.org/10.1002/etc.4290.
[3] A.M. Gorito, A.R.L. Ribeiro, S. Ramos, A.M.T. Silva, C.M.R. Almeida, Occurrence of micropollutants in surface waters: monitoring of Portuguese Lima and douro river estuaries and interconnecting northwest coast, Mar. Pollut. Bull. 209 (Dec. 2024) 117140, https://doi.org/10.1016/j.marpolbul.2024.117140.
[4] P. Bhatt, G. Bhandari, M. Bilal, Occurrence, toxicity impacts and mitigation of emerging micropollutants in the aquatic environments: recent tendencies and perspectives, J. Environ. Chem. Eng. 10 (3) (Jun. 2022) 107598, https://doi.org/10.1016/J.JECE.2022.107598.
[5] R. Hernández-Tenorio, E. González-Juárez, J.L. Guzmán-Mar, L. Hinojosa-Reyes, A. Hernández-Ramírez, Review of occurrence of pharmaceuticals worldwide for estimating concentration ranges in aquatic environments at the end of the last decade, J. Hazard. Mater. Adv. 8 (Nov. 2022) 100172, https://doi.org/10.1016/j.hazadv.2022.100172.
[6] S.D. Kayode-Afolayan, E.F. Ahuekwe, O.C. Nwinyi, Impacts of pharmaceutical effluents on aquatic ecosystems, Sci. Afr. 17 (Sep. 2022) e01288, https://doi.org/10.1016/J.SCIAF.2022.E01288.
[7] E. Fonseca, F. Hernández, M. Ibáñez, A. Rico, E. Pitarch, L. Bijlsma, Occurrence and ecological risks of pharmaceuticals in a Mediterranean river in eastern Spain, Environ. Int 144 (Nov. 2020) 106004, https://doi.org/10.1016/j.envint.2020.106004.
[8] M.E. Valdés, et al., Distribution of antibiotics in water, sediments and biofilm in an urban river (Córdoba, Argentina, LA), Environ. Pollut. 269 (Jan. 2021) 116133, https://doi.org/10.1016/j.envpol.2020.116133.
[9] A. Majumder, B. Gupta, A.K. Gupta, Pharmaceutically active compounds in aqueous environment: a status, toxicity and insights of remediation, Environ. Res 176 (Sep. 2019) 108542, https://doi.org/10.1016/j.envres.2019.108542.
[10] F. Desbiolles, L. Malleret, C. Tiliacos, P. Wong-Wah-Chung, I. Laffont-Schwob, Occurrence and ecotoxicological assessment of pharmaceuticals: is there a risk for the Mediterranean aquatic environment? Sci. Total Environ. 639 (Oct. 2018) 1334–1348, https://doi.org/10.1016/j.scitotenv.2018.04.351.
[11] K. European Commission: Directorate-General for Environment and Kümmerer, "Options for a strategic approach to pharmaceuticals in the environment – Final report," 2018.
[12] L. Shearer, S. Pap, S.W. Gibb, Removal of pharmaceuticals from wastewater: a review of adsorptive approaches, modelling and mechanisms for metformin and macrolides, J. Environ. Chem. Eng. 10 (4) (Aug. 2022) 108106, https://doi.org/10.1016/j.jece.2022.108106.
[13] S.D. Kayode-Afolayan, E.F. Ahuekwe, O.C. Nwinyi, Impacts of pharmaceutical effluents on aquatic ecosystems, Sci. Afr. 17 (Sep. 2022) e01288, https://doi.org/10.1016/j.sciaf.2022.e01288.
[14] S. Vumazonke, S.M. Khamanga, N.P. Ngqwala, Detection of pharmaceutical residues in surface waters of the eastern cape province, Int J. Environ. Res Public Health 17 (11) (Jun. 2020) 4067, https://doi.org/10.3390/ijerph17114067.
[15] "Surface water." European Commission. ⟨https://environment.ec.europa.eu/topics/water/surface-water_en⟩, (accessed Mar. 4, 2025).
