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Pharmaceuticals and personal care products (PPCPs) in the freshwater aquatic environment

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ABSTRACT

Pharmaceuticals and personal care products (PPCPs) are a unique group of emerging environmental contaminants, due to their inherent ability to induce physiological effects in human at low doses. An increasing number of studies has confirmed the presence of various PPCPs in different environmental compartments, which raises concerns about the potential adverse effects to humans and wildlife. Therefore, this article reviews the current state-of-knowledge on PPCPs in the freshwater aquatic environment. The environmental risk posed by these contaminants is evaluated in light of the persistence, bioaccumulation and toxicity criteria. Available literature on the sources, transport and degradation of PPCPs in the aquatic environment are evaluated, followed by a comprehensive review of the reported concentrations of different PPCP groups in the freshwater aquatic environment (water, sediment and biota) of the five continents. Finally, future perspectives for research on PPCPs in the freshwater aquatic environment are discussed in light of the identified research gaps in current knowledge.

1. Introduction

Pharmaceuticals are defined as prescription, over the counter and veterinary therapeutic drugs used to prevent or treat human and animal diseases, while personal care products (PCPs) are used mainly to improve the quality of daily life [16]. Over the past few years, there has been increasing awareness of the unintentional presence of PPCPs in various compartments of the aquatic environment (e.g. water, sediments and biota) at concentrations capable of causing detrimental effects to the aquatic organisms. This has become a major concern because PPCPs are extensively and increasingly used in human and veterinary medicine, resulting in their continuous release to the environment [119]. Priority pollutant lists have been developed both by the European Union (EU) and the United States Environmental Protection Agency (USEPA) identifying a wide variety of chemicals present in wastewaters and storm water runoff that may pose a threat to receiving water bodies including surface water. In the year 2000, an initial list of 33 priority substances was also identified under the EU Water Framework Directive (WFD) 2000/60/EC to be used as a control measure for the next 20 years. In 2007, PPCPs such as diclofenac, iopamidol, musks and carbamazepine were identified as future emerging priority candidates. Ibuprofen, clofibric acid, triclosan, phthalates and bisphenol A are proposed additions to this list [45].

Due to their large number and diverse chemical nature of PPCPs, the Environment Agency (EA) of England and Wales proposed a ranking system for these chemicals according to their perceived relative risk, with the aim of identifying substances with great potential to pose a risk to the aquatic environment. This ranking system used a combination of traditional risk assessment procedures, persistence, bioaccumulation and toxicity (PBT) criteria, occurrence data from various countries, availability of suitable analytical methods, and aimed to include compounds representative of different therapeutic classes. Based on this procedure, the top 10 compounds were: Lofepramine, Dextropropoxyphene, Procyclidine, Tramadol, Paracetamol, Clotrimazole, Thioridazine, Mebeverine, Aminophylline, and Tamoxifen [6]. In a similar exercise, using the OSPAR selection and prioritisation mechanism for hazardous substances (DYNAMEC), an alternative list of priority substances was identified, including: Lofepramine, Dextropropoxyphene, Procyclidine, Tramadol, Paracetamol, Clotrimazole,

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Thioridazine, Mebeverine, Aminophylline, Tamoxifen, Fluoxetine, Trimethoprim, Sulfamethoxazole, Fenofibrate1, and Diclofenac (OSPAR Commission, 2002 [188]).

Since then, several studies have investigated concentrations of these priority and related PPCPs in the fresh water aquatic environment. This paper aims to: (a) provide an overview of the environmental risk associated with PPCPs; (b) discuss the environmental fate and behaviour of PPCPs in the aquatic system; (c) review the current state-of-knowledge on the levels and trends of PPCPs in various compartments of the fresh water environment; and (d) discuss the current research gaps and provide recommendations for future research.

1.1. Environmental risk of PPCPs

The detection of chemical compounds in any environmental matrix does not necessarily mean that it is of concern or may cause harm. However, major concerns arise from the detection of chemicals for which there is evidence that they may adversely affect aquatic life [164]. The following sections summarise some of the major concerns about the presence of PPCPs in the freshwater aquatic environment.

