



Occurrence of persistent and mobile chemicals and other contaminants of emerging concern in Spanish and Portuguese wastewater treatment plants, transnational river basins and coastal water

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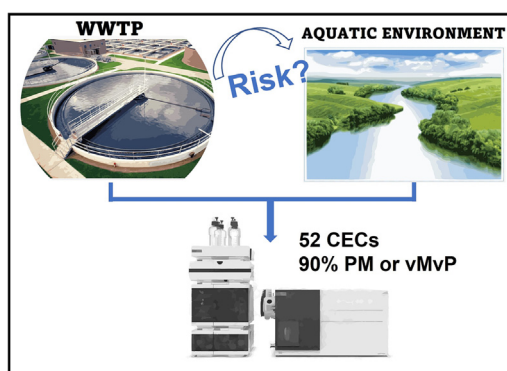
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HIGHLIGHTS

- 52 CECs and PMT/vPvM chemicals investigated into WWTPs and fresh and coastal water.
- Poor WWTPs removal of some CECs lead to high concentrations in the receiving media.
- PFOA, diclofenac, fipronil or metformin pose risk for aquatic organisms.
- Further experimental ecotoxicological data are necessary.
- Future research on PMT chemicals properties and behavior in WWTPs still required.

GRAPHICAL ABSTRACT



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ABSTRACT

This work investigated, during one year, the occurrence and fate of 52 contaminants of emerging concern (CECs) in transnational river basins and coastal areas of the North of Portugal and Galicia (NW Spain) and the wastewater treatment plants (WWTPs) discharging on these environments. The different CECs investigated included pharmaceuticals, personal care products, industrial chemicals, among others, of which ca. 90 % would fulfill the persistence, mobility and toxicity criteria proposed by the German Environmental Agency. The results showed the ubiquitous presence of these CECs and an incomplete removal of over 60 % of them with current conventional WWTPs. These findings highlight the requirement of a prominent and coordinated upgrade of WWTP treatments in order to meet the future European Union regulations on urban wastewater treatment and surface water quality. In fact, even some compounds exhibiting high removals, such as caffeine or xylene sulfonate, were frequently detected in river and estuarine waters at the high ng L⁻¹ level. Thus, our preliminary risk assessment study concluded that 18 of the CECs presented a potential

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risk for the environment, being caffeine, sulphide, perfluorooctanoic acid (PFOA), diclofenac, fipronil and perfluorobutanoic acid (PFBA) the most concerning ones. Yet, additional toxicity data as well as a more robust information on persistence and mobility of CECs are necessary for better estimating the magnitude of the problem and improve risk assessment. As an example, in the case of the antidiabetic metformin, recent research has revealed toxicity for model fish species at concentration levels below those found in 40 % of the river water samples analyzed in this work.

1. Introduction

The fate and occurrence of contaminants of emerging concern (CECs) in the water bodies, as well as the identification of hot spots and sources and associated risks for the aquatic environment are matters of current interest (Dulio et al., 2018; Pastorino and Ginebreda, 2021). Among the many families of CECs, those compounds that turn out to be persistent and mobile along the water cycle, due to their physico-chemical properties, are of particular concern. Such compounds are the so-called persistent and mobile organic contaminants (PMOCs), persistent mobile and toxic (PMT) or very persistent and very mobile (vPvM) chemicals (Hale et al., 2020a; Reemtsma et al., 2016). Their intrinsic properties would allow PMOCs to cross the natural and anthropogenic barriers of the water cycle and reach all water bodies, becoming a serious environmental problem if they also present high toxicity (Hale et al., 2022; Rüdell et al., 2020). In this sense, there is a growing interest in including these substances within the different water regulatory frameworks at an equivalent level of concern to that of well-known persistent, bioaccumulative and toxic substances (PBT), which are identified by the European Chemicals Agency (ECHA) as substances of very high concern under REACH (Hale et al., 2020b; Regulation (EC), 2006).

As a consequence of the abovementioned persistence (long environmental half-lives) of these substances, a slow degradation under secondary treatments, e.g., using active sludge in wastewater treatment plants (WWTP), would be expected, thus rendering low removal efficiencies (RE). Considering that the future European regulations on urban wastewater treatment (Proposal for a Directive of the European Parliament and of the Council concerning urban wastewater treatment (recast). COM, 2022) will focus on improving WWTP REs, monitoring certain CECs and forcing their elimination (RE > 80 %) through the use of advanced treatments, PMOCs may require a dedicated attention as regards their removal and robust analytical methodology for their determination both in wastewater and receiving aqueous environments.

The extraction and determination of such polar compounds in aqueous matrices present analytical difficulties. Thus, some authors have proposed lyophilization or azeotropic evaporative concentration for sample preparation (Neuwalde et al., 2021; Schulze et al., 2020; Zahn et al., 2020) that led to complex extracts when dealing with difficult matrices, such as wastewater. Also, the use of ionic exchangers has demonstrated good efficiency in most aqueous matrices, but failed when dealing with sea water (Montes et al., 2019). On the other hand, given that reversed phase chromatography does not provide adequate retention for PMOCs (Zahn et al., 2020), mixed-mode chromatography, HILIC and supercritical fluid chromatography have emerged as alternatives (Schulze et al., 2020; Montes et al., 2019; Schulze et al., 2019; Zahn et al., 2019). However, there is still a lack of analytical methods providing adequate recoveries for some particular PMOCs and more efforts are necessary to obtain robust values of measured environmental concentrations (MECs).

The MECs, together with predicted no-effect concentrations (PNECs) are commonly used in risk evaluation (Technical Guidance Document on risk assessment in support of Commission Directive 93/67/EEC on risk assessment for new notified substances, Commission Regulation (EC) No 1488/94 on risk assessment for existing substances, Directive 98/8/EC of the European Parliament and of the Council concerning the placing of biocidal products on the market. Part II, n.d.). The calculation of the risk quotients (RQ), as the ratio MEC/PNEC, is useful to better understand the

potential effects of PMOCs and CECs in the aquatic ecosystem (Lopez et al., 2022; Tsui et al., 2014; Mastroianni et al., 2016). Unfortunately, the lack of experimental data on the MECs of PMOCs and the use of predicted data in toxicity evaluation (PNEC) has led in some cases to values several orders of magnitude above actual toxic concentrations.

Thus, the aims of this work are i) the development of a robust analytical methodology for the determination of a group of 52 PMOCs and other CECs, prioritized on the basis of a former screening campaign (Montes et al., 2022), in 4 different aqueous matrices (freshwater, coastal water, and treated and raw wastewater), ii) the application of this methodology for a yearly monitoring of those CECs in different national and transnational (Spanish and Portuguese) river basins, coastal environment and WWTPs to evaluate the concentration levels (i.e. MECs), detection frequency (DF) and also RE, and iii) the assessment of the risk that these substances may pose for the investigated environments.

2. Material and methods

2.1. Chemicals and reagents

LC-MS grade acetonitrile (ACN) and methanol (MeOH) were purchased from Fisher Scientific (Waltham, MA, US). Acetic acid ($\geq 99\%$) and ammonium hydroxide solution (25 %) were purchased from Sigma-Aldrich (Steinheim, Germany). Ultrapure water was obtained from a Genie G system from Rephile Bioscience (Boston, MA, US). Detailed information regarding the analytical standards of the 52 compounds investigated is given in Table S1, including information regarding the uses, CAS number, PMT classification (Montes et al., 2022) and PNEC values (NORMAN Ecotoxicology Database — Lowest PNECs, n.d.) of these analytes. Mass labelled analogues of 20 compounds were acquired and used as surrogate internal standard (IS) of those compounds (Table S2). For the remaining 32 analytes (when the own analog was unavailable in the lab) the IS which provided the best accuracy was selected.

