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From monitoring to treatment, how to improve water quality: The pharmaceuticals case

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ABSTRACT

Water pollution is the most serious problem threatening global water resources. The release of both natural and anthropogenic factors in the aquatic environment is affecting the quality of water bodies, with Contaminants of Emerging Concern (CECs) being one of the major issues. In recent years, the availability of robust and sensitive analytical methods has allowed the detection and identification of a wide variety of pollutants. Pharmaceutically Active Compounds (PhACs) represent one large category of CECs detected in the aquatic environment, posing serious threats to human health and ecosystems. Hence, there is an urgent need for a better understanding of their environmental occurrence, fate, exposure-associated risks, and degradation in order to regulate exposure to pharmaceuticals in the environment. This review covers the current trends, newly developed state-of-the-art analytical methods, their challenges for PhACs detection in different water matrices, and the occurrence patterns in the aquatic environment. We also make a compressive assessment of the ineffective classic drinking water treatment plants (DWTPs) and the novel technologies such as membrane filtration and advanced oxidation processes that have been implemented to upgrade DWTPs. Their efficiency in removing PhACs is here discussed, as well as other embryonic technologies as promising solutions. The aim of this review article is to provide a comprehensive summary of the pathways and fate of PhACs in the environment, solutions for improving their monitoring assessments and the best methods for their removal in drinking water treatment plants.

1. Introduction

Nowadays, water pollution is a serious problem that undermines the already scarce water resources. Most countries rely on surface and groundwater sources for their drinking water needs, whose quality is affected from natural and anthropogenic factors. Metals, single organic ions, more complex organic molecules, and biological components can derive from various sources, such as natural disasters, agricultural runoff, industrial and domestic discharges, increasing population and economic growth, and can affect the quality of water bodies [1, 2]. The existence of these factors in the aquatic environment represents a serious threat for human health and ecosystems. In recent years, the availability of robust and sensitive analytical methods and techniques has allowed the identification and detection of a wide variety of pollutants, with those deriving from anthropogenic sources commonly being referred to as micropollutants since their presence in water bodies is usually at trace levels (between few ng/L to some μg/L) [1]. These contaminants may be classified as legacy – whose toxic effects are already known and control measures have been established – or as Contaminants of Emerging Concern (CECs) [2]. This last class comprises compounds that are not currently regulated or included in routine monitoring programs but are thought to have potential adverse effects to ecosystems and human health and may serve as candidates for future legislations.

Pharmaceutically Active Compounds (PhACs) are considered as one of the major categories of CECs present in the aquatic environment, with a variety of sources being responsible for their occurrence, such as hospital effluents, landfill leachates, and mainly industrial and domestic wastewater due to insufficient treatment techniques [3, 4]. Different

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studies have reported the inability of conventional treatment methods used in Waste Water Treatment Plants (WWTPs) to efficiently remove PhACs, posing threats to the receiving environment [5]. Pharmaceuticals were firstly discovered in the aquatic environment in the 1980s, with a huge variety of them being detected since then, and they can be classified into multiple groups according to their physicochemical properties or purpose of use. The main classes include, anti-inflammatory drugs, analgesics, antibiotics, antiepileptics, antidepressants, lipid lowering agents, antihistamines, beta-blockers, personal care products and other substances (psychoactive compounds, cytostatic drugs) [2]. Although, more than 3000 compounds are currently being active in the market, with their use continuously increasing, there are no existing regulatory limits for the majority of them [6]. However, some of them – and more specifically: 17-Alpha-ethinyleastradiol, 17-Beta-estradiol, Estrone, Erythromycin, Clarithromycin, Azithromycin, Methiocarb, Imidacloprid, Thiacloprid, Thiamethoxam, Clothianidin, Acetamiprid, Metaflumizone, Amoxicillin, Ciprofloxacin, Sulfamethoxazole, Trimethoprim, Venlafatine and its metabolite O-desmethylvenlafaxine, Clotrimazole, Fluconazole and Miconazole are currently included in the Watch List of the Water Framework Directive (WFD) [7].

Contamination caused by the release of pharmaceuticals in the environment is still a complex emerging problem due to the presence of various knowledge gaps concerning their occurrence and impact on the environment. Even if PhACs have been known to be present globally for more than forty years, their real environmental concentrations, as well as their consumption data, are still not available [8]. Moreover, it is known that these compounds can undergo chemical or biological transformations resulting to new transformation products (TPs), which are not yet identified or their toxicity to aquatic organisms is not known yet. Even if numerous studies have examined PhACs' occurrence in different environmental compartments, there is still lack of information concerning risk assessments or monitoring of ''hotspot'' locations, their effects when they bioaccumulate or the synergistic interactions of simultaneous contamination with multiple compounds [9]. Other critical knowledge gaps concerning PhACs in the environment include the adverse effects that can have both on human health and aquatic ecosystems in the long term, like morphological anomalies, endocrine disruption and increasing antimicrobial resistance [3, 10]. As an attempt to face these problems, in 2019 the European Commission published the European Union Strategic Approach to Pharmaceuticals in the Environment [11]. This approach proposes that Member States should develop compounds that are not harmful for the environment, promote the more careful use of PhACs, improve their environmental risk assessment and management of waste, broaden their environmental monitoring assessments, find cost-effective remediation methods towards the transition to a circular economy based environmental management, and finally identify further knowledge gaps to be resolved [11].

The main objective of this review was to provide a comprehensive summary of the current situation of pharmaceuticals' occurrence, removal, and fate in the aquatic environment, and identify future research needs. The review focuses on three different aspects, i) the advances in analytical techniques and methodologies used to detect PhACs in the aquatic environment, ii) the global occurrence of PhACs alongside with their pathways in the environment, and iii) the treatment techniques, both conventional and innovative, that can be adopted for reassuring the adequate removal of PhACs from drinking water. The search covered reports on PhACs monitoring and treatment worldwide, published since 2011 in Scopus and Google Scholar databases. The used keywords included "pharmaceuticals occurrence", "groundwater", "surface water", "aquatic environment", "treated water", "source and fate of pharmaceuticals", "analytical methods", "effluents", "conventional treatment methods", "drinking water treatment plants", "wastewater treatment plants", "advanced oxidation processes", "membrane filtering". Only studies dealing with i) PhACs' monitoring using LC-MS/MS methods, due to their advantages over other techniques, (e.g., better sensitivity, durability, ease of use, requiring less extensive and faster sample pre-treatment, capacity to analyze a wide range of compounds, and shorter run time [12], ii) different sampling campaigns per year, which took into account as well temporal and spatial monitoring (e.g., different locations, or same sampling points in different seasons), and iii) treatment techniques concerning pharmaceuticals present in drinking water sources, were considered.

2. Water analysis

Traditionally, detection of PhACs in the environment is done using water analysis of a wide range of aqueous samples, including surface and ground water utilized directly or indirectly to produce drinking water, rainwater, municipal and industrial wastewater, and process water. Fig. 1 depicts an overview of the main stages involved in water analysis using LC/MS-based techniques. Sampling, sample preparation, and analysis of these diverse types of water, which may differ not just in terms of the contaminants present, but also in the pollution level, requires careful planning and execution.

Surface and groundwater with low pollution levels generally require less time-consuming sample preparation than more complex samples such as soil and biological samples. Matrix components are less prevalent in aqueous samples, and sample preparation is often limited to the extraction of contaminants, e.g., pharmaceuticals, from the aqueous sample. Additional cleanup is less important for water analysis, often necessary only for highly polluted samples or in ultra-trace analysis.

It is important to note that water samples, in addition to the aqueous components, contain suspended particles in which hydrophobic compounds may preferably be adsorbed. Many standardized methods of water analysis require the removal of these suspended particles through a filtration step using, e.g., a 0.7 μm fiberglass filter. The purpose of this review is to survey the current state-of-the-art trends in the analysis of PhACs in aqueous systems using Liquid Chromatography coupled to Mass Spectrometry (LC–MS), including sample preparation. As this review is restricted to provide a general overview of the extraction techniques used in the analysis of pharmaceuticals in aqueous samples, compounds adsorbed on suspended particles will not be addressed.

Extraction of aqueous samples needs to meet requirements such as high analyte enrichment, increased recoveries, good accuracy and precision, and low detection limits [13]. However, the most common issue in water analysis is that samples prepared using exhaustive extraction procedures typically contain many matrix components, which may affect the quantitative analysis by co-eluting with the target analytes. Thus, sample pretreatments aiming at reducing the matrix components and the enrichment of the target compounds are used. These time-consuming and labor-intensive extraction and clean-up procedures account for the largest portion of the analysis time. In addition, laboratories that conduct monitoring studies need to use high-throughput and fully automated analytical techniques to keep up with the growing number of samples they must analyze. As a result, much effort is being devoted in the development of low-cost sample handling techniques that benefit from efficiency and simplicity.