1.1.1. Persistence

The physicochemical properties of many PPCPs, means that many are not easily removed by conventional water treatment processes, as demonstrated by their presence in drinking water [147]. The inability to effect complete removal of PPCPs from waste treatment plant poses a potential risk to aquatic organisms and public health. The overwhelming evidence from monitoring studies is that PPCPs have found their way into the aquatic environment and are ubiquitous [21]. The extensive nature of global PPCPs use, coupled with the escalating introduction of new pharmaceuticals to the market is contributing substantially to the environmental presence of these chemicals and their active metabolites in the aquatic environment [40]. Moreover, while not all PPCPs are persistent, their continuous use and release to the environment means many are considered “pseudo-persistent”. Pseudo-persistent pharmaceuticals are suggested to have greater potential for environmental persistence than other organic contaminants like pesticides, because their source continually replenishes even when acted on by environmental processes such as biodegradation, photodegradation and particulate sorption. Hence, pharmaceuticals that may degrade would eventually and effectively behave as persistent compounds because of their constant release into the environment [76]. Loffler et al. categorised 10 pharmaceuticals and pharmaceutical metabolites into low, moderate and high persistence compounds according to their dissipation time (DT50) in water/sediment samples. Paracetamol, Ibuprofen, 2-hyroxyibuprofen and CBZ-diol were classed as showing low persistent (DT50 = 3.1-7 days), Oxazepam, Iopromide and Ivermectin were deemed moderately persistent (DT50 = 15-54 days) while Clofibric acid, Diazepam, Carbamazepine were rated highly persistent (DT50 = 119-328 days) [101]. A more recent study demonstrated the anxiolytic drug (Oxazepam) to display extended persistence in freshwater lakes due to past input and growing urban population [89].

1.1.2. Bioaccumulation

Although PPCPs are detected in the freshwater environment at relatively low concentrations, many of them and their metabolites are biologically active and can impact non-target aquatic organisms. Several studies have examined the effect of PPCPs on non-target organisms especially fish. The exposure of goldfish (*Carassius auratus*) to waterborne gemfibrozil at an environmentally relevant concentration over 14 days resulted in a plasma bioconcentration factor of 113 [114]. Another study by Ref. [160], revealed bioaccumulation of the antiepileptic drug carbamazapine (CBZ) by algae - *Pseudokirchneriella subcapitata* and the crustacean - *Thamnocephalus platyurus* with bioaccumulation factors of 2.2 and 12.6 respectively. Furthermore [161], reported the uptake and depuration of pharmaceuticals in reclaimed water by mosquito fish (*Gambusia holbrooki*). The bioaccumulation factors measured for caffeine, diphenhydramine, diltrazem, carbamazepine and ibuprofen were 2.0, 16, 16, 1.4, and 28 respectively. Oxazepam was detected at high concentrations in Eurasian perch fish with a bioaccumulation factor of 12 [19]. Also [43] revealed the accumulation of fluoxetine in snails with the bioaccumulation factor of 3000 [42]. monitored 145 PPCPs in wild and caged mussels from the Grand River, Ontario. Forty-three pharmaceuticals from different classes were detected in mussel tissues, with bioaccumulation factors ranging from 0.66 for metformin to 32 022 for sertraline.

As distinct from pharmaceuticals, PCPs have been detected in algae which comprise the greatest abundance of plant biomass in the aquatic environment. The lipid content of algae provides an entry point for trophic transfer of lipophilic organic contaminants. A study conducted by Ref. [38] detected the presence of two widely used antimicrobial agents – triclocarban (TCC), triclosan (TCS) as well as its metabolite methyl-triclosan (M-TCS) in algae samples collected around a wastewater treatment plant (WWTP) in Texas. Concentrations of target PCPs in water samples were low ranging from 50 to 200 ng/L, while higher levels of 50–400 ng/g fresh weight were detected in algae. The resulting bioaccumulation factors ranged from (700–1500), (900–2100) and (1600–2700) for M-TCS, TCS and TCC respectively.

1.1.3. Toxicity

The major concern about the toxic implications of pharmaceuticals (c.f. persistent organic pollutants such as PCBs (polychlorinated biphenyls), PFASs (perfluoroalkyl substances) and PBDEs (polybrominated diphenyl ethers)) is that they were designed specifically to maximise their biological activity at low doses and to target certain metabolic, enzymatic, or cell-signalling mechanisms. The evolutionary conservation of these molecular targets in a given species potentially increases the possibility that these pharmaceuticals will be pharmacologically active in non-target organisms. This mode of action (MoA) concept can be applied to all aquatic biota, which are unintentionally exposed to pharmaceuticals in their natural environment, thus raising the risk of ecotoxicological effects [46]. The MoA conceptual frame work was tested using the anti-depressant agent Fluoxetine, which targets the serotonin (5-HT) signaling pathway. Because 5-HT is a high-tier physiological controller in aquatic organisms, alterations of the 5-HT pathway by fluoxetine had many adverse outcomes on key physiological functions, including reproduction, metabolism and locomotion in mussels at concentrations approaching or even below environmental levels [60,61]. A major concern raised by the presence of PPCPs in the aquatic environment is their ability to interfere with the endocrine system to produce undesired effects/disruption of homeostasis. The World Health Organization (WHO) defined endocrine disruptors (ED) as ‘exogenous substance or mixture that alters function(s) of the endocrine system and consequently causes adverse health effects in an organism, its progeny or sub-population’. EDs include a vast group of chemicals from natural (e.g. mycotoxins and phytoestrogens) and synthetic origin (e.g. diethylstilbesterol (DES) and Bisphenol A) in varieties of consumer products (e.g. PPCPs, cleaning products, antimicrobials, food preservatives and phthalates) [166]. Endocrine disrupting pharmaceuticals include sex hormones, glucocorticoids, veterinary growth hormones and few non-steroidal pharmaceutical