2.2. Sampling

Thirty-three sites, located in Galicia (NW Spain) and NW Portugal were sampled in three different campaigns (SC1-SC3) along the year 2021. Thus, ninety-three samples including river water (L1-L3, L5, A1, A2, C1, M1-M7, V5), coastal water (L4, V1-V4, V6) and raw (RWW1-RWW6) and treated wastewater (TWW1-TWW6) were processed. For river and coastal water grab sampling was performed whereas for wastewater 24 h composite samples were collected using a portable automatic sampler. The samples from the WWTP codified as RWW4 and TWW4 could not be collected in SC1. Sampling information is given in the supplementary material (Table S3).

2.3. Sample preparation

The samples were filtered through 0.45 μm PVDF filters (Merck Millipore, Darmstadt, Germany) and submitted to the following SPE protocol. One hundred milliliters of each sample were passed through an OASIS HLB 200 mg (Waters, Milford, MA, USA) cartridge previously conditioned with 5 mL of MeOH and 5 mL of ultrapure water. Then, the cartridge was dried and eluted with 6 mL of MeOH. The extract was finally evaporated to dryness under a nitrogen stream and reconstituted with 200 μL of ultrapure water:ACN (1:1), filtered through a 0.22 μm PTFE filter (Phenomenex, Torrance, CA, US) and injected in the chromatographic system.

2.4. Instrumentation and determination conditions

The liquid chromatography-tandem mass spectrometry (LC-MS/MS) system comprised a 1290LC chromatograph coupled to a 6495 triple quadrupole mass spectrometer (QQQ) (Agilent technologies, Santa Clara, CA, USA) with an electrospray (ESI) JetStream source operating in positive and negative polarities. Nitrogen was used as nebulization and collision induced dissociation gas. Ionization was performed either in positive or negative modes using the following parameters: 3.5 and 3.0 kV (capillary voltage in ESI positive and negative modes, respectively), 200 °C (gas temperature), 400 °C (sheath gas temperature), 11 L min⁻¹ (gas flow) and 12 L min⁻¹ (sheath gas flow). Collision energy (CE) values were adjusted individually for each compound. MS analyses were carried out in Multiple Reaction Monitoring (MRM) mode recording two precursor/product ion transitions per compound. For 2 compounds, PFBA and PFPeA, only one transition was recorded due to the specific fragmentation pattern of these analytes. Selected ions, together with their corresponding CE values are listed in Table S4.

The mixed-mode liquid chromatography column used was an Acclaim Trinity P1 (2.6 µm particle size; 3 mm internal diameter and 50 mm length), supplied by Thermo (Waltham, MA, USA). The final LC method was adapted from Montes et al. (Montes et al., 2019) and consisted of a simultaneous binary gradient from low organic content (2 % ACN) and buffer (5 mM ammonium acetate, pH 5.5) to high organic (80 % ACN) and buffer (20 mM ammonium acetate, pH 5.5) in 10 min, an isocratic step of 5 min (80 % ACN, 20 mM ammonium acetate, pH 5.5) and 5 min of conditioning at initial composition (total run time was 20 min). The flow rate was 0.2 mL min⁻¹. The injection volume was 10 µL.

2.5. Method performance evaluation

The analytical parameters evaluated were linearity, instrumental limits of quantification (iLOQs), accuracy, method limits of quantification (mLOQ) and (intra- and inter-day) precision. The linearity was evaluated in the concentration range between the iLOQ and 100 ng mL⁻¹ for each analyte through the injection in triplicate of standards at different concentrations. The iLOQs were determined through the injection of the same standards and established as the minimum concentration that provided a signal to noise ratio (S/N) of 10. The mLOQs were calculated by spiking real river and coastal water and treated and raw wastewater samples at 250 ng L⁻¹ (case of river and transitional water) and 2500 ng L⁻¹ (case of wastewater) levels, submitting them to the entire protocol, checking the S/N ratio and extrapolating these concentrations to a S/N ratio of 10. For those 21 compounds present in the procedural blanks, (see Table S5), the mLOQs were estimated by multiplying by 10 the standard deviation of the concentration found in the procedural blank ($n = 3$), in each sampling campaign. Instrumental precision was measured by the relative standard deviation (RSD) of 5 consecutive injections of standards (repeatability) or 15 injections in 3 different days (intermediate precision) at 1 and 10 ng mL⁻¹ levels. Full methodology precision was evaluated through four replicates of a spiked sample (250 ng L⁻¹ and 2500 ng L⁻¹ level, depending on the matrix) of river, sea, treated and raw wastewater submitted to the entire protocol (mRSD). Accuracy, defined as the overall recovery (R, %), i.e. composed as extraction efficiency and matrix effect (ME), was calculated at those same levels dividing the found concentration (obtained using internal standard calibration) by the spiked concentration.

2.6. Risk assessment

RQs were calculated by dividing the MEC at each sampling location by the PNEC. Values of RQ between 0.1 and 1 were considered as a potential risk for aquatic species, between 1 and 10 as moderate risk and values of RQ > 10 as high risk (Lopez et al., 2022; Mastroianni et al., 2016; Figüère et al., 2022). The PNEC for each compound has been extracted

from the Lowest PNEC search tool from the NORMAN Ecotoxicology Database (data in Table S1) (NORMAN Ecotoxicology Database — Lowest PNECs, n.d.). In this database, some of the PNECs are derived from freshwater experimental eco-toxicity data or, in case of no or insufficient empirical endpoints, from QSAR predictions. Also, for marine water, if no experimental value is available, the lowest freshwater PNEC divided by 10 is used.

3. Results and discussion

3.1. Compound selection and analytical methodology

The 52 compounds studied in this work comprise a variety of organic contaminants of 6 main classes including 22 pharmaceutical and personal care products (PPCPs) and their metabolites, 8 pesticides, 2 food additives, 18 industrial chemicals and 2 cleaning agents (Table S1). The classification is based on the compounds' main use, although some have multiple uses. For instance, methyl 4-hydroxybenzoate (methyl paraben) is used as preservative in pharmaceuticals, personal care products, and food. The selection of these CECs was based on their DF, which was higher than 25 % in the same sampling points of a previous screening work (Montes et al., 2022). According to the prioritization criteria based on the proposal of the German Environment Agency (REACH: Improvement of guidance and methods for the identification and assessment of PMT/vPvM substances, 2019), 90 % of these compounds would be classified as PMT, vMvP, persistent, mobile and potentially toxic (PM-PotT) or potential PMT (the latter two categories mainly contain compounds with inconclusive classifications), see Table S1.

In recent years, different analytical methods have been developed to extract PMOCs from water (Schulze et al., 2020; Montes et al., 2019; Zahn et al., 2019). However, no method is capable of efficiently extracting a wide range of very polar chemicals with different characteristics (Zahn et al., 2020). Although other alternatives have been proposed, in this work, SPE was selected for practical reasons, and because other CECs (not just PMOCs) were also targeted. Besides Oasis HLB, mixed-mode SPE cartridges (Oasis WAX and WCX) (Montes et al., 2019) were tested but failed to provide good performance when applied to water samples with a high ionic strength (i.e. coastal water). Thus, the Oasis HLB cartridges were chosen, as even when providing low absolute recoveries for some of the target chemicals (e.g. CAP or acesulfame), this could be compensated by their isotopically labelled IS. As regards chromatographic separation, the trimodal mixed-mode LC (Montes et al., 2019; Schulze et al., 2019) method provided acceptable performance for the 52 CECs.