2.1. Sample preparation for LC-MS analysis of PhACs

With regard to the analysis of PhACs in water samples, recent years have seen an increased focus on the development and application of generic multi-residue methods that allow simultaneous analysis of multiple-class compounds in environmental samples [14–16]. Such multi-residue methods allow us to attain a broader knowledge about the environmental occurrence, removal and fate of pollutants. Simultaneous analysis of compounds from different groups with varying physicochemical properties, on the other hand, necessitates a compromise in the experimental conditions between extraction, LC separation, and/or MS detection. Regarding the trends in recent years, four general approaches

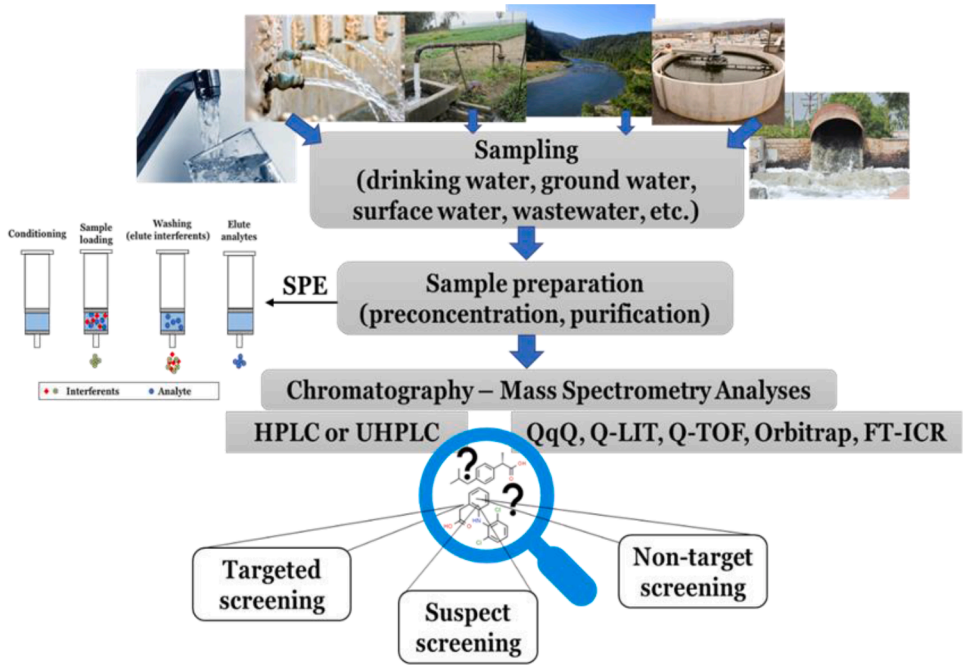

Fig. 1. Overview of PhACs analysis in aqueous samples using LC-MS.

to LC-MS analysis of PhACs in water samples can be identified: i) off-line SPE extraction of the target analytes followed by LC-MS analysis [15–18], ii) coupling sample preparation units and detection systems to automate the process - worth mentioning is the coupling of on-line solid phase extraction (SPE) with LC-MS systems [17, 19], iii) use of customized sorbents such as molecular imprinted polymers, immunosorbents, and nanomaterials [20], and iv) combination of several sample preparations steps (for example, using passive samplers for simultaneous sampling, extraction, and enrichment of pharmaceuticals from aqueous samples) [21]. It is worth mentioning that several recent studies [14, 22] have successfully implemented direct injection and obtained results that are comparable to SPE extraction. Although its applicability in modern analytical chemistry is limited, ultrasound-assisted dispersive liquid-liquid microextraction (DLLME), for example, has emerged as a viable alternative to the standard liquid-liquid extraction method by addressing the majority of its limitations [23].

The most widely used method is to extract all target analytes simultaneously in a single SPE step preferably by coupling it online to the LC-MS [13]. Because of its hydrophilic-lipophilic balance, Oasis HLB is predominantly used for the extraction of pharmaceuticals with a wide variety of polarities and pH values [18, 24]. The mixed-mode cation-exchanger Oasis MCX has also been widely used, thanks to its applicability towards neutral, polar, non-polar, and cationic compounds from aqueous media [17, 25].

The use of automated techniques and devices that combine extraction, separation, and detection steps has become increasingly popular over the past years due to their numerous advantages, including increased accuracy and precision owing to minimal sample handling, low sample volume, and decreased solvent use. As a result, combining extraction methods online with chromatographic instruments seems to be the future of multi-residue analytical methods. When it comes to online sample extraction coupled with LC-MS, various generic approaches have been developed using different extraction sorbents such as disposable or reusable cartridges, restricted access materials (RAM), large size particles or monolithic materials [26]. Some recent applications for the analysis of multi-class PhACs in water samples include the determination of 12 pharmaceuticals together with 25 endocrine-disrupting compounds [19]. After testing various on-line SPE cartridges, the best results were obtained with the Oasis HLB loading column, with quantification limits ranging from 0.25 to 10 ng/L. The authors reported that their on-line SPE method benefited from little sample handling, minimal solvent use, and high sample throughput, all of which resulted in time and cost savings. Similarly, Anumol and Synder [27] used multi-residue online SPE LC-MS method to determine 32 organic microcontaminants in ground water, surface water and wastewater samples, of which 16 were pharmaceuticals including ibuprofen, carbamazepine and trimethoprim. They compared three commercial on-line SPE columns to an in-house packed column and reported that the PLRP-s cartridge achieved higher recoveries (70–130% for 26 analytes) and method detection limits (MDLs) ranged from 0.1 to 13.1 ng/L. Along with reduced solvent use and increased throughput, their on-line SPE method had the advantage of requiring only a 1.7 mL sample volume and of exhibiting enhanced reproducibility. Another study by Rubirola et al. [28] on 24 Water Framework Directive priority substances including diclofenac, erythromycin and clarithromycin applied an on-line SPE LC-MS methods for the analysis of surface water, drinking water, and wastewater effluents achieving detection limits between 0.1 and 1.4 ng/L. Even though reproducibility varied significantly amongst methods, it was consistently noted that online SPE was more time and cost effective than its offline counterpart.

2.2. *Major analysis trends for PhACs in the aquatic environment*

The overall tendency in chromatographic analysis of PhACs in water samples is to adopt fast LC methods with short, narrow bore columns allowing high mobile phase flow-rates and ultrahigh pressures. Achieving the highest chromatographic resolution in the shortest time feasible is crucial for laboratories undertaking monitoring studies, as extended run durations are not acceptable for true high-throughput analysis. For example, ultra-high performance liquid chromatography (UHPLC), which uses columns packed with sub-2 μm particles, enables elution of sample components into much narrower and more focused bands resulting in greater chromatographic resolution and increased peak capacity. In fact, UHPLC is becoming increasingly popular for PhACs analysis in water with reports of increased sensitivity and speed as compared to the typical 5 or 3 μm HPLC columns [29–32]. In addition, hydrophilic interaction chromatography (HILIC) has emerged as a useful analytical tool for the separation of polar PhACs, reportedly

increasing sensitivity in MS detection when compared to conventional reversed-phase liquid chromatography (RPLC) [33]. However, environmental applications using HILIC are scarce. Castro et al. [34] used four chromatographic retention modes, including HILIC and RPLC, to screen more than 3000 chemicals including pharmaceuticals, pesticides, illicit drugs and human metabolites in surface waters.

In order to properly assess risks and monitor the quality of surface and drinking water, multi-residue methods that allow measurement at trace and ultra-trace levels are required. With the use of a single analytical technique, it is possible to save time, money and resources by analyzing multiple types of pharmaceuticals that belong to different classes. Various studies have been underway in response to the need of monitoring pharmaceutical compounds in the environment, and resulted in the development of numerous sensitive, accurate and reliable analytical methods for determining PhACs and their metabolites, including transformation products, in water samples. Psychiatric drugs, analgesics and anti-inflammatory drugs, antibiotics, lipid regulators, and β-blockers have very high consumption worldwide and are the most abundant in environmental waters. As a result, these pharmaceuticals are often included in analyses using multi-residue methods.

As indicated in Section 2.1, the most commonly used methods for screening and quantification of PhACs in environmental and wastewaters are methods based on SPE sample preparation combined with LC tandem MS (LC–MS/MS) (Table 1). The rapid advancement in the capabilities of mass spectrometry instruments has significantly improved the scope and quality of information gathered in the field of PhACs analysis. As a result, in recent years, state-of-the-art analytical methods have been applied in the analysis of PhACs and their transformation products in environmental samples and wastewaters using advanced chromatographic techniques (HPLC or UHPLC) coupled to low- and high-resolution MS detection systems such as hybrid quadrupole time-of-flight (Q-TOF-MS) [20], quadrupole linear ion trap (Q-LIT-MS) [15, 18, 35, 36], Fourier transform ion cyclotron resonance MS (FT-ICR-MS) [37] and Orbitrap MS [16]. The advantages associated with the advanced high-resolution MS (HRMS) instruments are their high resolution, outstanding mass accuracy, excellent isotopic abundance accuracy, and extremely high sensitivity [38].

Quantification using selected reaction monitoring (SRM) in triple quadrupole instruments is a well-established approach with excellent sensitivity and selectivity. For example, Guan et al. [23] developed a method based on triple quadrupole (QqQ) MS for the determination of 12 pharmaceuticals in surface water and wastewater influent and effluents. Similarly, Nieto-Juarez et al. [39] determined more than 38 pharmaceuticals through direct injection of water samples into a QqQ instrument. SRM was used in both methods to perform highly specific and sensitive quantification of target analytes. However, structural elucidation of compounds is impossible using QqQ because of the lack of qualitative data required to support this. Hybrid MS techniques, such as Q-LIT-MS, Q-TOF-MS, and Orbitrap-MS, are widely used to overcome this shortcoming. For example, Q-LIT-MS offers the option to perform full scan enhanced MS (EMS) and enhanced product ion (EPI) scan using the third quadrupole (Q3) leading to increased sensitivity and thus improved performance. Pereira et al. 2021 [40] developed a multi-residue method based on off-line SPE and LC-MS/MS using Q-LIT instrument for the simultaneous analysis of 18 pharmaceuticals in drinking water catchments, tap water and drinking fountain waters. The developed method was highly sensitive, with method quantification limits of 3.41–16.53 ng/L. Another study by Khulu et al. [20] used Q-TOF-MS to determine 5 pharmaceutical drugs in surface waters. In both cases, quantification was done in SRM mode, while qualitative confirmation was achieved using the information dependent acquisition (IDA) mode. A faster MS/MS scan (reduced dwell time) can be achieved with Q-LIT-MS because of the increased velocity of the ions through the collision cell. This, in contrast to QqQ, allows for the monitoring of more than two SRM transitions per compound. Additional IDA experiments can also confirm low intensity transitions.