substances (Fig. 1). Furthermore, toxicity arising from complex mixtures of PPCPs at low concentrations could lead to synergistic interactions. This means that while individual PPCPs may be present at low concentrations that do not elicit significant toxic effects when acting singly; PPCP mixtures can still exert considerable ecotoxicity. This was demonstrated by Ref. [35]; whereby the antiepileptic drug – carbamazepine and the lipid lowering agent clofibric acid (both belonging to different therapeutic classes) exhibited much stronger effects to *Daphnia magna* than single compounds at the same concentration [154]. also revealed that the mixture effect of estradiol (E2) and 4-tert-nonylphenol (NP) can give an additive/synergistic reaction, and consequently induce vitellogenin production in juvenile rainbow trout. A study on the brown trout, a salmonid species native to German rivers, investigated the effect of diclofenac, one of the most prevalent pharmaceuticals in surface water. Results revealed that water-borne diclofenac at levels of 5–50 μg/L affects kidney and gill integrity and selected immune parameters in the fish [75]. A laboratory and field study conducted in France revealed that exposure to 17β-estradiol on a freshwater fish; chub (*Leuciscus cephalus*) resulted in a significant and rapid increase in plasma vitellogenin (Vtg) in both male and female chub [58]. Mimeault et al. also demonstrated that exposure to waterborne gemfibrozil on goldfish (*Carssius auratus*) resulted in reduction on plasma testosterone by over 50% after 14 days [114].

Another important concern related to the presence of PPCPs in the environment is the potential creation of antibiotic resistant strains in natural bacterial populations. Extensive use of antibiotics in human medicine and animal husbandry is the major cause for the emergence and spread of antibiotic resistant bacteria, which has become a threat to the effective prevention and treatment of various infectious diseases caused by antibiotic-resistant pathogenic bacteria [164]. Six antibiotics (ciprofloxacin, tetracycline, ampicillin, trimethoprim, erythromycin and trimethoprim/sulphamethoxazole) detected in the effluent of a WWTP in Australia increased the resistance of 2 natural bacterial strains found in the receiving waters [39]. Positive correlations have been found between antibiotic-resistant microorganisms and trace concentrations of aquatic antibiotic contaminants [120]. Furthermore, the presence of antibiotics could have a detrimental effect on naturally occurring bacteria present in the environment. Specifically [41], showed that even at sub-inhibitory concentrations, antibiotics may still exert their biological impact on natural microbial communities by influencing transcription in microbes. Some studies have reported adverse effects on aquatic organisms including: toxicity of ciprofloxacin to green algae [68], toxicity of oxolinic acid (a commonly used feed additive in fish farms) to *Daphnia magna*, as well as the toxicity of fluoroquinolone antibiotics (ciprofloxacin,