The figures of merit for instrumental and entire protocol validation are given in Table S5. Regarding instrumental parameters, the determination coefficients (R^2) were higher than 0.991 for all compounds in the iLOQ-100 ng mL⁻¹ range. The inter-day and intra-day iRSD were lower than 16 % for all analytes at the two concentration levels (1 and 10 ng mL⁻¹). The iLOQs ranged between 0.01 and 0.5 ng mL⁻¹ except for propanil and DTG, due to different reasons. Propanil presented a poor ionization behavior whereas DTG was present in instrumental blanks at ca. 0.8 ng mL⁻¹.

Regarding the entire protocol, the accuracy (R, %), repeatability (RSD, %), and sensitivity (LOQ, ng L⁻¹) of the method were evaluated for the 4 studied matrices, sea/coastal and river water, treated and raw wastewater. Average accuracies were 91, 88, 96 and 94 %, respectively. In the case of xylenesulfonate, the accuracy of the method could not be evaluated due to native levels higher than 2500 ng L⁻¹ in the samples used for method validation. Therefore, an addition level of 10 µg L⁻¹ was used. In all cases RSD was lower than 20 %. These values are in agreement with the method performance acceptability criteria of the SANTE/11312/2021 guidelines, usually referred to pesticide residue analysis, but commonly used in the environmental field too. The mLOQ ranged between 0.02 and 90 ng L⁻¹ depending on the matrix and the compound, with the average mLOQ being 4 ng L⁻¹ (Table S5). The highest mLOQs corresponded to compounds that were present at relatively high levels in procedural blanks, such as TCP and CAP. Considering the blank contamination and to avoid false positives, three replicates of procedural blank were performed in each sampling campaign, and the mLOQs were reevaluated for the

compounds detected within each sample batch. Thus, special contamination issues were detected in SC1 for DPG, in SC2 for CAP, PFMS and TCP and in SC3 for PFMS.

3.2. Occurrence of the investigated CECs

All the investigated CECs were found in at least one sample, except DTG, atraton and dinoseb (Table S6). Further discussion is presented below according to their main use category.

3.2.1. PPCPs and their metabolites

Fig. 1 shows the DF and average concentration (in log-scale) per matrix of the studied PPCPs. The average DF for PPCPs is higher than 90 % in both treated and raw WW and 56 % in river water. Regarding sea water, although 7 PPCPs were not detected, a high average DF (50 %) was observed for those detected compounds (Table S6).

Mexiletine is the pharmaceutical presenting the lowest average concentration and DF in all the matrices, whereas metformin and acetaminophen are at the highest levels. Although the concentration in raw wastewater is high for both compounds ($>10 \mu\text{g L}^{-1}$) acetaminophen levels in treated wastewater are considerably lower ($<100 \text{ ng L}^{-1}$) than metformin levels ($>3 \mu\text{g L}^{-1}$). This leads to high discharges of metformin in the receiving media (average concentrations in river water $>500 \text{ ng L}^{-1}$), reinforcing the increasing concern on this compound (Barros et al., 2022; Barros et al., 2023). Both compounds have been reported at similar concentration levels in other Spanish river basins (Lopez et al., 2022; Ambrosio-Albuquerque et al., 2021; López-Serna et al., 2012; Kuzmanović et al., 2015), although data for metformin are currently scarce (Ambrosio-Albuquerque et al., 2021). Among the remaining monitored pharmaceuticals, the macrolide-type antibiotics azithromycin and clarithromycin and the anti-inflammatory diclofenac, that were included in the 1st watch list (1st WL) (Commission Implementing Decision (EU) 2015/495 of 20

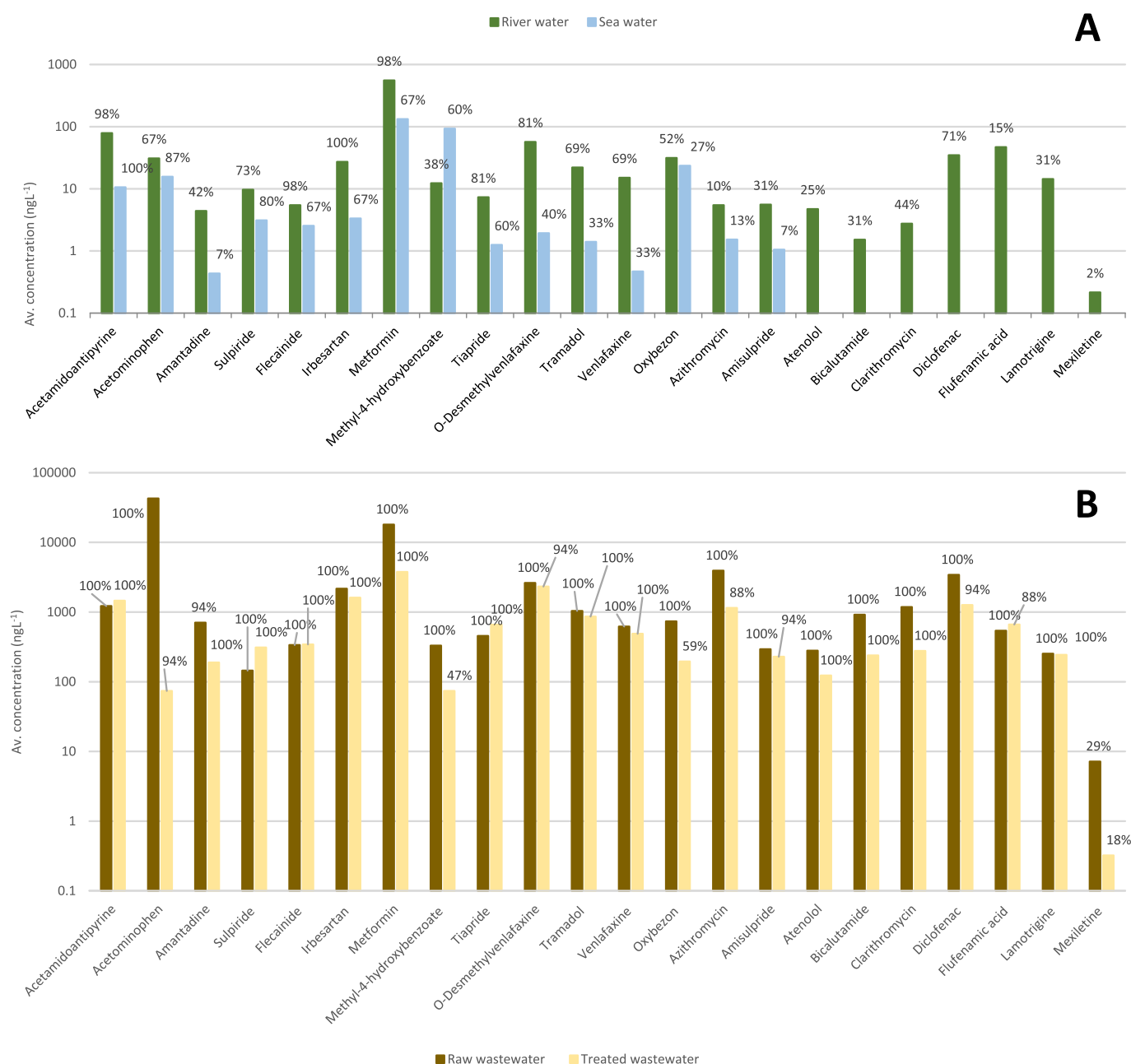


Fig. 1. Average concentration (ng L^{-1} , N.B. log scale) and DF (as labels on top of bars) of PPCPs in the analyzed samples of river ($n = 48$) and coastal (sea) water ($n = 15$) (A) and treated ($n = 17$) and raw wastewater ($n = 17$) (B). N.B. average concentrations were calculated from those samples above mLOQ.