Table 1
Examples of current LC-MS multi-residue methods used to simultaneously analyze multi-class PhACs in water.

Analytes	Matrix	Extraction method	Detection	Ref.
5 pharmaceuticals belonging to different classes	Surface water	A combination of membrane assisted solvent extraction and a molecularly imprinted polymer (MASE-MIP)	Q-TOF MS	[20]
135 pharmaceuticals and personal care products (plus, 37 illicit drugs, PFCs and flame retardants)	Wastewater influent and effluents	Off-line SPE with Oasis HLB	Orbitrap-MS	[16]
58 pharmaceuticals (plus, 16 antibiotics and 33 pesticides)	Treated wastewater	QuEChERS-based	Q-LIT-MS	[35]
12 pharmaceuticals belonging to different classes	Surface water and wastewater influent and effluents	Ultrasound-assisted dispersive liquid-liquid microextraction (DLLME)	QqQ-MS	[23]
16 pharmaceuticals (and hormones)	Surface water, ground water, and treated water	Off-line SPE with Oasis HLB	Q-LIT-MS	[18]
38 pharmaceuticals belonging to different therapeutic groups	Surface water and wastewater influent and effluents	Not used (direct injection)	QqQ-MS	[39]
18 human pharmaceuticals belonging to 6 therapeutic groups	Drinking water catchments, tap and drinking fountain waters	Off-line SPE with Oasis HLB	Q-LIT-MS	[15]
20 psychoactive pharmaceuticals (plus, 10 illicit drugs)	Wastewater influents and effluents	Off-line SPE with Oasis HLB and Oasis MCX	QqQ-MS	[17]
73 pharmaceuticals (plus, 62 pesticides, illicit drugs, and their metabolites)	Wastewater influents	Not used (direct injection)	QqQ-MS	[14]
37 psychoactive pharmaceuticals (including illicit drugs)	Wastewater influents	On-line SPE with PLRPs column cartridge	Q-LIT-MS	[40]
12 pharmaceuticals (plus, 25 other CECs including alkyl phenols, pesticides and hormones)	Surface water	On-line SPE with Oasis HLB column cartridge	Q-LIT-MS	[19]
11 pharmaceuticals (antiretroviral drugs and metabolites)	Surface water and municipal waste	Direct injection and off-line SPE with Strata SDB-L cartridges	QqQ-MS	[22]

Orbitrap-MS is another high-resolution, accurate mass instrument that has gained popularity in recent years for PhACs analysis in water. Even though Orbitrap-MS instruments are most commonly used for non-target screening of a wide range of unknown contaminants, their application in target analysis of PhACs in water has been significant. Ofrydopoulou et al. [16] used a UHPLC—Orbitrap-MS to assess organic micropollutants in wastewater influents and effluents, including 135 pharmaceuticals and personal care products. Another study by Kosma et al. [30] assessed more than 35 multiclass pharmaceuticals in

wastewater influents and effluents using UHPLC—Orbitrap-MS. The analyzed pharmaceutical compounds included sulfamethoxazole, carbamazepine, bezafibrate, sertraline, diclofenac and others. Recently, many similar studies have been reported [29], and the Orbitrap-MS appears to be one of the future mass spectrometry trends due to its high-resolving power and high sensitivity gained by Fourier transform-ion detection.

While multi-residue methods are appropriate for dealing with highly demanding monitoring and assessment requirements of pharmaceuticals in various water matrices, it is also important to be aware of the disadvantages. First, compromises between performance parameters (SPE, LC or MS) are often required when analyzing multiple classes of PhACs with very different physico-chemical properties using a single multi-residue method. Then, enhanced signal suppression could be a potential problem, especially when analyzing complex samples like wastewater. In such cases, proper sample preparation protocols become even more critical, and thus due consideration must be given when working with simplified clean-up procedures.

2.3. Nontarget analysis and identification of unknowns

The increasing number of chemicals released in the aquatic environment, as well as the occurrence of their transformation products, makes evaluating the quality of water bodies practically impossible if only target analyses depending on specific standards are used. To deal with this, various analytical approaches and strategies based on biological or chemical analyses have been developed over the last years [41], including both semi-targeted (suspect) screening, and untargeted (nontarget) screening.

In recent years, there has been a rise in the number and quality of publications regarding the identification of transformation products (TPs) of pharmaceuticals in various water matrices. To this end, different MS methodologies have been used. Performing collision-induced dissociation (CID) on QqQ and ion trap (IT) instruments, for example, allows MS/MS data acquisition either in space or in time. Hybrid MS instruments such as Q-LIT-MS and Q-TOF-MS can also similarly utilize CID. For example, Krakstrom et al. [42] used ion trap mass spectrometry with electrospray ionization (ESI) source for the identification of ibuprofen and diclofenac TPs formed as a result of ozonation treatment. MS data was generated in full scan and automatic MS^5 scan modes, allowing for further fragmentation of the precursor and product ions, which provided valuable information for elucidation of the TPs. Another study by Gosetti et al. [36] employed a hybrid Q-LIT-MS instrument to identify eight photodegradation products of the antineoplastic drug irinotecan. In this work, data was acquired using IDA, which allowed linking a nontarget "survey scan" with "dependent scans" when pre-defined IDA criteria were met. The Enhanced MS (EMS) was chosen as a survey scan for the nontarget screening, with the Q3 working as an ion trap collecting the ions of interest. The two dependent scans, Enhanced Resolution (ER) and Enhanced Product Ion (EPI), were performed automatically when the EMS detected a signal that exceeds a certain threshold. Each survey-dependent scan is repeated in a cycle of the entire chromatographic run. The ER scan confirms the isotope pattern, while the EPI provides an enhanced MS/MS scan resulting in a greater abundance of the product ions.

In recent years, the evolution of high-resolution mass spectrometry (HRMS) has sparked a new trend in the analysis of environmental samples. As a result of their high mass resolution, instruments such as TOF-MS and Orbitrap-MS can produce mass errors in the low ppm range, overcoming one of the limitations of QqQ and Q-LIT-MS devices. Moreover, when compared to TOF-MS analyzers, Orbitrap-MS analyzers offer a higher dynamic range of detection and, in general, higher mass resolution (>100 000 FWHM). In addition, Orbitrap-MS can be calibrated externally to achieve superior mass accuracy, the only pitfall being their much slower scanning speed. HRMS instruments are also suitable for elucidating the structure of unknown compounds and have emerged as powerful techniques for the nontarget identification of pharmaceuticals and their transformation products in water [43–45]. Other HRMS instruments such as FTICR-MS have also been used [46] but their application has been limited due to their high cost and specialist demands.

Recent developments in suspect and nontarget screening have enabled the identification of unknown TPs in wastewater [47], surface water [44, 45], and drinking water [48], following various water treatment methods such as ozonation, hydrolysis, filtration, chlorination, photolysis, and advanced oxidation processes. Targeting potential TPs has become an integral part of the recent research in environmental monitoring and assessment of pharmaceuticals. For instance, Stadlmair et al. [49] employed MS-based workflows using both Q-TOF-MS and Q-LIT-MS instruments for the identification of peroxide- and enzyme-catalyzed TPs of diclofenac, mefenamic acid and sotalol. The complementary MS information obtained from both Q-TOF and Q-LIT-MS analyzers increased the confidence in the identification of TPs. Another study by Tian et al. [50] applied HRMS for the suspect and nontarget screening of emerging contaminants in a marine environment. Eight out of the 87 identified compounds were pharmaceuticals including metoprolol, methamphetamine, lamotrigine, and their TPs.

Evaluation of nontarget data, on the other hand, is not an easy task due to the enormous number of peaks representing potentially relevant CECs, which can be time-intensive and necessitates expertise. When screening large LC—HRMS data in spectral libraries, it is common to get multiple hits for the same exact mass values, which may lead to the detection of false positives. Thus, data pre-processing and cleanup are immensely required to remove/reduce false positives. Furthermore, removal of false positives and minimization of the large data pre-processing work can be achieved by employing a proper suspect list potentially related to the environmental scenario and regulatory concern. Such suspect lists also allow evaluation of whether the compounds can be detected by the analytical method, hence avoiding false-negative results due to an ineffective analytical methodology. Understandably, when a high degree of certainty is required, the complexity rises dramatically, and the task becomes extremely challenging [38, 51].

Another important trend of employing LC—HRMS is the possibility to undertake retrospective screening, which is extremely useful in environmental monitoring programs. Digital Sample Freezing Platforms (DSFP) can be used to store HRMS data [51], allowing for the retrospective screening of various contaminants. The realization of DSFPs has shown to be crucial in the screening of CECs that were previously unknown [52, 53], including TPs [44, 45], thanks to the capacity to compare MS data across several environmental matrices such as water, biota, sediment, air and indoor environment. While target analysis is critical in monitoring and exposure assessment, nontarget retrospective screening of digitally archived HRMS data has the potential to be used as a first screening step to improve the environmental risk assessment of CECs by triggering further target analysis.