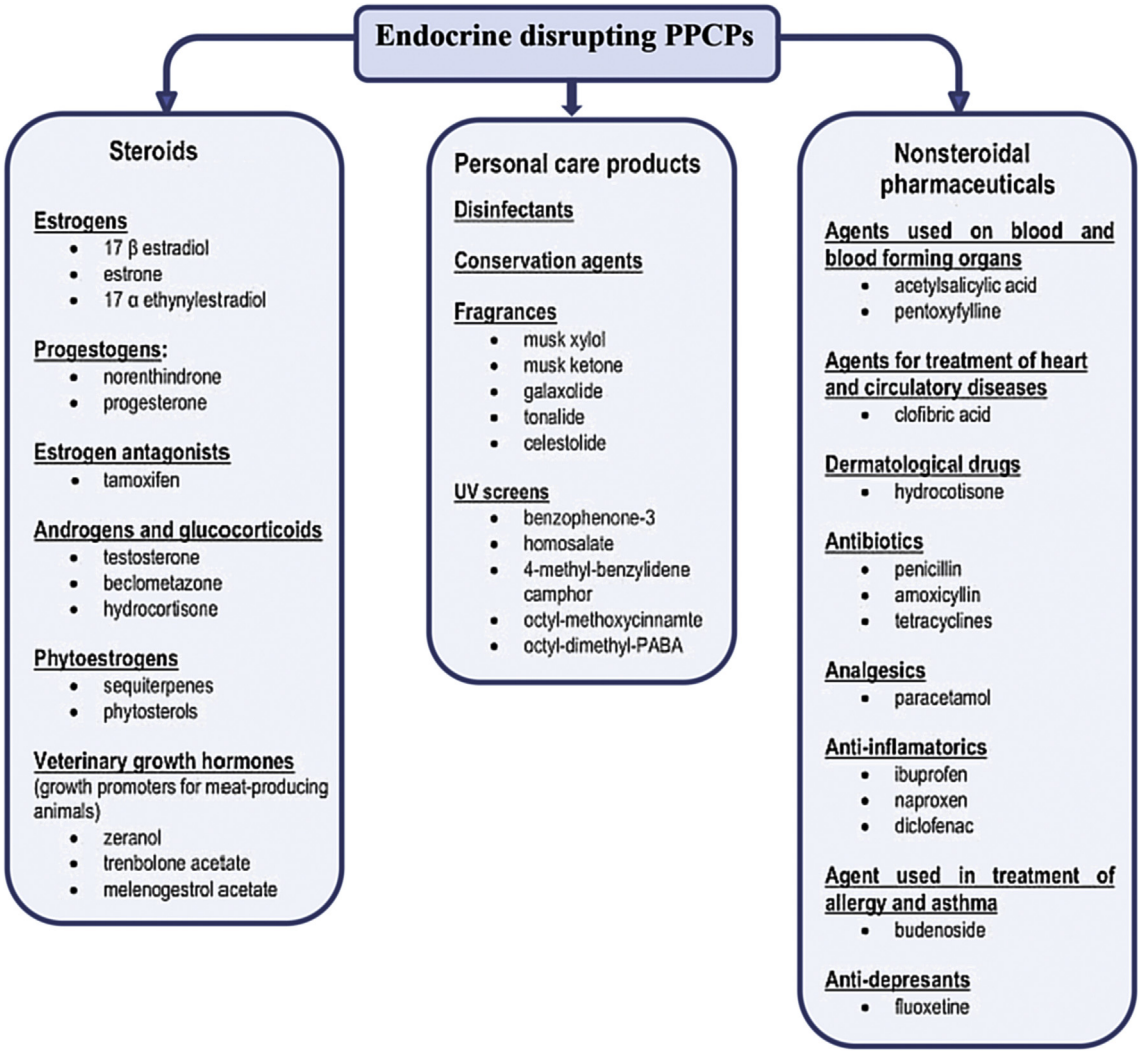

Fig. 1. Summary of endocrine disrupting PPCPs.

lomefloxacin, ofloxacin, levofloxacin, enrofloxacin and flumequine) on five aquatic organisms, the cynobacterium; *Microcystis aeruginosa*, duckweed; *Lemna minor*, the green alga; *Pseudokirchneriella subcapitata*, the crustacean; *Daphnia magna* and fathead minnow; *Pimephales promelas* [139].

Overall, the toxicity of PPCPs in the aquatic environment extends beyond the acute effects observed when therapeutic levels are reached or exceeded. Recent studies have shown PPCP toxicity to vary depending on the exposed organism, duration of exposure, contaminant concentration, and developmental window at which exposure occurs. Moreover, the effects of chronic trace-level exposure, especially at certain sensitive stages of development, are more likely to explain observed abnormalities within exposed non-target organisms than acute high dose exposure [167]. As many pharmaceutical contaminants are environmentally introduced after human or veterinary use, metabolite concentrations may be more significant than that of parent compounds. For instance, some acetylated metabolites of antibiotics (such as N4-acetylsulfapyridine) were found to be more toxic than the parent compound (sulfapyridine) in algae [62]. In addition, the presence of active pharmaceutical agents under undesirable conditions in the aquatic environment may alter their toxicological properties. To illustrate, the photodegradation products of naproxen were reported to have more toxic effects than the parent compound on algae, rotifers, and microcrustaceans [82]. Acidic pharmaceutical compounds may elicit different toxicological responses at different pH levels in exposed non-target organisms [50] and metals shown to accumulate in river biofilms have been shown to increase the toxicity of certain antibiotic contaminants (fluoroquinolones and tetracyclines) in an additive manner [182].