March 2015 establishing a watch list of substances for Union-wide monitoring in the field of water policy pursuant to Directive 2008/105/EC of the European Parliament and of the Council (notified under document C (2015) 1756), 2015) and are considered as priority substances in the new proposal amending WFD (Proposal for a Directive amending the Water Framework Directive, the Groundwater Directive and the Environmental Quality Standards Directive, 2022) and the antidepressants venlafaxine and *o*-desmethylvenlafaxine, included in the 3rd and 4th watch list (3rd WL, 4th WL) (Commission Implementing Decision (EU) 2020/1161 of 4 August 2020 establishing a watch list of substances for Union-wide monitoring in the field of water policy pursuant to Directive 2008/105/EC of the European Parliament and of the Council (notified under document number C(2020) 5205) (Text with EEA relevance), 2020; Commission implementing decision (EU) 2022/1307 of 22 July 2022 establishing a watch list of substances for Union-wide monitoring in the field of water policy pursuant to Directive 2008/105/EC of the European Parliament and of the Council, 2022), presented an extremely high DF in treated wastewater (>88 %). These five pharmaceuticals are persistent and mobile (and toxic/potentially toxic) substances. Although the DF decreased considerably in river water for the antibiotics (<44 %), remained high for the other three compounds (>69 %). Venlafaxine and *o*-desmethylvenlafaxine were even detected in around 30 % of sea water samples. These findings agree with previous works reporting a venlafaxine DF of around 60 % in coastal water samples of the same region (Fernández-Rubio et al., 2019). These high DFs in surface water point out the ubiquity and dispersion of these compounds in the aquatic environment and likely a high environmental persistence.

3.2.2. Food additives

The two substances studied from this class, caffeine and acesulfame, presented extremely high concentrations in wastewater (up to $30 \mu\text{g L}^{-1}$ in raw wastewater and ca. $1 \mu\text{g L}^{-1}$ in treated wastewater) and DF of 100 % (Fig. 2). Although the concentrations in river and sea water were 1–2 orders of magnitude lower than those observed in treated wastewater, the DF for both compounds remained at 100 % in both environments, except for caffeine in sea water (still detectable in 73 % of the samples). Acesulfame is considered as PMT and caffeine as potential PMT (due to inconsistent persistence data) (Montes et al., 2022; REACH: Improvement of guidance and methods for the identification and assessment of PMT/vMvP substances, 2019). However, considering the decrease in concentration levels along the water cycle and the expected dilution (especially in marine environment), the high DF could be attributed both to the originally high concentration in wastewater effluents and their high persistence and mobility. The ubiquity of both compounds in surface water has been already reported before (Kuzmanović et al., 2015; Celma et al., 2022).

3.2.3. Pesticides

The 6 (out of 8) pesticides detected in wastewater (raw and treated) were also detected in river water whereas only DEET and diuron were found in coastal water (Fig. 2). All these pesticides are PMT or vMvP chemicals (Montes et al., 2022). The average DF was higher than 80 % in wastewater (both raw and treated) and average concentration levels were $0.16 \mu\text{g L}^{-1}$ and $0.3 \mu\text{g L}^{-1}$ in treated and raw wastewater, respectively. Regarding their distribution in river and coastal water, diuron was found both in coastal water (DF 20 %, average concentration 2.2 ng L^{-1}) and river

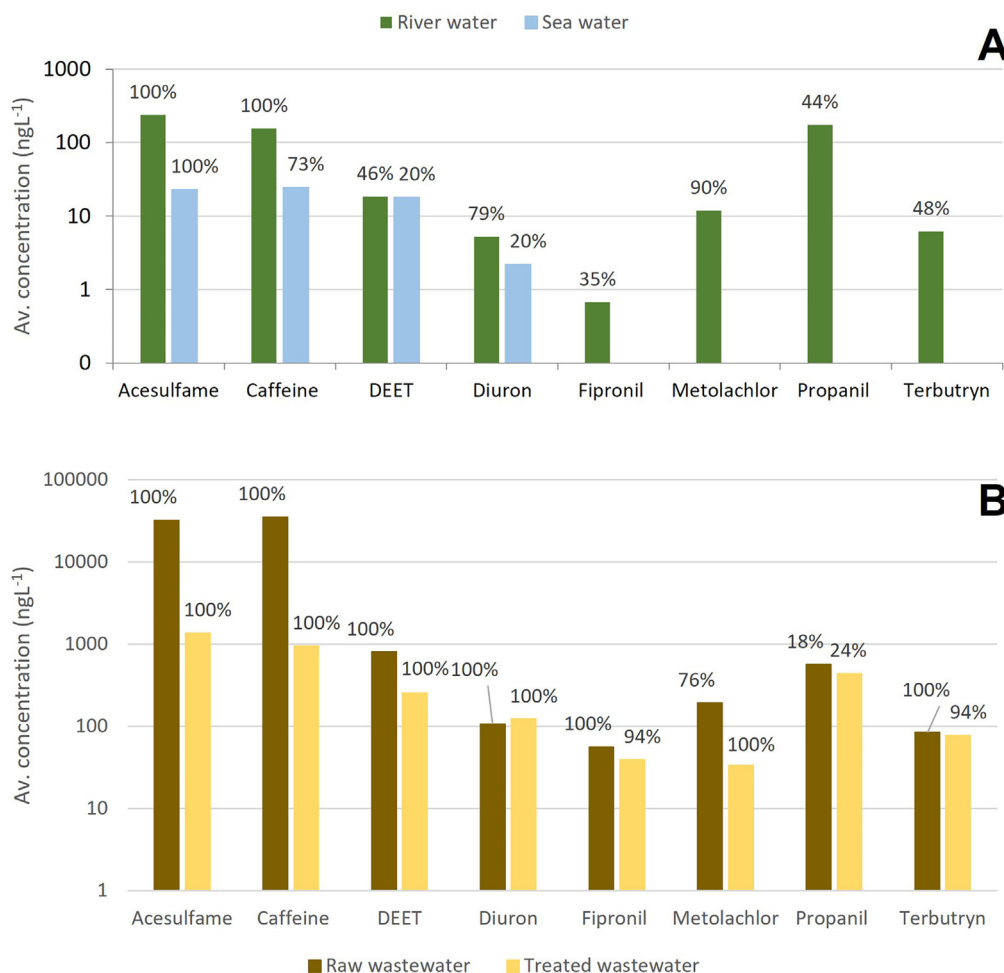


Fig. 2. Average concentration (ng L^{-1} , N.B. log scale) and DF (as labels on top of bars) of food additives and pesticides in the analyzed samples of river ($n = 48$) and coastal (sea) water ($n = 15$) (A) and treated ($n = 17$) and raw wastewater ($n = 17$) (B). N.B. average concentrations were calculated from those samples above mLOQ.

water (DF 79 %, average concentration 5.2 ng L^{-1}) and terbutryn was found only in river water (DF 48 %, average concentration 6.2 ng L^{-1}). Both pesticides are in the list of priority substances (Annex X) in the field of water policy to be monitored in the WFD 2000/60/EC (DIRECTIVE 2000/60/EC of the European Parliament and of the Council of 23 October 2000 establishing a framework for Community action in the field of water policy, 2000) and also in the new proposal for its amendment (Proposal for a Directive amending the Water Framework Directive, the Groundwater Directive and the Environmental Quality Standards Directive, 2022). The levels found are, however, lower than the environmental quality standards (EQS) proposed in such Directive (Proposal for a Directive amending the Water Framework Directive, the Groundwater Directive and the Environmental Quality Standards Directive, 2022; DIRECTIVE 2000/60/EC of the European Parliament and of the Council of 23 October 2000 establishing a framework for Community action in the field of water policy, 2000). Propanil presented the highest concentrations in all the studied matrices, however, its DF was low, especially in wastewater (lower than 25 %), which could point to specific sources/areas of contamination, other than WWTPs. It should be noted that the mLOQs for this compound are the highest within this class. Metolachlor was only found in river water, with high DF (90 %), and DEET in both river (DF 46 %) and coastal (DF 20 %) water at similar concentration levels (18 ng L^{-1}).