The significant advancements in LC-MS instrumentation and analytical methods over the last decade have enabled the detection of several pharmaceuticals at very low concentrations in a variety of aqueous matrices. Despite these improvements there are still methodological challenges to overcome, most of which are related to the large diversity of aqueous matrices available, as well as the complicated mixture of PhACs within them. SPE, which is employed in more than 80% of LC-MS methods developed for pharmaceutical analysis [54], allows for an average volume of water samples between 100 and 200 mL to be passed through the solid sorbent without significantly lowering the extraction speed and efficiency [55]. As concentrations of pharmaceuticals in various surface waters and especially in drinking waters are usually very low (Table 2 & 3), large volume extraction up to 1000 mL is required to achieve the LOD of current LC-MS instrumentation. Because some interferents cannot be completely removed from the matrix, they are concentrated with the analytes during large-volume extractions, resulting in a significant matrix effect. The amount of organic matter in

Table 2
Minimum (Min) and maximum (Max) detected concentrations of selected PhACs in surface and groundwater in different countries.

Compounds	Detected concentrations min-max (ng/L)	Matrice	Location	Ref
Azithromycin	11.10–29.6	Surface water	Portugal	[84]
	2.55–82.46	Surface/ groundwater	Italy	[18]
Acetaminophen	<MDL-29.00	Surface/ groundwater	Japan	[85]
	<MDL-4.17	Surface/ groundwater	India	[77]
	N/A-17.00	Groundwater	USA	[74]
	N/A-30.00	Surface/ groundwater	Portugal	[86]
Atenolol	<MDL-1.30	Surface/ groundwater	India	[77]
	N/A-8.70	Groundwater	USA	[76]
	N/A-4.00	Surface/ groundwater	Portugal	[86]
	1.07–483.94	Surface/ groundwater	Italy	[18]
Caffeine	15.2–743	Surface/ groundwater	India	[77]
	N/A-677.00	Groundwater	USA	[76]
	N/A-47.00	Surface/ groundwater	Portugal	[86]
	11.38–38.41	Surface water	Hungary	[75]
	1.15–65.92	Surface/ groundwater	Italy	[18]
Carbamazepine	<MDL-100.00	Surface/ groundwater	Japan	[85]
	<MDL-27.20	Surface/ groundwater	India	[77]
	N/A-162.00	Groundwater	USA	[76]
	N/A-19.00	Surface/ groundwater	Portugal	[86]
	0.15–77.16	Surface water	Hungary	[75]
	7.00–10.00	Surface water	Italy	[62]
Ciprofloxacin	<MDL-28.80	Surface/ groundwater	India	[77]
	N/A-46.68	Surface/ groundwater	China	[78]
	2.86–7.00	Surface/ groundwater	Italy	[18]
Citalopram	N/A-7.40	Groundwater	USA	[76]
	0.24–0.59	Surface water	Hungary	[75]
	5.60–107.70	Surface water	Sweden	[87]
Clarithromycin	<MDL-199.00	Surface/ groundwater	Brazil	[88]
	0.10–101.30	Surface/ groundwater	Italy	[18]
Diclofenac	<MDL-44.00	Surface/ groundwater	Japan	[85]
	<MDL-41.30	Surface/ groundwater	India	[77]
	N/A-12.00	Surface/ groundwater	Portugal	[86]
	N/A-4.20	Surface water	Hungary	[75]
	170.00–2550.00	Surface water	Germany	[89]
	28.60–470.00	Surface water	Poland	[90]
	10.00–50.00	Surface water	Netherlands	[91]
	46.00–700.00	Surface water	Finland	[92]
	26.87–30.06	Surface water	France	[93]
	15.00–17.00	Surface water	Italy	[62]
Erythromycin	14.34–26.40	Surface/ groundwater	China	[78]
	N/A-32.00	Surface/ groundwater	Portugal	[86]
	<MDL-5.00	Surface/ groundwater	Italy	[18]
Fenofibrate	<MDL-61.00	Surface/ groundwater	Japan	[85]
	N/A-32.90	Groundwater	USA	[76]
	<MDL-290.00	Surface water	Brazil	[88]
Ibuprofen	<MDL-17.00	Surface water	Japan	[85]
	<MDL-49.40	Surface/ groundwater	India	[77]
	N/A-44.42	Surface/ groundwater	China	[78]
	N/A-22.00	Surface/ groundwater	Portugal	[86]
	<MDL-302.00	Surface/ groundwater	Brazil	[88]
	1.46–10.54	Surface/ groundwater	Italy	[18]
Ketoprofen	<MDL-60.00	Surface/ groundwater	Japan	[85]
	<MDL-107.00	Surface/ groundwater	India	[77]
	<MDL-1020.00	Surface/ groundwater	Brazil	[88]
	<MDL-9.00	Surface water	Italy	[62]
Naproxen	<MDL-2.62	Surface/ groundwater	India	[77]
	2.12–3.23	Surface/ groundwater	China	[78]
	N/A-6.00	Surface/ groundwater	Portugal	[86]
Sulfamethoxazole	<MDL-38.00	Surface/ groundwater	Japan	[85]
	<MDL-27.50	Surface/ groundwater	India	[77]
	23.45–60.58	Surface/ groundwater	China	[78]
	N/A-120.00	Groundwater	USA	[76]
	N/A-24.00	Surface/ groundwater	Portugal	[86]
	1.50–125.80	Surface water	France	[94]
	0.41–99.47	Surface/ groundwater	Italy	[18]
Trimethorpim	N/A-14.90	Groundwater	USA	[76]
	0.97–1.27	Surface/ groundwater	China	[95]
	12.87–87.16	Surface/ groundwater	Italy	[18]

MDL: Method detection limit.

the water is also critical since it may impede the extraction process due to cartridge clogging. As a result, the conventional SPE is challenged when large volume extraction is required. Some studies have demonstrated the use of Disk SPE as viable solutions to overcome this [56, 57], however environmental applications are currently scarce.

Another challenge arises from the complicated mixture of PhACs (e.g., high polarity, chirality, ionizability) and their fate (e.g., unknown transformation products) in different aqueous matrices. While recent developments have focused on the more standard RPLC, it is evident that our chromatographic separation problems cannot be solved using only more conventional RP chromatographic screening procedures. To provide a complete picture of the occurrence, fate, and risk of PhACs in the aquatic environment, new highly sensitive and robust analytical methods based on the less often used techniques such as HILIC [33], supercritical fluid chromatography [58], and gas chromatography [59] are required. Additionally, analytical methods for TPs in different water matrices are lacking. However, it is important to recognize the considerable amount of effort being expended in this field, especially with non-target screening (NTS) approaches. Although NTS approaches are still in their infancy, we anticipate that more comprehensive data will become accessible within the next decade, allowing us to have a better grasp of the TPs issue.

3. Occurrence of PhACs in the environment

Although the presence of PhACs in the water cycle is not a new

Table 3
Concentrations of most detected PhACs in drinking water samples from different countries.

Compounds	Detected concentration min-max (ng/L)	Location	Ref
Azithromycin	N/A-193.00	Poland	[99]
Carbamazepine	0.04–27.20	India	[77]
	0.02–0.30	Spain	[100]
	1.50–1.60	Sweden	[101]
	N/A-25.00	Japan	[85]
	N/A-77.16	Hungary	[75]
	1.05–1.16	China	[95]
Caffeine	16.73–44.19	Spain	[100]
	4.80–5.60	Sweden	[101]
	15.2–208.00	India	[77]
	N/A-38.41	Hungary	[75]
	N/A-159.00	Poland	[99]
	71.03–81.85	China	[95]
Ibuprofen	1.63–11.29	Spain	[100]
	8.00–24.00	Colombia	[102]
	16.90–49.40	India	[77]
	N/A-4.70	China	[95]
	N/A-16.00	Japan	[85]
	N/A-224.00	Poland	[99]
Ketoprofen	4.76–23.40	India	[77]
	15.18–31.67	China	[95]
	N/A-392.00	Brazil	[88]
Sulfamethoxazole	1.59–5.29	Spain	[100]
	0.22–4.13	India	[77]
	N/A-7.65	China	[95]

phenomenon, noticeable attention has been drawn to them within the last decade, mainly due to the advance of analytical methods and instruments -as reported in the previous section- that allowed their detection even at trace level concentrations ranging from ng/L to few μg/L [8, 60, 61]. Several studies in the literature have reported the occurrence of PhACs in various water bodies, including groundwater, surface and wastewater, even in treated water intended for human consumption, raising concerns about their potential effects on human health, especially after a long-term exposure to low level concentrations. Nonetheless, pharmaceuticals' use is expected to rise in the future, as western populations are aging, increasing in this way worries about their environmental rates [62]. In general, the two most abundant categories of PhACs in the aquatic environment are antibiotics and analgesics, but results may vary depending upon the country, region, area's consumption pattern and manufacturing industry locations [6].