[16] M. Canle, A.M. Antão-Geraldes, A snapshot on the occurrence and risk assessment of organic pollutants in an urban river, Appl. Sci. 13 (1) (Dec. 2022) 146, https://doi.org/10.3390/app13010146.
[17] "Censos 2021-População Residente em Bragança." Instituto Nacional de Estatística. ⟨https://censos.ine.pt/xportal/xmain?xpgid=censos21_populacao&xpid=CENSOS21⟩, (accessed Mar. 29, 2025).
[18] "Instituto Português do Mar e da Atmosfera." ⟨https://www.ipma.pt⟩, (accessed Mar. 8, 2025).
[19] "ECETOC. Soil and Sediment Risk Assessment of Organic Chemicals Technical Report No. 92, Brussels, 2004", ⟨https://www.ecetoc.org/wp-content/uploads/2014/08/ECETOC-TR-092.pdf⟩.
[20] S.M.L. de Souza, E.C. de Vasconcelos, M. Dziedzic, C.M.R. de Oliveira, Environmental risk assessment of antibiotics: an intensive care unit analysis, Chemosphere 77 (7) (Nov. 2009) 962–967, https://doi.org/10.1016/j.chemosphere.2009.08.010.
[21] "Estatísticas regionais." Gabinete de Estratégia e Estudos. ⟨https://www.gee.gov.pt/pt/lista-publicacoes/estatisticas-regionais/distritos-concelhos/braganca/3036-distrito-de-braganca/file⟩.
[22] A.M. Geraldes, M. Boavida, Seasonal water level fluctuations: implications for reservoir limnology and management, Lakes Reservoirs Science Policy Management Sustainable Use 10 (1) (Mar. 2005) 59–69, https://doi.org/10.1111/j.1440-1770.2005.00257.x.
[23] A.A. Aryee, R. Han, L. Qu, Occurrence, detection and removal of amoxicillin in wastewater: a review, J. Clean. Prod. 368 (Sep. 2022) 133140, https://doi.org/10.1016/j.jclepro.2022.133140.
[24] A. Rosso, D. Vione, Pollutant photodegradation affected by evaporative water concentration in a climate change scenario, Molecules 29 (11) (Jun. 2024) 2655, https://doi.org/10.3390/molecules29112655.
[25] L. Carena, D. Vione, Mapping the photochemistry of european Mid-Latitudes rivers: an assessment of their ability to photodegrade contaminants, Molecules 25 (2) (Jan. 2020) 424, https://doi.org/10.3390/molecules25020424.
[26] J.C.G. Sousa, et al., Monitoring of the 17 EU watch list contaminants of emerging concern in the ave and the sousa rivers, Sci. Total Environ. 649 (Feb. 2019) 1083–1095, https://doi.org/10.1016/J.SCITOTENV.2018.08.309.
[27] A.M.P.T. Pereira, L.J.G. Silva, C.S.M. Laranjeiro, L.M. Meisel, C.M. Lino, A. Pena, Human pharmaceuticals in Portuguese rivers: the impact of water scarcity in the environmental risk, Sci. Total Environ. 609 (Dec. 2017) 1182–1191, https://doi.org/10.1016/j.scitotenv.2017.07.200.
[28] Pharmaceutical residues in freshwater, OECD, 2019, https://doi.org/10.1787/c936f42d-en.
[29] D.G.J. Larsson, C.-F. Flach, Antibiotic resistance in the environment, Nat. Rev. Microbiol 20 (5) (May 2022) 257–269, https://doi.org/10.1038/s41579-021-00649-x.
[30] M. Canle L, M.I. Fernández, C. Martínez, and J.A. Santaballa, "(Re)Greening photochemistry: Using light for degrading persistent organic pollutants," Sep. 2012. doi:10.1007/s11157-012-9275-x.
[31] C.I. Kosma, D.A. Lambropoulou, T.A. Albanis, Analysis, occurrence, fate and risks of proton pump inhibitors, their metabolites and transformation products in aquatic environment: a review, Sci. Total Environ. 569–570 (Nov. 2016) 732–750, https://doi.org/10.1016/j.scitotenv.2016.06.160.