3.2.4. Industrial chemicals and cleaning agents

Among the 20 studied compounds from both classes, xylenesulfonate, CAP, TBEP and TCPP presented the highest concentration levels in wastewater. High concentrations and DF are still observed in effluents for these last three. In the case of the cleaning agent xylenesulfonate, also presented the highest concentrations in most of the surface water sampling points. The average concentration of this pollutant decreased significantly, ca. 1 order of magnitude in surface water and ca. 2 orders of magnitude in coastal water (Fig. 3), when compared with treated wastewater. On the other hand, the cleaning agent naphthalene sulfonic acid presented higher DF in river water (15 %) than in treated wastewater (6 %) and even higher concentrations (averages from the samples where it was detected) in river water (766 ng L^{-1}) than in treated wastewater (77 ng L^{-1}), pointing to alternative discharge media other than WWTPs. The casuistry of CAP is noteworthy, originally classified as not PMT due to its low persistence but presenting high mobility and toxicity (Table S1, (Montes et al., 2022; REACH: Improvement of guidance and methods for the identification and assessment of PMT/vPvM substances, 2019)). The DF for CAP markedly fell from treated wastewater to river and coastal water (41 %, 10 % and 7 %, respectively). However, when detected, the average concentration levels are at the same order of magnitude in all the studied matrices ($0.59\text{--}1.9 \mu\text{g L}^{-1}$), revealing specific sampling points in river and marine environment contaminated with CAP

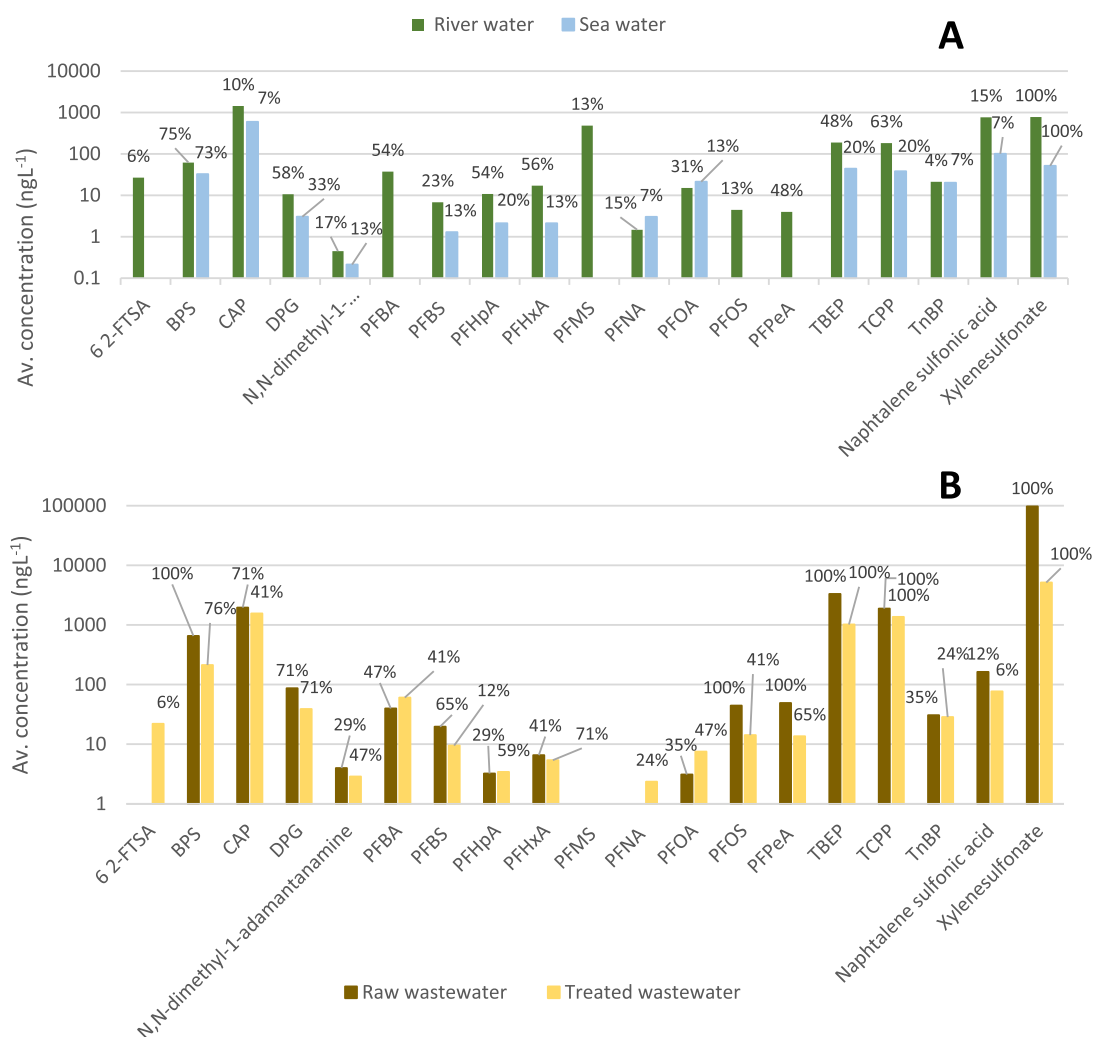


Fig. 3. Average concentration (ng L^{-1} , N.B. log scale) and DF (as labels on top of bars) of industrial chemicals and cleaning agents in the analyzed samples of river ($n = 48$) and coastal (sea) water ($n = 15$) (A) and treated ($n = 17$) and raw wastewater ($n = 17$) (B). N.B. average concentrations were calculated from those samples above mLOQ.

at the same level that treated wastewater (Fig. 3, Table S6). Previous studies reported similar DF and concentration levels for CAP and xylenesulfonate in this region (Montes et al., 2019; Schulze et al., 2019).

3.3. Spatial patterns in surface water

Fig. 4 shows the overall loads of contamination (as the concentration sum of CECs according to their main use category, average of the 3 sampling campaigns) in the river basins and coastal water samples. As it can be appreciated, the most polluted sampling points in each river basin were M1, L1, A1 and C1, corresponding M1 to a point in the urban river's course (city of ca. 105,000 inhabitants) and L1, A1 and C1 to sampling points located after WWTP discharges. In most cases, cleaning agents and PPCPs represented the most abundant pollutants followed by industrial chemicals and food additives. Sampling point V5, corresponds to a river point highly impacted by industry, thus, in this specific point cleaning agents and industrial chemicals were the major contributors. Points V1-V4 and V6 correspond to marine/estuarine environment, and presented the lowest contamination levels, as expectable due to the high dilution effect. In all cases regarding coastal water, except point V1, PPCPs were the most abundant pollutants. It should be mentioned that the pesticide propanil was found only in the sampling points located in the Portuguese area of river basins (Table S6) pointing to specific application routines in that area.