3.1. Sources and pathways of PhACs in the environment

Due to their large consumption, pharmaceuticals can reach the aquatic environment through different routes, including animal and human excretion after consumer use, improper domestic or industrial discharge, and landfill leaching [3] depending upon the substance and its properties (Fig. 2). In general, the main pathway of pharmaceuticals in the environment is considered to be the emissions from urban wastewaters, including both compounds that have not been entirely metabolized from the human body arriving into waste, and those released during washing or bathing [63]. Even if according to regulations and laws, treatment of wastewater is obligatory [64], it is well-known that the majority WWTPs rely on conventional physical and biological treatment technologies that are unable to efficiently remove [65]. A study from Lee et al. [66] showed that different compounds, such as diclofenac, acetaminophen, sulfamethoxazole and trimethoprim were barely removed after treatment and detected between 0.006 and 0.61 μg/L in the effluents of a public WWTP in China, with their concentrations being higher in winter affected by the consumption trends. Another study by Čelić et al. [67] based on a suspect screening approach, revealed the presence of 26 contaminants and 11 transformation products from different classes in both wastewater effluents, river water and marine water samples in Spain, with pharmaceuticals being the most abundant compounds in effluents, and highlighting the fact that WWTPs are the greatest PhACs' pollution source for the aquatic environment. Subsequently, PhACs can be released in the environment, through the effluents and sludge, as parent compounds, metabolites or transformation products formed during the different treatment processes [15]. The problem is greater particularly nowadays that intense reuse of treated wastewater in agriculture is practiced all over the world, especially in water-scarce regions as an attempt to meet the current needs

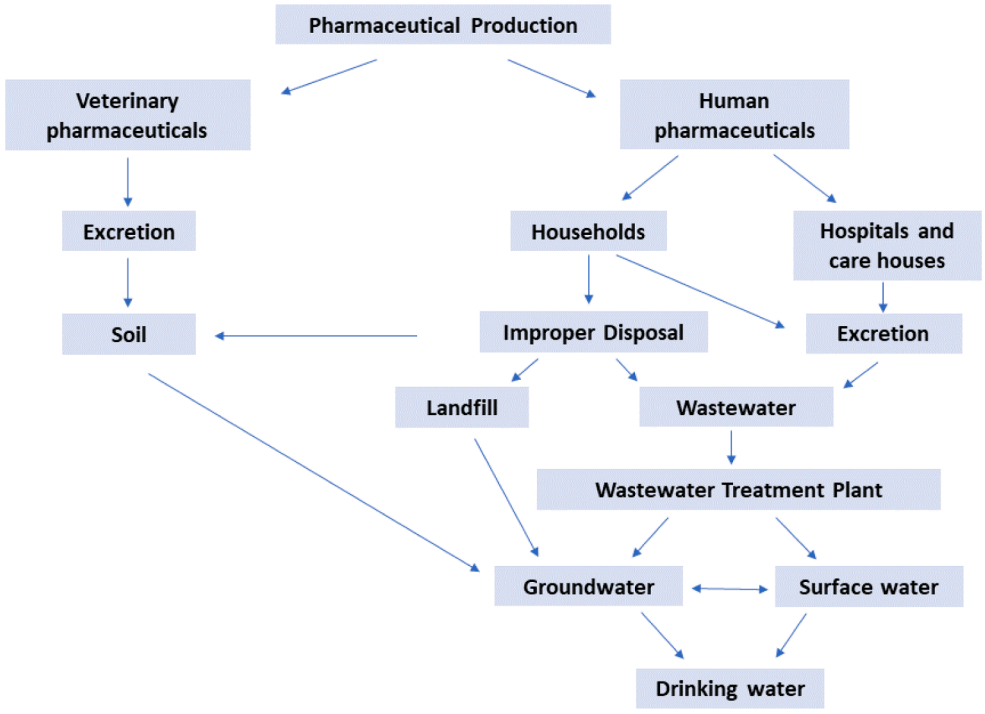

Fig. 2. Main pathways of PhACs in the aquatic environment.

without jeopardizing the natural resources. In doing so, pharmaceutical residues present in the treated effluents are irrigated to the soil and subsequently can infiltrate into the local aquifers [68]. Moreover, untreated household effluents or effluents from industries, hospitals and care houses may directly discharge pharmaceuticals into various receiving water bodies [2]. Even if there are no specific guidelines or directives for managing hospital wastewater, in general, their direct disposal to surface water is forbidden. However, different studies by Carraro et al. [69], Wang et al. [70] and Azuma et al. [71] reported the occurrence of PhACs in high concentrations (order of μg/L) and antibiotic resistance genes into surface water impacted with untreated hospital effluents.

Nevertheless, PhACs may reach the aquatic environment through storm water, surface runoff or atmospheric particulates and precipitation. This is a bigger concern in urban areas, as they are more contaminated by a cocktail of anthropogenic contaminants, mainly caused by runoff, illegal dumping of wastewater and overflow in combined sewer systems. A study by Fairbairn et al. [72] showed that the concentrations of acetaminophen, caffeine and metformin in storm water were similar to those detected in wastewater effluents, while another study by Yin et al. [73] reported the presence of antibiotics and non-steroidal anti--inflammatory drugs (NSAIDs) in storm water in China raising concerns about the effects of storm water discharges to natural water resources.

3.2. PhACs in surface and groundwater

Several studies have reported the occurrence of PhACs mainly in surface and groundwater sources, with antibiotics and analgesics being the most detected compounds in Asia and Europe, while estrogens the most abundant in Latin American, Caribbean States and Africa [74]. Table 2 summarizes detection results of different PhACs around the world. More specifically, a large screening study from A.C. Kondor et al. [75] examined the occurrence of 111 PhACs along the Hungarian section of the Danube River. The results showed occurrence of alkaloids (between 0.18 and 3400 ng/L), antipsychotics/antidepressants (between 0.16 and 64.7 ng/L), antiepileptics (between 0.81 and 498 ng/L), anxiolytics (between 0.02 and 45.07 ng/L), cardiovascular drugs (between 0.06 and 233 ng/L), hormones (between 0.10 and 9.82 ng/L), NSAID's (between 1.71 and 115 ng/L) and local anaesthetics (between 0.11 and 298 ng/L). In the same concentration ranges were the PhACs' occurrence results obtained from studies in USA [76], India [77], China [78], and Italy [79]. A study from Perreira et al. [15] showed that the range of PhACs concentrations observed in Portuguese rivers was significantly lower than others recorded in Europe, with detection frequencies of 27.8% and average (7.78–39.21 ng/L) and maximum (69.15 ng/L) concentration in the low ng/L levels.

In general, the most abundant pharmaceutical in the aquatic environment is diclofenac with its detection rates varying across the countries. More specifically, maximum concentrations of diclofenac in surface and groundwater samples were found to be 44 ng/L in Japan, 41.30 ng/L in India, 12.00 ng/L in Portugal, 4.20 ng/L in Danube River basin, 2550 ng/L in Germany, 470.00 ng/L in Poland, 50.00 ng/L in Netherlands, 700.00 ng/L in Finland, 30.06 ng/L in France and 17.00 ng/L in Italy. Another widely spread compound in the environment is caffeine. Different studies have reported its occurrence in raw water samples as well, with concentration ranges between 1.15–65.92 ng/L in Italy [18], 4-1080 ng/L in Nigeria [80], 1170-60,530 ng/L in South Africa [81]. Another study in California reported a maximum concentration of 290 ng/L of caffeine in groundwater [82].

Occurrence data of PhACs in different aquatic compartments can be affected by various factors during long-term monitoring assessments such as consumption trends and seasonal variations. A study by Lindholm-Lehto et al. [83] supports this assumption by presenting the occurrence of naproxen, ketoprofen, ibuprofen, diclofenac and carbamazepine in a lake in Finland, in higher concentrations during winter, while their detection rate was found to be higher in wastewater effluents from WWTPs in the same region during summer. Ebele et al. [80] focused on the determination of 28 compounds in surface and groundwater samples during different seasons in Lagos state, Nigeria. The results showed that the sum of PhACs' concentration was between 503 ng/L and 283.86 μg/L in surface water in the dry season and between 2480 and 29,803 ng/L during the rainy season, while for groundwater concentrations ranges were 130-6674 ng/L and 184-9141 ng/L during dry and rainy season, respectively. Furthermore, in a study by Patrolecco et al. [79] higher concentrations for carbamazepine, naproxen, diclofenac, ibuprofen and gemfilbrozil were detected during summer in river water upstream of an urban contamination site.

Another factor that may influence the concentrations of PhACs in the environment is the pandemics, as they increase the use of specific drugs for specific periods. After the COVID-19 pandemic, various studies reported sharp peaks in the increase of pharmaceuticals' concentrations around the world. More specifically, a study from Chen et al. [96] showed that five categories of drugs used against COVID-19 were detected in surface water (lakes and WWTP river estuary system) near hospitals in the city Wuhan (China), with their total amount ranging from 2.61 to 1122 ng/L. Another study by Castillo-Zacarías et al. [97] highlighted the fact that the COVID-19 pandemic will also affect the occurrence of antidepressants in the environment, as it increased depression and anxiety cases around the world, boosting in that way the use of medications to relieve their symptoms.

3.3. PhACs in treated/drinking water

The majority of countries rely on surface and groundwater for their drinking water needs. However, distribution of safe drinking water becomes a complex issue, as these sources are often contaminated with a variety of pollutants. Occurrence of PhACs has been reported in tap water around the world (Table 3), raising concerns about the health risks that these compounds can pose to humans after a lifelong exposure to contaminated water. It is considered that their presence in treated water is due to insufficient treatment in Drinking Water Treatment Plants (DWTPs) [95, 98].

Wu et al. [78] reported the occurrence of carbamazepine, amitriptyline, diazepam, ternazepam and alprazolam in treated samples but in concentrations significantly lower than those found in raw samples. The same results were confirmed from a study conducted in Portugal [15], which showed as well that pharmaceuticals even if detected in treated samples they had concentrations lower than their individual MDLs. Another study from Jiang et al. [95] reported the presence of 12 PPCPs in treated water from a DWTP in China, with caffeine and ketoprofen being the most abundant; these results were confirmed also from Papagiannaki et al. [18], who reported their detection alongside with ibuprofen and carbamazepine in treated samples from a DWTP in Italy. In most of the studies reporting occurrence of pharmaceuticals in drinking water, the detected concentrations are in trace level (few ng/L). However, Santos et al. [98] reported the existence of atorvastatin, betamethasone, fluconazole, gemfibrozil, loratadine and prednisone in treated water in Brazil, with maximum detected concentrations varying between 150 and 2800 ng/L. Even if the results are significantly higher than those reported in other counties, they are following the trends of other reports from the same area [88]. Different studies claim that the consumption trends in an area, and the compounds' hydrophilic behavior -which allows them to pass from the different stages of DWTPs- are mainly responsible for their occurrence in drinking water [18].