1.2. Environmental fate and behaviour of PPCPs

1.2.1. Sources

Post-use, many PPCPs find their way into the environment through different routes (Fig. 2). The major sources of PPCPs to the environment are via sewage treatment plants (STPs) [40], WWTPs, and landfill leaching. PPCPs are often not completely and consistently removed during conventional wastewater treatment processes, and thus are frequently detectable in reclaimed surface water at concentrations ranging from ng/L to μg/L [30]. The contamination of the freshwater environment with pharmaceuticals can occur in various ways – an important pathway is absorption of PPCPs by the body following therapeutic use, followed by excretion and release into the sewage system or septic tank. After treatment of sewage, the wastewater may be used for irrigation with the biosolids (treated sludge) potentially applied as fertilizer to agricultural land [178]. Another source of PPCPs to the environment is via their manufacture as the wastewater from the production facility goes directly into STPs [57]. After treatment, the sludge is deposited on the soil as fertilizer, with the liquid effluent discharged directly into the freshwater environment. In addition, PPCPs can reach the groundwater through leaching from the soil and this could pose a threat to drinking water. Not only that, pharmaceuticals can also reach freshwater through run-off from land treated with digested sludge for agricultural purposes [119]. Veterinary drugs are released into the environment when animal wastes either in solid or liquid states are sprayed on agricultural field as fertilizers. These veterinary drugs together with their metabolites pollute the soil and could enter the food chain. Consequently, agricultural run-off can enter freshwater systems and leach to groundwater [49]. Furthermore, externally applied PCPs are mostly discharged through shower waste, bathing, swimming and washing sinks. They can pass through WWTPs, and reach the

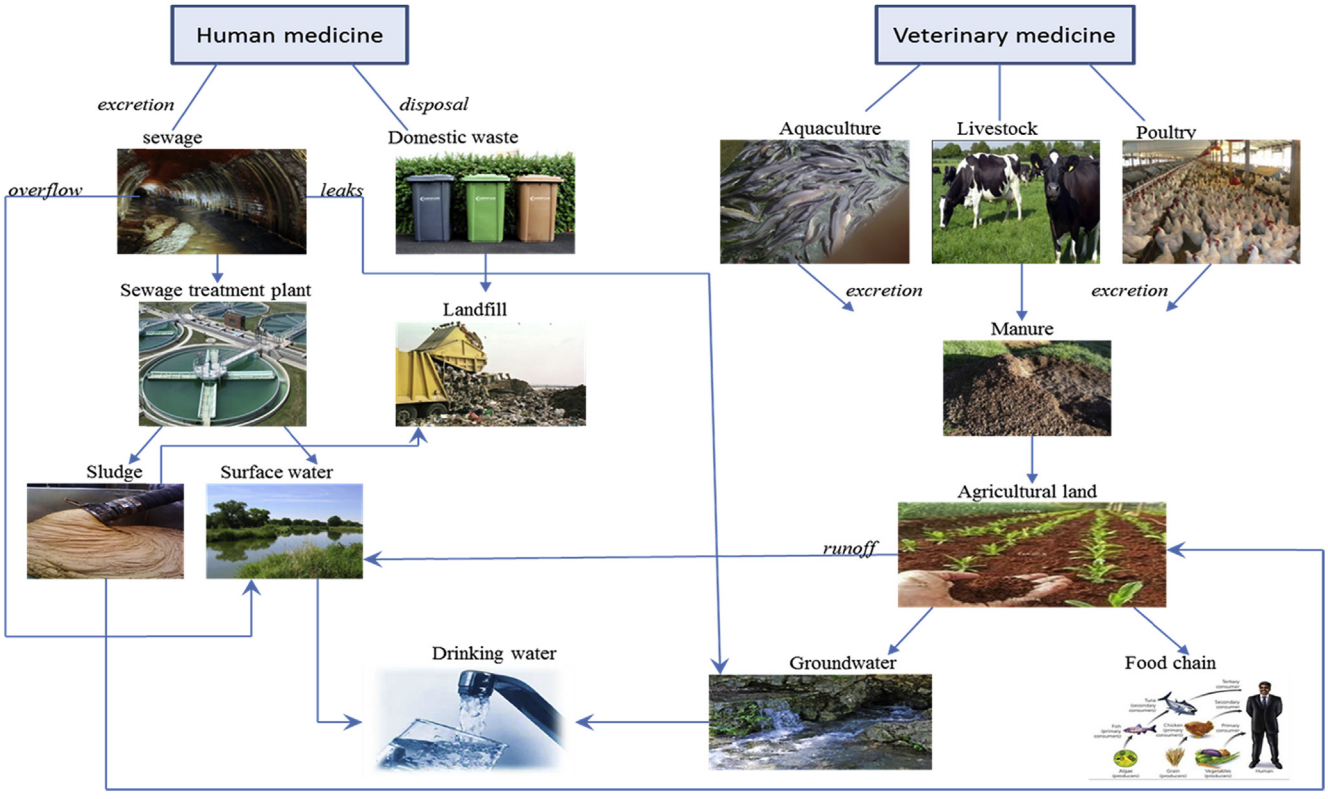

Fig. 2. Illustration of sources of environmental contamination with PPCPs.

environment [128] (Fig. 2).