3.4. Seasonal patterns in surface water

Considering that in the studied region, the summer season (SC2) corresponds to dry weather and rainy events occur frequently in spring (SC1) and autumn (SC3) a higher dilution in the rivers' flow would be expectable in the last two sampling campaigns and subsequently lower DF and concentration levels. Fig. 5 shows the sum of average concentration per CEC class in river and coastal water samples during these three seasons. For PPCPs and food additives a higher concentration is actually observed during dry weather (SC2) in river water (Fig. 5a). On the contrary, pesticides and industrial chemicals presented higher concentrations in SC1, which decreased in summer and autumn in both types of surface water. It should be noted that the higher concentrations observed in SC3 for cleaning agents are attributed to a point source

contamination of xylenesulfonate in basin A (samples A1 and A2, Table S6). If those samples were not considered the cleaning agents' concentration would be similar to that found in SC1 and SC2. Regarding coastal water, no systematic seasonal variation was observed (Fig. 5b). The concentrations of PPCPs were apparently lower in SC2 (summer), in contrast to the results obtained in river water, which is striking since dragging through rivers should comprise a major route for these pollutants to reach sea water, thus a similar behavior in both environments was expected. The extremely high concentrations of industrial chemicals in SC1 are attributable to a specific contamination with CAP and BPS in sampling point V1 in SC1 (Table S6). If that samples were not considered, the concentration values of this pollutants class are similar along the three sampling campaigns.

3.5. Removal efficiency at WWTPs

Removal efficiency (RE) was evaluated in the 6 WWTPs included in the study (Table S7). All of them operate primary and secondary treatments with activated sludge, and additionally WWTP3 operates a final chlorination step. The medians of the REs were calculated for each compound including data from the 3 sampling campaigns (Table S7). As no differences were evident in RE for WWTP3 (tertiary chlorination treatment) data from this WWTP were also included in the median's calculations. Medians were employed because of the high variability in calculated REs for several compounds, not following a normal distribution.

Fig. 6 represents RE, persistence and mobility (as log D) classification of the compounds that were found in >33 % of the wastewater samples. When negative values of RE were obtained (i.e. higher concentrations were found in treated wastewater than in raw wastewater), the RE was set as 0 % for visualization (Fig. 6), which means inefficient removal. This could be attributed to different causes, for example, if the compounds reached the WWTP as conjugated metabolites and suffer a deconjugation process (Gewurtz et al., 2022), if the residence time in the WWTP does not match the 24-sampling delay, or if the chemical is leached out from some WWTP components (e.g. CAP or PFAS from pipes). It should be noted that sampling conditions should be studied and considered in each WWTP accounting for specific residence times and treatment processes duration in order to obtain more robust RE values and the results derived from our study should be considered as exploratory.

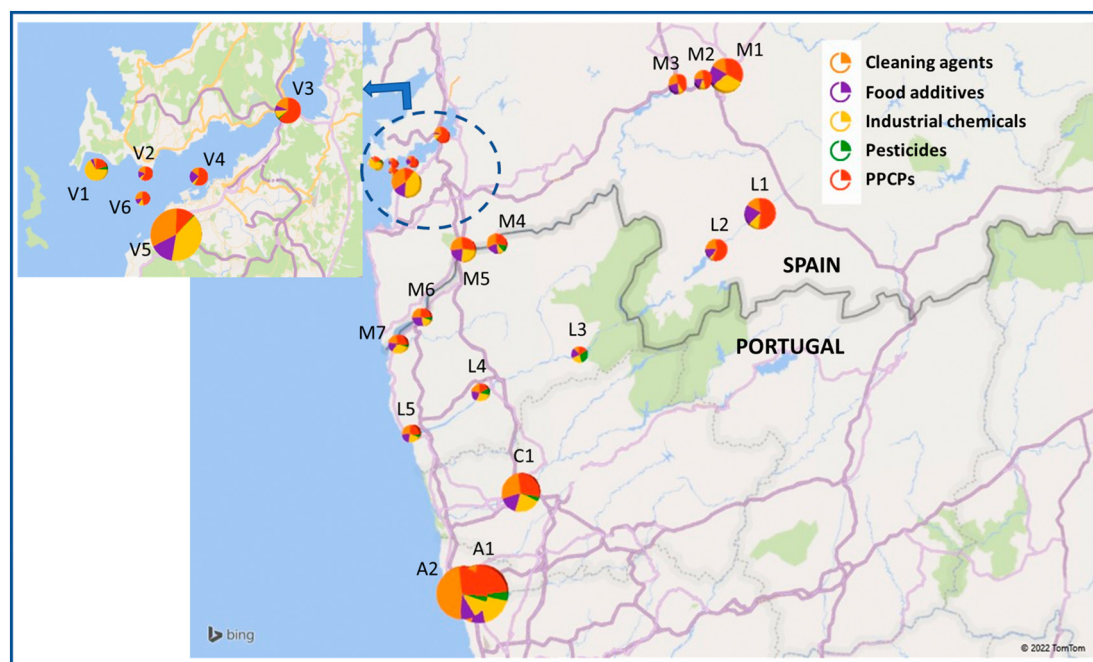


Fig. 4. Overall loads of CECs (average of the 3 sampling campaigns) in the river basins and coastal waters.

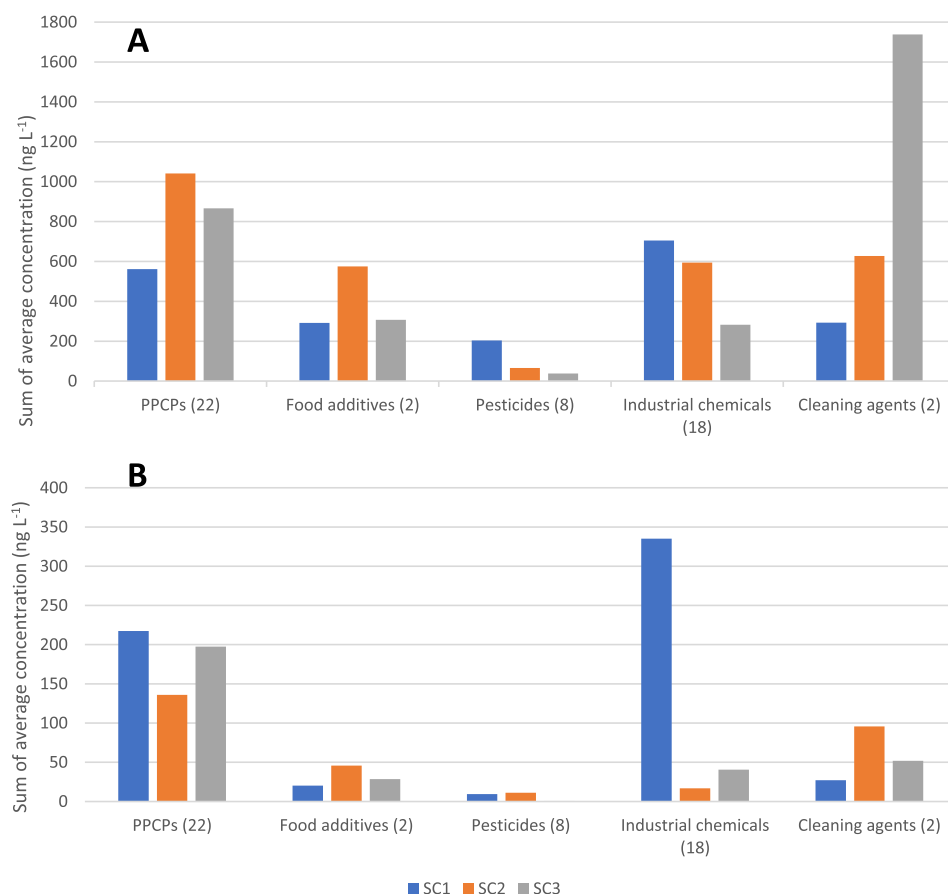


Fig. 5. Sum of average concentrations (ng L⁻¹) according to pollutants classes in the three sampling campaigns in river water (A) and coastal water (B).