3.4. PhACs monitoring assessments

PhACs' monitoring assessments in the aquatic environment are mainly based on target chemical analyses of different compounds. In the last years, advances of the analytical techniques allowed the use of High Resolution Mass Spectrometry for identifying and detecting a vast variety of newly emerging compounds and their transformation products.

Practically this means that the combination of target, suspect and non-target screening analyses based on HRMS is able to detect simultaneously complex mixtures of a huge variety of substances at a high level of sensitivity, while identifying unknowns as well [38]. Complementary to chemical analyses, bioassays are increasingly used as bioanalytical tools for water quality assessments in order to measure the combined effects of trace-level mixtures of chemicals. Different biological tests, including cell models, receptors, tissues or small organisms can be used for measuring the effects of PhACs on various biological endpoints. Although bioassay data cannot be used for thorough risk assessments, they can identify the presence of one or more compounds that cause effects on biological battery tests relevant to human health and the environment [103, 104]. Moreover, as PhACs are detected in drinking water raising concerns about the adverse effects to human health, monitoring assessments started to also include a risk evaluation approach. More specifically, various studies have considered a human health or environmental risk assessment towards reassure the safe quality of water distributed to consumers. In general, the Risk Quotient (RQs) methodology is applied, which for human health risks evaluation is based on comparing PhACs' concentrations to guideline values, or when they don't exist to calculated provisional guideline value ((p)GLV) [105]. The pGLVs are calculated as the ratio between the Acceptable Daily water Intake (μg/kg bw/day), the body weight of a person (set at a default of 70 kg), a 10% allocation factor as drinking water is not the only exposure way for humans and the mean drinking water intake (L/day) [60, 91, 105]. For RQ values ≥ 1 there is the possibility of risk, if a lifelong exposure to the compound occurs only after drinking water consumption, while for RQ values $\leq$ 0,2 the risk for adverse human health effects is considered negligibly low [60, 105]. In all the studies, none of the PhACs detected in drinking water was linked with any human health risk [60, 75, 105]. Similarly, the environmental risks are assessed by calculating the RQ as a ration between the detected environmental concentration and the predicted no-effect concentration (PNEC). PNECs are calculated for both acute and chronic toxicity data, as the ratios between acute and chronic toxicity endpoints and assessment factors (AF) [106]. The combination of all these approaches, alongside with the use of modeling tools for identifying contamination hotspots [4], will provide water utilities with tools for more comprehensive and realistic monitoring assessments, and subsequently with information to help take decisions about abatement.

4. Technologies for the removal of PhACs

Due to their distinct low concentration, chemical properties (polarity, functional groups, solubility) and persistence, CECs and particularly PhACs are not or only partially removed by conventional wastewater treatment plants, Fig. 3 [107]. Consequently, as already said, their effluents are one major source of these substances in the environment [108–110]. The drinking water quality and safety, concerning CECs, strongly depends on the source of water contamination and drinking water treatment strategies applied. To improve the overall water quality and avoid potential negative ecological effects by CECs, different measures to reduce their discharge should be taken by upgrading the wastewater treatment plants; however, this topic is beyond the scope of this review. Drinking water treatment plants (DWTPs) have been progressively challenged to deal with the rising occurrence of CECs. Treatment processes can reduce or even completely remove these pollutants; however, it is highly dependent on the applied technologies, and the conventional treatment has shown largely inefficient.

4.1. Conventional drinking water treatment technologies

The conventional DWTPs apply a multi-step process to improve the drinking water quality, as represented in Fig. 3. During the conventional treatment, which usually includes coagulation/flocculation, filtration, and oxidation/disinfection processes (usually, chlorination), the concentration of these pollutants can remain relatively unaffected. Coagulation/flocculation removes the suspended solids by the addition of coagulants to change the electrostatic state of particles. As a result, it is ineffective in the CECs removal, as only those substances adsorbed to the suspended matter are removed [111, 112]. Nam et al. [111] investigated the coagulation process for the removal of four frequent PhACs: metoprolol, carbamazepine, caffeine and sulfamethoxazole. As summarized in Table 4, using polyaluminum chloride as coagulant, less than 60% of the sulfamethoxazole was removed, while only less than 20% of the remaining PhACs were eliminated. On is turn, Rigobello et al. [113] shown no impact of coagulation using aluminum sulfate on the concentration of diclofenac. On the contrary, Vieno et al. [112] reported interesting removal of diclofenac, ibuprofen, carbamazepine and sulfamethoxazole by adding ferric sulfate, although this was achieved at laboratory conditions difficult to apply in realistic DWTPs.

Filtration usually follows the sedimentation processes that are applied through different filter media such as sand, activated carbon and anthracite. The filtration is driven by the pore size, surface area and surface interaction to the selected media surface [114]. Su et al. [115] reported that sand filtration had a positive impact on the removal of 27 antibiotics (between 45–60%) in two different DWTPs, while, on the contrary, granular activated carbon increased the abundance of those substances on the final water. Activated carbon can be selectively efficient towards some pollutants depending on the carbon material and pollutants properties that may affect the adsorption (polarity, octanol-water coefficient). Recently, Kårelid et al. [116] proved that recirculating setups were able to significantly increase the removal by up to 97 - 99% of 21 of the most common PhACs using powdered activated carbon. Tröger et al. [117] compared seven DWTPs along the Göta Älv river in Sweden and concluded that those employing granulated active carbon filters were more effective (60%) than those applying a more conventional strategy (38%) for the removal of 8 PhCAs among 27 CECs. Additionally, Delgado et al. [118] reported the removal of greater than 85% of carbamazepine and sildenafil drugs using powdered activated carbon while Rigobello et al. [113] observed more than 99% of diclofenac removal by applying granular activated carbon after the oxidation with chlorine.

Chlorination is a cost-effective process typically applied as disinfection; however, it can also degrade organic molecules by the high oxidative potential of chlorine able to react with aromatic compounds. The excess use of chlorine is yet limited due to the production of harmful byproducts (e.g., trihalomethane, haloacetic acid, haloacetonitrile), also considered as emerging contaminants [119].

With the rising number CECs in environmental waters, these

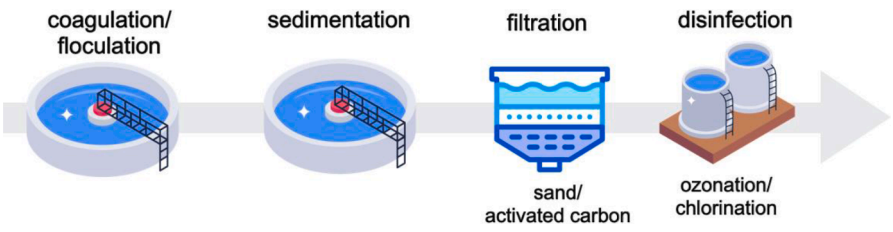

Fig. 3. Schematic representation of the conventional drinking water treatment plants.

Table 4
PhACs removal efficiency in drinking water by different treatment processes.

Treatment	Conditions	PhACs	Removal (%)	Ref.
Coagulation	polyaluminum chloride	metoprolol; carbamazepine; caffeine; sulfamethoxazole	<5; <20; <20; <60	[111]
Coagulation	ferric sulfate	diclofenac, ibuprofen, bezafibrate, carbamazepine and sulfamethoxazole	77; 50; 36; >99; >99	[112]
Coagulation	aluminum sulfate	diclofenac	< 0.5	[113]
Pre-ozonation; flocculation	ozone (0.4 to1.1 mg/L)	21 PhACs	avg.= 41.5	[122]
Adsorption	activated carbon	metoprolol; carbamazepine; caffeine; sulfamethoxazole	<20; 79.6; >80; >80	[111]
Filtration	powdered activated carbon	carbamazepine and sildenafil	>85	[118]
Filtration	powdered activated carbon (recirculated)	21 PhACs	> 97	[116]
Filtration	activated carbon filters	8 PhCAs	avg. = 60 5 of 8 > 80	[117]
Filtration	sand	27 antibiotics	45 – 60	[115]
Chlorination; filtration	chlorine; granular activated carbon	diclofenac	>99	[113]
Chlorination	NaOCl	metoprolol; carbamazepine; caffeine; sulfamethoxazole	<5; <5; <10; <55	[111]
Filtration; chlorination	granular activated carbon/sand; sodium hypochlorite	21 PhACs	Avg.= 10.3	[122]
Advanced Oxidation Processes				
Ozonation	ozone	metoprolol; carbamazepine; caffeine; sulfamethoxazole	30; >99; >99; >99	[111]
Ozonation; filtration	ozone (0.75 mg/L); biological activated carbon columns (Filtrasorb 400)	22 PhACs (avg. = 1.76 ng/L)	avg. > 85 13 of 22 > 95	[121]
Ozonation	ozone (0.5 to 0.9 mg)	21 PhACs	avg.= 54.1	[122]
UV based	UV (254 nm)	metoprolol; carbamazepine; caffeine; sulfamethoxazole	>20; >30; 85; >90	[111]
	UV/H_2O_2	metoprolol; carbamazepine; caffeine; sulfamethoxazole	>65; >75; >99; >99	[111]
	Cl_2/UV (254 nm)	metoprolol; carbamazepine; caffeine; sulfamethoxazole	>90; >95; >99; >99	[111]
	UV-LEC/ chlorine	diclofenac, caffeine	>85	[123]
	VUV (185/254 nm)	clotrimazole	>95	[124]
		sulfamethoxazole	>96	[141]
		oxytetracycline	>99	[125]
		sulfamethazine	>98	[142]
		amoxicillin	>80	[143]
		trimethoprim	>15	[144]
	VUV (185/254 nm)/Fe(II/III)	tetracycline	>95	[124]
	VUV (185/254 nm)/H_2O_2	trimethoprim	>98	[144]
	VUV (185/254 nm)/NaS_2O_8	trimethoprim	>98	[144]
Electrolysis	Anode: RuO_2/ $IrO_2 - TiO_2$; cathode: stainless-steel; 400 mA	metoprolol; carbamazepine; ciprofloxacin; trimethoprim	65; >98; >99; >99	[133]
	Cl_2/UV-electrolysis anode: RuO_2/ $IrO_2 - TiO_2$; cathode: stainless-steel; 400 mA	metoprolol; carbamazepine; ciprofloxacin; trimethoprim	>99; >99; >99; >99	[133]
Sonochemistry	1000 kHz	ibuprofen; sulfamethoxazole	85; 75	[140]
	20 kHz, 10 min	piroxicam	96	[145]
Membrane filtration				
NF/filtration	hollow fiber (X-Flow HFW1000)	32 PhACs	Avg. = 90	[101]
RO	low-pressure RO Thin-film composite ESPA2-LD-4040	7 polar PhACs	75–99	[146]
NF	tubular carbon nanofiber/ carbon/ alumina composite membrane	13 PhACs	Avg. = 45	[147]
Electrocoagulation/ electrofiltration; electro-NF	tubular carbon nanofiber/ carbon/ alumina composite membrane	13 PhACs	Avg. = 77	[147]