[32] M. Kah, C.D. Brown, LogD: lipophilicity for ionisable compounds, Chemosphere 72 (10) (Aug. 2008) 1401–1408, https://doi.org/10.1016/j.chemosphere.2008.04.074.
[33] A.C. Kondor, et al., Pharmaceuticals in water and sediment of small streams under the pressure of urbanization: concentrations, interactions, and risks, Sci. Total Environ. 808 (Feb. 2022) 152160, https://doi.org/10.1016/J.SCITOTENV.2021.152160.
[34] E. Hiller, Z. Krascsenits, and M. Bartaľ, "Distribution of Four Human Pharmaceuticals, Carbamazepine, Diclofenac, Gemfibrozil, and Ibuprofen Between Sediment and Water," 2008. [Online]. Available: ⟨https://www.researchgate.net/publication/44165833⟩.
[35] D.J. Milan, Sediment routing hypothesis for pool-riffle maintenance, Earth Surf. Process Land. 38 (14) (Nov. 2013) 1623–1641, https://doi.org/10.1002/esp.3395.

[36] A. Ghermandi, V. Vandenberghe, L. Benedetti, W. Bauwens, P.A. Vanrolleghem, Model-based assessment of shading effect by riparian vegetation on river water quality, Ecol. Eng. 35 (1) (Jan. 2009) 92–104, https://doi.org/10.1016/j.ecoleng.2008.09.014.
[37] P. Fuentes-Aguilera, D. Caamaño, H. Alcayaga, A. Tranmer, The influence of Pool-Riffle morphological features on river mixing, Water 12 (4) (Apr. 2020) 1145, https://doi.org/10.3390/w12041145.
[38] J.L.M. Hermens, J.H.M. de Bruijn, D.N. Brooke, The octanol–water partition coefficient: strengths and limitations, Environ. Toxicol. Chem. 32 (4) (Apr. 2013) 732–733, https://doi.org/10.1002/etc.2141.
[39] P. Sathishkumar, R.A.A. Meena, T. Palanisami, V. Ashokkumar, T. Palvannan, F. L. Gu, Occurrence, interactive effects and ecological risk of diclofenac in environmental compartments and biota - a review, Sci. Total Environ. 698 (Jan. 2020) 134057, https://doi.org/10.1016/j.scitotenv.2019.134057.
[40] L. Gutiérrez, Y. Alcalá Canto, A.B. Alberti-Navarro, L. Carrillo González, H. Sumano López, Neglected ecological and health risks associated with the use of diclofenac in veterinary Medicine: a mini-review, Vet. México OA 10 (Aug. 2023), https://doi.org/10.22201/fmvz.24486760e.2023.1183.
[41] European Medicines Agency, Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use, Committee for Medicinal Products for Human Use (CHMP), EMEA/CHMP/SWP/4447/00 Rev. 1 - Corr., Aug. 22, 2024. [Online]. Available: ⟨https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-environmental-risk-assessment-medicinal-products-human-use-revision-1_en.pdf⟩, (accessed: Mar. 14, 2025).
[42] Y.-Y. Yang, G.S. Toor, P.C. Wilson, C.F. Williams, Micropollutants in groundwater from septic systems: transformations, transport mechanisms, and human health risk assessment, Water Res 123 (Oct. 2017) 258–267, https://doi.org/10.1016/j.watres.2017.06.054.
[43] C.M. Gopal, et al., Seasonal occurrence and risk assessment of pharmaceutical and personal care products in bengaluru rivers and lakes, India, J. Environ. Chem. Eng. 9 (4) (Aug. 2021) 105610, https://doi.org/10.1016/j.jece.2021.105610.
[44] T. Thiebault, et al., Record of pharmaceutical products in river sediments: a powerful tool to assess the environmental impact of urban management? Anthropocene 18 (Jun. 2017) 47–56, https://doi.org/10.1016/j.ancene.2017.05.006.