1.2.2. Transport

Once released into the environment, there is possibility of long range transport of some PPCPs depending on the physicochemical properties of the compound and the characteristics of the receiving environment. PPCPs generally have low volatility and are highly polar and hydrophilic in nature; therefore their distribution through the environment will primarily occur through aqueous transport and food chain dispersal [26]. Transport of PPCPs between different environmental media depends on the sorption behaviour of the compound in treatment plants, soil, and the water-sediment system [17]. Several groups of PPCPs can be found in sludge samples of STPs through adsorption. This creates a potential pathway for PPCPs into the environment by direct release or application of sludge to agricultural land as fertilizer [156]. A study observed that PPCPs were transported into groundwater when biosolids were applied onto agricultural land [70] as well as fields irrigated with treated wastewater [129]. This resulted in the uptake of PPCPs by crops, which may constitute a potential pathway of human exposure to PPCPs through dietary intake [170,171]. Runoff from biosolids containing PPCPs either from landfills or applied on agricultural land may be transported into the surrounding surface water or leach into the groundwater [90], thereby posing a risk to aquatic life and public health. Sorption in sediment is another mechanism through which PPCPs are transported to the aquatic environment. The sediment acts as a sink and accumulates these environmental contaminants which may be released back to the aquatic environment [183]. Several studies have shown some PPCPs (e.g. sulfamethoxazole, carbamazepine, triclosan and ciprofloxacin) to be more persistent in sediment than water [31,36]. Osenbruck et al. identified local river water infiltration, sewer exfiltration, and urban stormwater recharge as the major sources of carbamazepine, galaxolide, and bisphenol A in groundwater underlying the city of Halle (Saale), Germany [126].

Nevertheless, the fact that adsorption to sediment or suspended solids may influence concentrations of PPCPs in receiving water does not necessarily result in a reduction of their bioavailability or toxicity. Several studies have reported accumulation of PPCPs in different environmental compartments including sediments [8,29,145]. Therefore, there exists the possibility of continuous release of these chemical compounds from sediments to overlying water. This may have adverse effects on benthic organisms that are continuously exposed to these chemicals within the sediments, interstitial water and in overlying water [66]. Tamura et al. estimated the combined contribution of triclosan, triclocarban and galaxolide to total river sediment toxicity to be as high as 8.2% using the benthic organism, *Chironomus yoshimatsui* [151]. Further understanding of the toxicological impacts of PPCPs in freshwater sediments appears imperative as sediment acts as a sink for these chemicals.

1.3. Environmental degradation and transformation

Biodegradation, photodegradation and other abiotic transformation processes such as hydrolysis [14], may reduce concentrations of PPCPs in the environment and result in partial loss and mineralization of these compounds [3].

The extent of photodegradation depends on the intensity of solar irradiation, water depth, organic matter composition, eutrophic conditions, latitude and seasonality. A study conducted by Ref. [32]; revealed that under artificial estuarine water condition, a photodegradation product of carbamazepine is acridine. This metabolite has shown to be toxic, mutagenic and carcinogenic. Another study suggested that tetracycline, an antibiotic used widely for animal husbandry, cannot be photodegraded because of its adsorption onto sediment [155]. However, the analgesic diclofenac could be easily and rapidly degraded through direct photolysis with a (pseudo) first-order elimination rate and a short half-life of <1 h [23] [140]. reported 11–68% of propranolol was removed by photodegradation in US rivers and predicted removal of up to 27% in the River Aire, UK, during the summer. Similar results were reported for Ibuprofen, Metronidazole, Acetaminophen and several other PPCPs, suggesting photolysis as one of the major degradation pathways of PPCPs in surface waters [15,27].

Biodegradation stems from the reaction with natural microbial flora in the environment. Many PPCPs undergo microbial mediated reactions during WWT processes [72] and in the environment, resulting in the formation of transformation products. Oenesois et al. provided a comprehensive review on biodegradation and removal of PPCPs in treatment systems. They concluded that accurately predicting biodegradability based on a PPCP's intended function may not be possible. Since biodegradation involves enzymatic reactions specific to chemical structures, the biodegradability of PPCPs with different structures grouped in the same therapeutic class is expected to vary, thwarting efforts to observe general trends [125]. Microorganisms that utilize PPCP substrates at certain concentration either as a carbon or energy source would be expected to increase in microbial growth and thereby resulting in further degradation of PPCPs. However, the increase in PPCP concentrations could inhibit biodegradation, therefore becoming toxic to the natural occurring microorganisms. Despite an initial increasing trend of degradation up to concentrations of 100 μg/L; none of the studied PPCPs including 4-isopropyl-3-methylphenol (biosol), p-chloro-m-xylenol, gemfibrozil, ketoprofen, and phenytoin achieved their highest degradation at the highest respective concentration of 1000 μg/L, thereby suggesting enzyme saturation at such high concentrations [124].