technologies proved to be ineffective at keeping the water safety and quality at acceptable levels. As an example, Ren et al. [120] investigated the removal of 291 CECs, including 108 PhACs from different therapeutic areas, on five DWTPs exploiting the current treatment processes, observed an average removal of only 25%. Focusing on the particular case of PhACs, they reported a 74 ± 49% removal which is still alarming considering that these substances are designed to be highly biologically active. Moreover, the authors found a positive correlation between the quality of the final drinking water and the source of water contamination. Therefore, more effective drinking water treatment tools are needed to constraint the exposure to CECs via drinking water, which can combine the advantages of the conventional approaches with innovative solutions.

4.2. Advanced oxidation processes

Advanced oxidation processes (AOPs) involve the generation of highly reactive species (mostly hydroxyl radicals, $^{\bullet}OH$, $E^{\circ} = 2.8$ V) able to degrade or even completely mineralize a wide range of chemical pollutants also at trace levels. During the last decades, many AOPs have been explored for water and wastewater remediation such as photolytic,

chemical, photochemical, physical, and photocatalytic processes. The application of many of these has been restricted to scientific purposes or for wastewater treatment due to some concerns regarding the safety of some materials and chemicals to be applied for drinking water treatment, for this reason in this review we are concentrating on those that are focused on drinking water treatment, as shown in Fig. 4. The most common AOPs applied for DW treatment are ozonation and UV based processes. Ozone is non-harmful and cost-effective used in drinking water treatment due to its disinfection and oxidation potential. Ozone can react with highly electronic dense molecules and is also able to generate $^{\bullet}OH$ radicals that can react with a large spectrum of pollutants. Ullberg et al. [121] investigated the incorporation of ozonation followed by filtration using biological activated carbon columns in a pilot-plant scale on the removal of 99 target CECs, of which 22 were PhACs from different therapeutic classes (pain killers, antipsychotics, anesthetics, hormones, beta-blockers, among others). Ozonation followed by adsorption showed high efficiency to remove most of the pollutants with an average of above 85%, thirteen of those being removed with more than 95%. This was significantly greater than the 30% removal in PhACs attained using the conventional approach. Moreover, the authors reinforced the role of using the combined technologies by analyzing the dissolved organic matter (DOM) elimination after ozonation. Despite the high degradation efficiency of CECs, it was observed a DOM decay of only 4% after the ozonation. However, the oxidation step boosted the DOM reduction by increasing their adsorption properties to the activated carbon. In parallel, in a study that followed 21 PhACs from different classes along with the different steps of a DWTP during one year, Padhye et al. [122] determined an overall average removal of 75.9%, assigning to the ozonation step the biggest contribution (54.1%), while flocculation and sedimentation removed 41.4%, and the filtration/chlorination represented a removal of 10.3%.

UV-based AOPs have also been applied not only for drinking water disinfection but also for the removal of pollutants, as a single process or combined with oxidizing agents to boost their ability to generate reactive species. Nam et al. [111] explored UV photolysis, UV/H_2O_2, and UV/chlorine for the removal of metoprolol, carbamazepine, caffeine and sulfamethoxazole, and compared them to ozonation. All the UV based systems showed a significantly higher pollutants removal rate when compared to the traditional technologies. Among those, the UV/chlorine reaction was the most effective removing all the pollutants with more than 90% efficiency, even more effective than ozonation, which was inefficient in removing metoprolol (30%). Likewise, Yin et al. [123] recently demonstrated that the use of combined UV-LED/chlorine enhanced the chlorine potential to remove diclofenac and caffeine. When combined with activated carbon the system was effective in removing the PhACs and their transformation products.

Vacuum UV (VUV), with UV radiation at a wavelength lower than 200 nm combined with 254 nm, is another oxidation process that allows the in-situ generation of reactive species, mainly hydroxyl radicals by direct water dissociation without any chemical addition. Recently, Gonçalves et al. [124] reported the removal of more than 50% removal of the persistent antifungal drug clotrimazole within just 1 min of VUV exposition in a continuous flow photoreactor, and more than 95% within 32 min. The authors also observed a high degree of total organic carbon removal combined with a substantial decrease in the toxicity towards non-target organisms. Likewise, Moradi et al. [141] showed that VUV was effective in mineralizing 98.5% of 100 mg/L sulfamethoxazole within 30 min of continuous exposition. When adding oxidative agents $S_2O_8^{2-}$, H_2O_2 and O_3 the antibiotic removal rate was substantially increased. Kim et al. [144] reported a poor removal of the highly persistent trimethoprim of only 15% within 30 min exposition of VUV, however, when adding H_2O_2 or NaS_2O_8 the drug was removed with more than 98% in the same period. Yan et al. [125] observed analogous oxytetracycline removal ability under VUV exposition compared with UV/H_2O_2. Even if both led to more than 99% of antibiotic degradation, the first revealed advantages by promoting the formation of fewer byproducts that can be potentially less harmful. Moreover, by assessing the energy efficiency of the VUV process, the authors highlighted the cost-competitiveness of this technology by estimating an electrical energy-per-order of only 0.209 kWh/m^3/order, substantially less than 10.0 kWh/m^3/order that is typically considered as cost-effective for an AOPs [126]. However, it was found heavily dependent on the reactor configuration, flow, turbulence and the mixing efficiency to improve the contact between the hydroxyl radical and the pollutants. The continuous progress on the VUV lamps and green energy, together with their high efficiency, without the addition of any chemicals, open the potential of VUV as a promising and sustainable solution for drinking water treatment. However, efforts should be focused on the scalability of continuous-flow reactors designed for the high flow and volumes required for the DWTPs.

With the dropping cost of renewable energy, the electrochemical oxidation process (EOP) is another AOPs that has attracted increased attention in recent years as an alternative to traditional methods. By using electricity as the main reactant to conduct the treatment process, the degradation occurs: *i)* via direct oxidation or electrolysis by direct charge transfer between the surface of the anode and the organic pollutants; *ii)* via indirect electrochemical oxidation by the in situ electrogenerated oxygen reactive species (mainly $^{\bullet}OH$) on the surface of an anode of the electrochemical cell, without the addition of auxiliary chemicals [127]. In the electrochemical process, the reactor configuration the nature of the electrode materials heavily impacts the efficiency of the process [128, 129]. Electrochemical can further improve the pollutants removal rates of well-developed water treatment methods such as coagulation, flocculation [130], photocatalysis [131] and

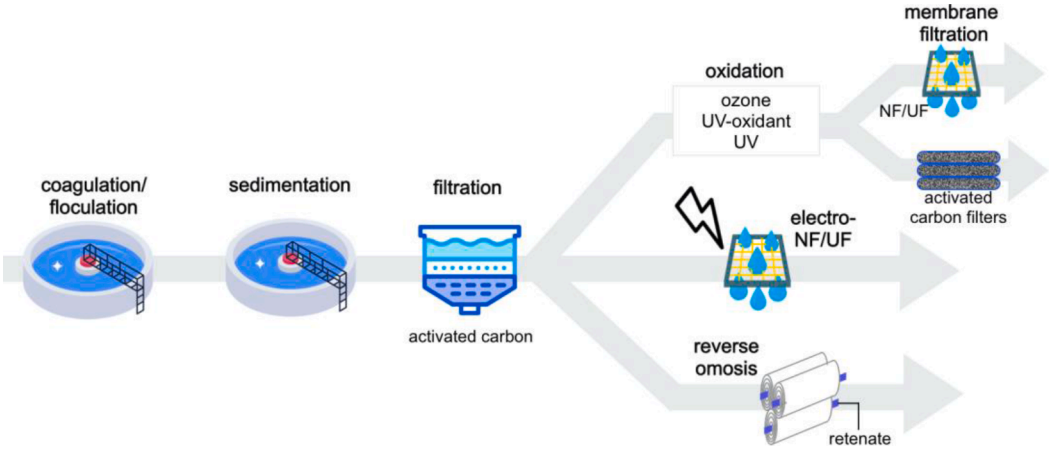

Fig. 4. Schematic representation of updated drinking water treatment plants incorporating treatment processes.