The RE could not be evaluated for seven out of the 52 analytes, DTG, 6:2-FTSA, atraton, dinoseb, naphtalene sulfonic acid, PFMS and PFNA, which were not found in both (raw and treated wastewater) matrices

or directly not found in wastewater. From them, 6:2-FTSA, naphtalene sulfonic acid, PFMS and PFNA were only found in a few of the analyzed surface water samples, pointing out to diffuse or point sources, other

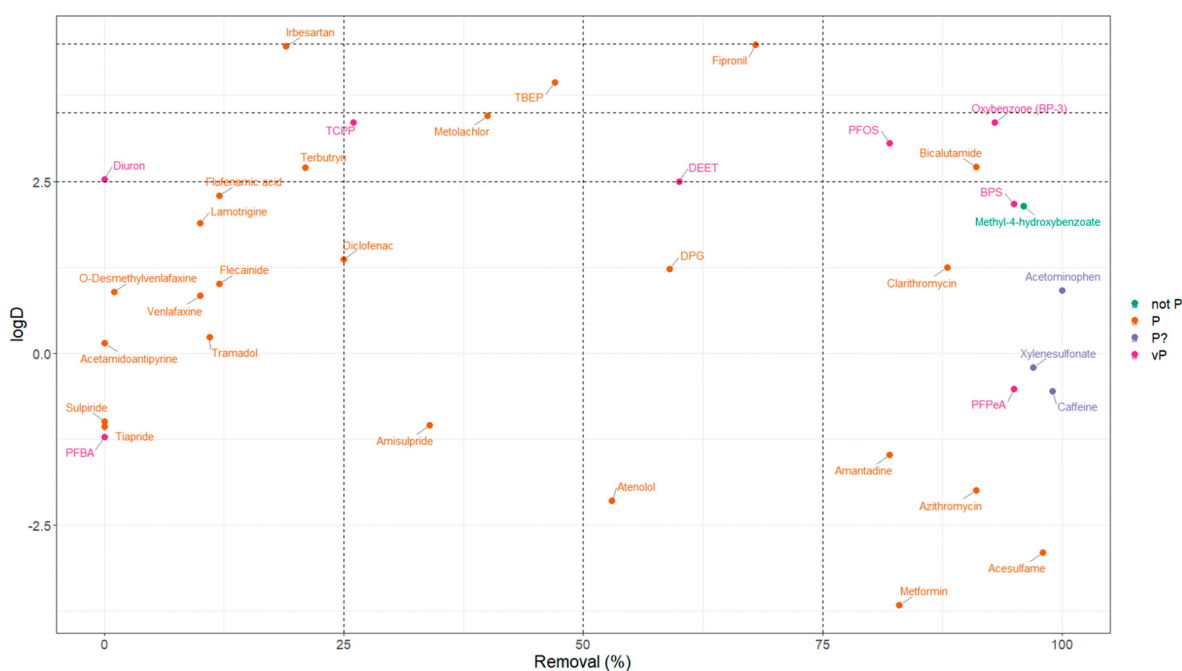


Fig. 6. Median of the RE for all WWTP and sampling campaigns ($n = 17$) against mobility (log D at pH 7) and persistence (P) classification for those chemicals present in at least 33 % of samples. log D axis lines at 2.5, 3.5 and 4.5 represent cut-off values for vM and M substances, according to guidelines (REACH: Improvement of guidance and methods for the identification and assessment of PMT/vPvM substances, 2019; Comission delegated regulation (EU) of 19.12.2022).

than WWTP effluents for those compounds. As observed, the studied analytes presented variable RE. The substances with an adequate RE (>75 %) are the least persistent one, i.e. methyl-4-hydroxybenzoate, or those with doubtful persistence classification, such as acetaminophen (Lopez et al., 2022). Low RE were found for some PPCPs, such as venlafaxine and *o*-desmethylvenlafaxine, tramadol or irbesartan, among others, which agree with other previous works reporting results for secondary treatment in WWTPs (Lopez et al., 2022). Moreover, as it can be observed in Fig. 6, these compounds, together with the antipsychotics sulpiride and tiapride, showed low RE and are all persistent compounds, and in fact, also presented a high DF (>60 %) in the analyzed river water samples. Similar behavior was reported for the antibiotics azithromycin and clarithromycin in literature (poor RE in secondary treatments) (Lopez et al., 2022; Guerra et al., 2014). However, in this work the estimated REs were high for both compounds, despite their classification as persistent.

Diuron, is a well-known pesticide recalcitrant in WWTP which undergoes limited degradation, so that some authors have proposed the use of UV/chlorine oxidation processes (Xiang et al., 2018). The RE observed in this study were very low (median 19 %), even in WWTP3, the only one in this study including chlorination step. It is worth noting that BPS, PFOS, BP3 and PFPeA, although very persistent compounds, are efficiently removed in WWTPs. It has been described that the secondary treatment through both aerobic and anaerobic digestion renders high RE for benzophenone- and salicylate-derivatives UV filters, specially BP3 (Tsui et al., 2014), which agree with the median RE >90 % found in this work. In the case of BPS, its degradation (or adsorption to sludge) in WWTP has been described as highly pH-dependent and high RE has been reported under adequate conditions (Qian et al., 2021). However, perfluorinated compounds, e.g. PFOS and PFPeA are difficult to biodegrade in WWTP through secondary treatments, thus low RE were expectable. Although adsorption mechanisms onto sludge can occur due to both hydrophobic and electrostatic interactions (Arvaniti and Stasinakis, 2015), such interactions would be more likely to be suffered by PFOS and the expected behavior of PFPeA would be like that observed for PFBA, with similar log D and poor RE.

Overall, the findings shown in Fig. 6 seem to point to the fact that conventional WWTPs (as the ones investigated in this work) may perform better than expected for PMT/vPvM chemicals. This may be explained by the persistence criteria, which is meant to represent environmental persistence, rather than biological removal at WWTPs. Moreover, removal due to sorption to sludge may already take place at log D > 2. Nevertheless, it must be noted that the PMT/vPvM classification from our former work (Montes et al., 2022) was derived in a great extent from *in silico* predictions and that log D values may not always be a robust predictor of mobility for all compound classes (Arp et al., 2017). Indeed, further studies are required to get such a robust PMT/vPvM classification and investigate whether this is also a good predictor of their fate in activated sludge WWTPs.

As an additional conclusion, as established in the recent proposal for revision of the European Directive concerning urban wastewater treatment (Annex I) (Proposal for a Directive of the European Parliament and of the Council concerning urban wastewater treatment (recast). COM, 2022), some performance-indicator compounds should be monitored in wastewater by the state members in the future, and the minimum required RE for them would be 80 %. These performance-indicator compounds include irbesartan, amisulpride, clarithromycin, diclofenac and venlafaxine (investigated in this work). Among them, clarithromycin (median RE 88 %) would be the only one fulfilling this requirement in most WWTPs. However, the RE for the other 4 indicators monitored is far from this value, being lower than 35 % in all cases. Thus, a large upgrade in WWTP treatments will be necessary in the following years to accomplish new regulations by implementing advanced treatment, as stated in the proposal for revised directive.

3.6. Risk assessment

The calculated RQ for each compound and sample (river and coastal water) are given in Table S8. A total of 18 compounds were present in at least one sample with an RQ > 0.1, of which 6 presented RQ > 1 and another one (PFOS) an RQ > 10. Those compounds are shown in Fig. 7, where the % of samples above such threshold is represented for both coastal and riverine surface waters.