[45] N.C. Huynh, T.T.T. Nguyen, D.T.C. Nguyen, T.Van Tran, Occurrence, toxicity, impact and removal of selected non-steroidal anti-inflammatory drugs (NSAIDs): a review, Sci. Total Environ. 898 (Nov. 2023) 165317, https://doi.org/10.1016/j.scitotenv.2023.165317.
[46] J.P. Bavumiragira, J. Ge, H. Yin, Fate and transport of pharmaceuticals in water systems: a processes review, Sci. Total Environ. 823 (Jun. 2022) 153635, https://doi.org/10.1016/J.SCITOTENV.2022.153635.
[47] I. Pinto, M. Simões, I.B. Gomes, An overview of the impact of pharmaceuticals on aquatic microbial communities, Antibiotics 11 (12) (Nov. 2022) 1700, https://doi.org/10.3390/antibiotics11121700.
[48] G. Bernier-Turpin, R. Moilleron, C. Cenik, F. Alliot, S. Guérin-Rechdaoui, T. Thiebault, Do suspended particles matter for wastewater-based epidemiology? Water Res 280 (Jul. 2025) 123543 https://doi.org/10.1016/J.WATRES.2025.123543.
[49] D.G.S. Burch, D. Sperling, Amoxicillin—current use in swine Medicine, J. Vet. Pharm. Ther. 41 (3) (Jun. 2018) 356–368, https://doi.org/10.1111/jvp.12482.
[50] W. Kuller, S. Sietsma, S. Hendriksen, D. Sperling, Use of paracetamol in sows around farrowing: effect on health and condition of the sow, piglet mortality, piglet weight and piglet weight gain, Porc. Health Manag 7 (1) (Dec. 2021) 46, https://doi.org/10.1186/s40813-021-00224-z.
[51] Z. Mazhandu, T. Mashifana, Active pharmaceutical contaminants in drinking water: myth or fact? DARU J. Pharm. Sci. 32 (2) (Sep. 2024) 925–945, https://doi.org/10.1007/s40199-024-00536-9.
[52] S. Zanni, V. Cammalleri, L. D'Agostino, C. Protano, M. Vitali, Occurrence of pharmaceutical residues in drinking water: a systematic review, Environ. Sci. Pollut. Res. (Aug. 2024), https://doi.org/10.1007/s11356-024-34544-8.
[53] F.J. Lopez, et al., Removal efficiency for emerging contaminants in a WWTP from Madrid (Spain) after secondary and tertiary treatment and environmental impact on the manzanares river, Sci. Total Environ. 812 (Mar. 2022) 152567, https://doi.org/10.1016/j.scitotenv.2021.152567.
[54] E.R. Jones, M.F.P. Bierkens, N. Wanders, E.H. Sutanudjaja, L.P.H. van Beek, M.T. H. van Vliet, Current wastewater treatment targets are insufficient to protect surface water quality, Commun. Earth Environ. 3 (1) (Oct. 2022) 221, https://doi.org/10.1038/s43247-022-00554-y.
[55] S. Li, et al., Linking antibiotic residues and antibiotic resistance genes to water quality parameters in urban reservoirs: a seasonal perspective, Environments 12 (3) (Mar. 2025) 96, https://doi.org/10.3390/environments12030096.
[56] S.K. Ahmed, et al., Antimicrobial resistance: impacts, challenges, and future prospects, J. Med. Surg. Public Health 2 (Apr. 2024) 100081, https://doi.org/10.1016/j.glmedi.2024.100081.
[57] C. Martínez, M. Canle L, M.I. Fernández, J.A. Santaballa, J. Faria, Aqueous degradation of diclofenac by heterogeneous photocatalysis using nanostructured materials, Appl. Catal. B 107 (1–2) (Aug. 2011) 110–118, https://doi.org/10.1016/j.apcatb.2011.07.003.
[58] A.K. Mohammed, S.M. Saadoon, Z.T. Abd Ali, I.M. Rashid, N. Hussin AL Sbani, Removal of amoxicillin from contaminated water using modified bentonite as a reactive material, Heliyon 10 (3) (Feb. 2024) e24916, https://doi.org/10.1016/j.heliyon.2024.e24916.