(photo)-Fenton [132], eliminating drawbacks and extending the applicability of existing electrochemical water treatment methods as well as improve cost-efficiency. As an example, Zhang et al. [133] explored electrolysis for the degradation of metoprolol, carbamazepine, ciprofloxacin and trimethoprim using $RuO_2/IrO_2 - TiO_2$ anode and stainless-steel cathode. More than 65% removal applying 400 mA for 10 min was achieved, while the complete removal was reached when applying the electrochemically driven UV-chlorine process. EOPs present enormous potential however, their application can still be limited because of lower energy efficiencies, ineffective in mineralization, as well as high investment and maintenance costs [134].

Sonolysis is one of the most recent oxidation processes, where the propagation of high-intensity ultrasound waves through water produces alternating cycles of positive and negative pressure generating bubbles (cavitation) with allow to produce $^{\bullet}OH$ and $^{\bullet}H$ from the pyrolysis of water. By applying power with a frequency usually between 200 and 400 kHz this " green" method allows the degradation of water pollutants without adding chemicals [135, 136]. For example, Mendez-Arriaga et al. [137] demonstrated the degradation of ibuprofen by ultrasound radiation at a frequency of 300 kHz and 80 W applied power promoted 98% removal of ibuprofen. The reactor configuration and the frequency are critical for the process efficiency, Al-Hamadan et al. [138] increased up to 1000 kHz to achieve 85% and 75% removal of ibuprofen and sulfamethoxazole, respectively. Likewise previous observed, higher removal rates can be achieved by combining ultrasounds with UV, photocatalysis, Fenton and ozonation [139] or even to prevent the membrane fouling [140]. Generally, sonochemistry has slow degradation rates and poor mineralizing ability at elevated economical costs of operation due to the high electrical energy consumption. From an industrial perspective, the developments in reactors design, scale-up, and ultrasonic transduction efficiency, for the pollutants removal at commercial scale are still needed to allow its adoption.

Despite the recognized AOPs effectiveness in removing several CECs, and in particular PhACs, questions remain regarding the formation and removal of their intermediates with unknown properties and harmful impacts. Therefore, it is important to combine the oxidation processes with filtration to ensure the reduction of their content.

4.3. Membrane filtration

Due to the recent advances on membrane technologies, membrane filtration has been progressively applied for the advanced treatment with a significant impact on DWTPs. Nanofiltration (NF), ultrafiltration (UF) and reverse osmosis (RO) systems are the most common in drinking water treatment for desalination or pollutants removal. During the water filtration, the water molecules permeate the membrane while pollutants are retained depending on their physical and chemical properties, through the pressure differential or electrical potential difference, as shown in Fig. 5. Tröger et al. [101] compared the efficiency of a conventional full-scale DWTP applying flocculation ($Al_2(SO_4)_3$), sand filter, granulated active carbon, and disinfection via UV/chloramine (NH_2Cl) with a pilot plant scale using nanofiltration plus granulated active carbon for the removal of 41 identified CECs, including 32 PhACs with different physicochemical properties (size, hydrophobicity, and polarity). The authors reported little or no impact on the concentration during conventional treatment, while in the case of the nanofiltration pilot plant was able to remove 90% on average. Albergamo et al. [146] reported the use of RO membrane for the removal of 7 polar PhACs among 27 other CECs, with removal rates ranging between 75–99%. A strong correlation concerning the physicochemical properties was also found, those with lower molecular weight were more capable to permeate the membrane especially at lower pressure. Moreover, NF and RO have been also reported to be effective in removing highly persistent perfluoroalkyl and polyfluoroalkyl pollutants, the so-called forever chemicals, that are poorly affected by the conventional methods or AOPs [148, 149].

One of the main limitations of membrane filtration is related to the folding effect resulted from the interaction of organic molecules, inorganic salts, and microorganisms with the membrane surface that reduces the performance and shortens membrane lifetime. These challenges have prompted the development of different strategies to prevent the folding, which can involve the modification of the membrane surface [150], combination with AOPs [151, 152] or through the application of an electric field (electrified membranes - EMs). The electric field prevents the formation of a surface cake that keeps its permeate flux, while allows the pollutants removal and water disinfection [153]. Yang et al. [147] observed an improvement from 45% (without electric field) up to 77% on the removal of thirteen PhACs by applying electrocoagulation followed by electro-filtration using an alumina composite membrane. However, this process is still not cost-effective comparing with the classic membrane filtration due to the energy consumption. More recently, 3D printed membranes are pointed to open new perspectives to water treatment technologies. Critical factors such as fouling resistance, selectivity and water permeability can be controlled by the assistance of bespoke and precise 3D printing fabrication. It also allows flexible and customized designs and speed up product commercialization at lower costs [154–156]. Yet, the membrane filtration is pressure driven (Fig. 5) with consequent impact on the overall cost treatment of the process due to the energy consumption.

Innovative technologies represent a new opportunity for water safety and quality, nevertheless, the great challenge is to find a compromise

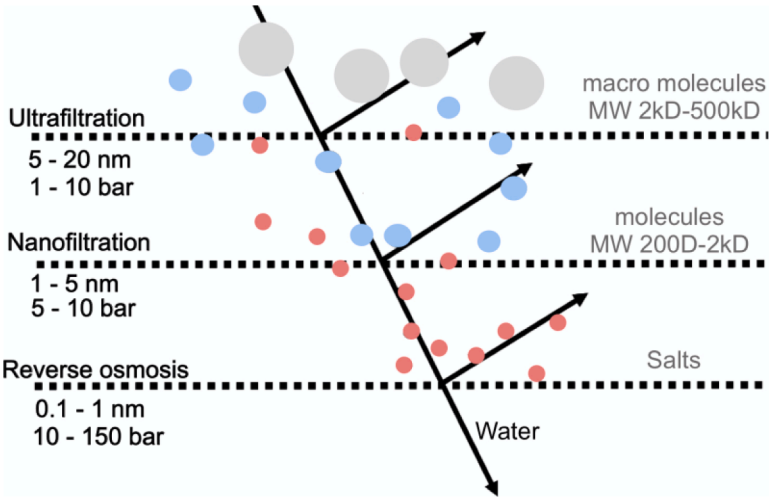

Fig. 5. Principles of membrane filtration. Pof the different Scheme of the conventional drinking water treatment plant.

between efficiency and economic feasibility. The complex nature of CECs, the variability of the water source and their impact on the final water is a challenge for the regulatory agencies, the scientific community and DWTPs. The update of the DWTPs through the combination of conventional and innovative technologies can considerably reduce the occurrence of harmful substances on our drinking water. Therefore, it is crucial not only to advance the DWTPs to deal with the rising concern of CECs but also to reduce their release into the environment by updating the wastewater treatment plants.

5. Conclusion and future needs

This review has briefly demonstrated the trends in analytical methods based on LC-MS, highlighting that an increasing number of studies in the last decade has reported the development of new analytical techniques achieving extremely low quantification levels for a vast variety of pharmaceuticals. However, they mainly focus on target analyses of parent compounds, failing in this way to report the existence of a compound's transformation products and subsequently evaluate the holistic quality status of the different water compartments. Although the development and improvement of analytical methods over the last decade have demonstrated the enhanced potential of determining very low concentrations of PhACs in a variety of water matrices, there is still a knowledge gap that needs to be addressed in future research.

The occurrence and fate of several "less investigated" PhACs, as well as the coexistence of a large, complicated mixture of them is lacking. As more and more new pharmaceuticals are entering the market every day, and their use is continuously increasing, improving monitoring assessments with an emphasis on the documentation of PhACs that are less studied in the literature is vital. Furthermore, the occurrence and fate studies of PhACs should not be limited to the parent compounds but should include their metabolites and transformation products. Additionally, exhaustive studies involving a variety of matrices such as wastewater, freshwater, and seawater are important to have a better understanding of the pathways contributing to biota and the food chain. Despite the large number of publications in this field confirming the detection of PhACs and some TPs, even in drinking water due to insufficient treatment methods used in DWTPs, the potential effects of long-term exposure to low concentrations on human health are not well understood. Moreover, little is still known about the synergistic effects of their mixtures, and their adverse environmental effects such as toxicity and bioaccumulation in organisms.

Therefore, there is a need for future research and great attention should be given to the development of highly sensitive and robust multiresidue analytical methods for the determination of PhACs, their metabolites, and TPs in various aquatic environments. This should be explored further, with a particular emphasis on the development of multiresidue methods that are convenient to apply in routine analysis. Thus, further research concentrating on the application of on-line coupling, automatic and semiautomatic methods, as well as the use of novel and more selective sample preparation approaches, is critical. In parallel, the development of advanced analytical methods based on a combination of target and non-target analyses will achieve a better understanding of their complex chemical mixtures. An important aspect in this regard is that analytical methods should be standardized to allow comparisons not just among different studies and water compartments, but also with PhACs concentrations in biota and the food chain.

Expanding monitoring assessments will contribute to evaluate their rates globally, while using modeling methods in order to identify contamination "hotspots" areas will provide the water sector with smart tools for more realistic monitoring. Moreover, combination of chemical analyses with risks evaluation and bioassays are fundamental for understanding the effects of PhACs on human health and ecosystems. Finally, more efficient and cost-effective remediation methods are necessary to be implemented both in WWTPs – for reducing as much as possible PhACs release – and DWTPs – for reassuring good drinking water quality. Advanced oxidation processes, such as UV based process, chemical oxidation, electrolysis and membrane filtration represent some very promising techniques, although with an impact on the process cost, while their combination with conventional methods can be a vital solution for water companies. Investigations should be focused on the optimization, engineering, reactors development and scale-up of those hybrid methodologies to meet the rising requirements of sustainable drinking water.

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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