With these considerations in mind, the most relevant compound would be caffeine, presenting a potential ($0.1 < RQ < 1$) or moderate risk ($1 > RQ > 10$) in most of the sampling points (both marine and river environments, Fig. 7), in agreement with other studies in the region (Canle and Antão-Geraldes, 2023). Even when this compound presents high RE values at WWTPs, its concentrations in effluents are still high enough to become a risk, as dilution and environmental transformations are not capable to mitigate its high loads. The second most relevant compound (Fig. 7) is sulpiride, an antipsychotic drug used also to treat dizziness, with negligible elimination during WWTP treatment (see 3.5).

The PFAS, PFOA, PFBA and PFMS are other relevant compounds, in particular PFOA which presents high risk in some coastal and river sampling points and moderate risk in 12 sampling points, especially in the second sampling campaign when dry weather and lower dilution occurred. It should be noted that the freshwater PNEC extracted from Norman Database for PFOA ($0.18 \mu\text{g L}^{-1}$) is derived from experimental data, whereas for PFMS ($142 \mu\text{g L}^{-1}$) or PFBA ($28 \mu\text{g L}^{-1}$) PNECs are predicted values. In fact, the PNEC for the PFAS included in this work are much lower when derived from experimental data than from QSAR models, suggesting once again that an underestimation of toxicity for PFMS, PFBA and the other PFAS may exist. As an additional example, recent research has demonstrated that the PNEC for metformin is overestimated when using predicted PNEC values. Barros et al. (Barros et al., 2022; Barros et al., 2023) found adverse effects in a model fish species at 390 ng L^{-1} in freshwater, being the concentrations of the 40 % of river water samples analyzed in this work over that concentration, thereby highlighting the relevance of this pharmaceutical too.

Diclofenac, presented a moderate or potential risk in different sampling points and campaigns, the concern about this pharmaceutical was already expressed with its inclusion in the 1st WL (Commission Implementing Decision (EU) 2015/495 of 20 March 2015 establishing a watch list of substances for Union-wide monitoring in the field of water policy pursuant to Directive 2008/105/EC of the European Parliament and of the Council (notified under document C(2015) 1756), 2015) concluding with a change in the EQS for this compound (Scientific Opinion on "Draft Environmental Quality Standards for Priority Substances under the Water Framework Directive" Diclofenac from the Scientific Committee on Health, Environmental and Emerging Risks SCHEER, 2022). Diclofenac is now included in the proposal for the new directive with EQS of 40 ng L^{-1} (annual average in inland surface water) (Proposal for a Directive amending the Water Framework Directive, the Groundwater Directive and the Environmental Quality Standards Directive, 2022), being 9 of the analyzed samples over this value (Table S6). Although this compound, as well as fipronil (among others), does apparently represent a risk only for freshwater environments (Fig. 7), this could be only a consequence of dilution, rendering them below mLOQ in coastal waters.

On the other hand, the plasticizer BPS and the UV filter BP-3 would only represent a potential risk for coastal environments. Given the fact that dilution would be expected to be similar than for other chemicals shown in Fig. 7, this may indicate that there are other sources rather than WWTP effluents contributing to their occurrence in coastal water (e.g. bathing for BP-3 or portuary activities for BPS).

4. Conclusions

In this work we have investigated the occurrence and fate of a total of 52 PMOCs/CECs in wastewater and the subsequent receiving fresh and coastal

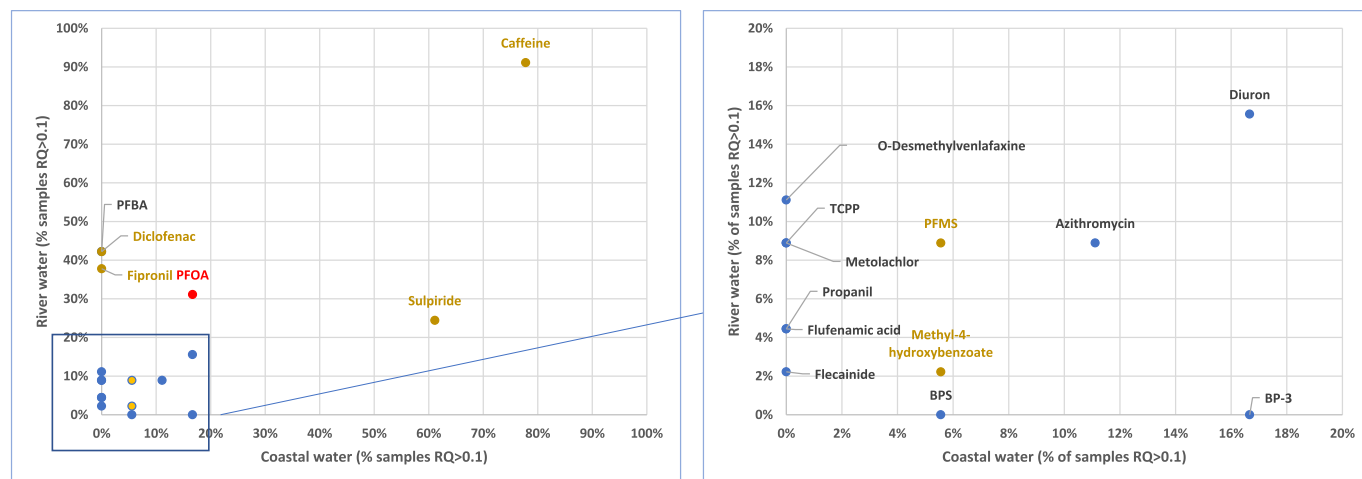


Fig. 7. Compounds presenting environmental risk in river and coastal water (as percentage of samples with $RQ > 0.1$). Those substances with at least one sample where $1 > RQ > 10$ are highlighted in orange; while those with at least a sample with $RQ > 10$ are highlighted in red.

water environments in a transnational region and the results have shown the ubiquity of the investigated compounds and an inefficient RE in WWTP. Considering that the minimum RE required according to the new regulations on urban wastewater treatment for the indicator substances should be 80 %, we observed that >60 % of the studied compounds rendered a RE under this value which reflect that big improvements in WWTP will be necessary to fulfill legislation requirements. In this sense, it is evident that a deeper knowledge of the actual mobility and persistence of CECs is required, as well as a better understanding of the relationship of these parameters with their behavior at WWTPs.

The risk assessment performed (based on Norman database PNEC) revealed that some CECs present a moderate or high risk at some sampling points, such as PFOA, fipronil or diclofenac. However, robust experimental toxicity data for those compounds with high DF and concentration levels (e.g. the pharmaceuticals sulpiride and metformin or short-chain PFAS) are required to better evaluate their environmental risk.

CRedit authorship contribution statement

Rosa Montes: Conceptualization, Methodology, Validation, Formal analysis, Investigation, Resources, Writing – original draft, Writing – review & editing, Visualization, Supervision, Project administration. **Sandra Méndez:** Methodology, Validation, Formal analysis, Investigation, Writing – review & editing. **Julio Cobas:** Resources, Writing – review & editing. **Nieves Carro:** Resources, Funding acquisition, Writing – review & editing. **Teresa Neuparth:** Resources, Writing – review & editing. **Nelson Alves:** Resources, Writing – review & editing. **Miguel M. Santos:** Resources, Writing – review & editing. **José Benito Quintana:** Conceptualization, Methodology, Formal analysis, Resources, Visualization, Supervision, Project administration, Funding acquisition, Writing – review & editing. **Rosario Rodil:** Conceptualization, Methodology, Formal analysis, Resources, Visualization, Supervision, Project administration, Funding acquisition, Writing – review & editing.

Data availability

Data on the sampling sites, dates and individual concentrations detected are available on the Supporting Information and will also become openly available at <https://doi.org/10.5281/zenodo.6603302> upon publication.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.scitotenv.2023.163737>.

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