During waste water treatment (WWT), transformation of PPCPs may occur depending on the physicochemical properties of the compound and the conditions of the WWT. During the process, PPCPs may be completely destroyed, or partially transformed to metabolites or in some instances left unchanged [172]. It is important to bear in mind that the breakdown or removal of the parent compounds during WWT does not necessarily mean the removal of toxicity, it is expected that a great number of transformation products with unknown toxicity and persistence may still be present in the final effluent as well as in receiving water bodies [80]. Typical examples of the transformation of pharmaceuticals are presented below for the anti-inflammatory/analgesic ibuprofen, the X-ray contrast media diatrizole and an antihypertensive drug (valsartan).

[187] used a biofilm reactor (BFR) and batch experiment with activated sludge (BAS) to study the transformation of ibuprofen. The result revealed hydroxyibuprofen (OH-Ibu) to be the major metabolite of ibuprofen under oxic conditions and carboxyhyratropic acid (CA-HA) under anoxic conditions. Moreover, carboxyibuprofen (CA-Ibu) was identified as a major metabolite under both oxic and anoxic conditions. These transformation products either generated by human metabolism or by microorganisms present in the WWTPs and in the natural environment may increase the probability of their environmental presence [51].

In contrast to ibuprofen, diatrizole does not metabolize and is excreted unchanged. In WWTPs, it has been shown to be persistent under aerobic conditions. Therefore, diatrizole has been detected at elevated concentrations in the effluents of WWTPs, surface water, groundwater and even in finished drinking water [136].

[72] reported on the transformation of valsartan. The transformation products formed followed a sequence of transformation steps. The first reaction was an N-dealkyation reaction, yielding

dealkylated valsartan. This transformation product further transformed to amino-valsartan by an amide hydrolysis reaction and subsequently another transformation product was formed [2'-(1H-tetrazol-5-yl)biphenyl-4-yl]acetaldehyde (otherwise referred to as valsartan acid), through the hydrolysis and oxidation of amino-valsartan. These transformation products were suggested to provide the rationale for the environmental persistence of valsartan.

1.4. PPCPs in the freshwater aquatic environment

The environmental occurrence of pharmaceuticals was first reported in Kansas City, US in 1976, where clofibric acid was detected in treated wastewater at concentrations ranging from 0.8 to 2 μg/L [50]. Subsequently [137], investigated the presence of 25 pharmaceuticals in the river Lee (a source of potable water for North London) with concentrations up to 1 μg/L in 1981. Since then, several studies have detected PPCPs in different environmental compartments across the globe [74,92,134]. Despite the fact that reported concentrations of these PPCPs are low; many of them have the potential to persist in the natural environment for months to years [16]. The detection of pharmaceuticals in the environment varies not only between countries but also between different regions of the same country. That is to say, detectable pharmaceuticals in one country or region may not appear in other countries/regions where they are not highly prescribed [83]. This precludes meaningful global comparison of PPCPs levels due to variations of the targeted compounds and detected chemicals in each reported study. For instance, we compared the reported concentrations of NSAIDs in surface water from different countries (Fig. 3). While this figure may provide indicative information on the global contamination levels, it should be studied carefully because studies from different countries have targeted and/or detected different members of the NSAIDs group. Therefore, concentrations of different classes of PPCPs reported in the freshwater aquatic environment from each continent will be reviewed separately in the next section.

1.5. Europe

1.5.1. Wastewater and surface water

Richardson and Bowron reported the presence of 25 pharmaceuticals in water samples taken in 1981 from the river Lee, UK with concentrations of dextropropoxyphene, erythromycin, sulphamethoxazole, tetracyclin and theophylline up to 1 μg/L [137]. Subsequently, a study in German municipal STPs and rivers, investigated 32 pharmaceuticals from different classes including antiphlogistics, lipid regulators, psychiatric drugs, antiepileptic drugs, betablockers and β_2-sympathomimetics in discharged effluents, stream and river waters. More than 80% of the selected drugs were detectable in at least one municipal STP effluent with concentrations of carbamazepine up to 6.3 μg/L with resultant contamination of the receiving waters. The lipid regulator "bezafibrate" showed the highest concentration of 3.5 μg/L in the sampled river waters [152]. Concentrations of ibuprofen detected in influent and effluent samples from various German WWTPs displayed a maximum of 3.5 and 0.3 μg/L respectively [81]. Hirsch et al. investigated STP effluents and random river water samples collected in Germany for the presence of antibiotic residues. The results showed frequent detection of erythromycin, roxithromycin and sulfamethoxazole at concentrations up to 6 μg/L [74]. Another German study [52] reported detection of 6 pharmaceuticals: carbamazaepine, clofibric acid, diclofenac, propranolol and sulfamethoxazole at concentrations 6.3, 1.6, 2.1, 0.29 and 2 μg/L in effluent and 1.1, 0.55, 1.2, 0.59, and 0.48 μg/L in surface water, respectively. In addition, carbamazepine, diclofenac, ibuprofen, as well as a variety of antibiotics and lipid regulators were detected in water samples collected from the River Elbe in 1998 at concentrations ranging between 20 and 140 μg/L [165]. Moreover, a study examined the fate of triclosan and its active transformation product, triclosan-methyl in STPs and surface water (River Ruhr) in Northern Germany. Concentrations of both compounds ranged between <3 and 10 ng/L for triclosan and between 0.3 and 10 ng/L for triclosan-methyl [13].

In the UK, Hilton et al. detected mefenamic acid, diclofenac, propranolol, erythromycin, trimethoprim and acetyl-sulfamethozole in both effluent samples and surface water sampled downstream of effluent discharge [73]. Ashton et al. investigated effluent and surface water samples from Corby, Great Billing, East Hyde, Harpenden and Ryemeads STPs in the UK. Ten pharmaceuticals were detected in the STP effluent samples: propranolol (detection frequency = 100%, median = 76 ng/L), diclofenac (86%, 424 ng/L), ibuprofen (84%, 3086 ng/L), mefenamic acid (81%, 133 ng/L), dextropropoxyphene (74%, 195 ng/L), trimethoprim (65%, 70 ng/L), erythromycin (44%, <10 ng/L), acetyl-sulfamethoxazole (33%, <50 ng/L), sulfamethoxazole (9%, <50 ng/

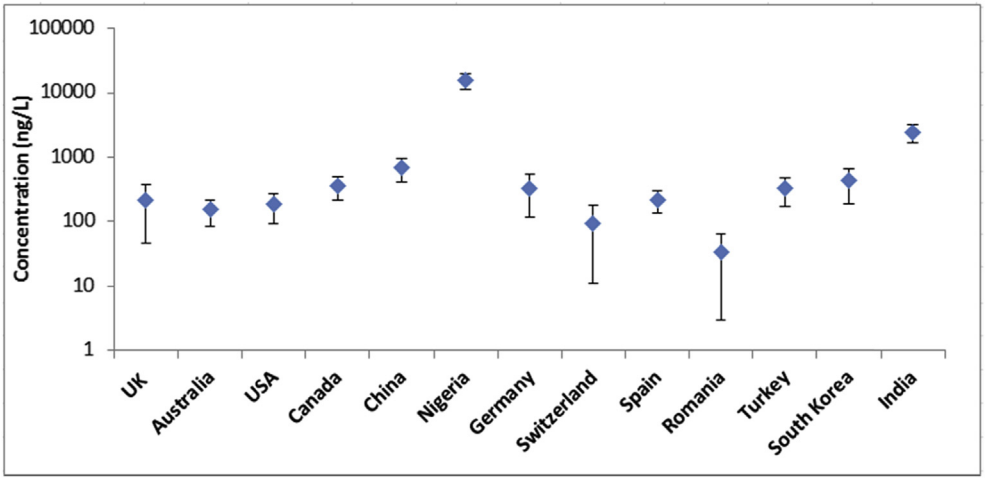

Fig. 3. Concentrations (ng/L) of non-steroidal anti-inflammatory drugs (NSAIDs)* reported in surface water samples from different countries**.
* NSAIDs include Ibuprofen, Naproxen, Diclofenac, Ketoprofen and Acetaminophen.
** Data from [116], [86], [85], [87], [144], [18], [111], [112], [177], [122], [52], [165], [23], [24], [67], [33], [7].

L), tamoxifen (4%, <10 ng/L). In the corresponding receiving streams, fewer compounds and lower concentrations were found [6]. Another study conducted in the UK by Ref. [153] detected clofibric acid, clotrimazole, dextropropoxyphene, diclofenac, ibuprofen, mefenamic acid, propranolol, tamoxifen, and trimethoprim at measurable concentrations in water samples collected from the lower reaches of the rivers Tyne, Tees, Mersey, and Thames as well as Belfast Lough in the UK. Clotrimazole appeared to be the most frequently detected in 59% of all the samples collected at a maximum concentration of 22 ng/L and a mean concentration of 7 ng/L [138]. surveyed wastewater effluent and surface waters of the lower River Tyne, UK. Out of 9 compounds analyzed in the raw effluent samples, sulfamethoxazole and acetyl-sulfamethoxazole were detected at concentrations ranging from 11 to 69 570 ng/L. In surface water samples, clotrimazole, dextropropoxyphene, erythromycin, ibuprofen, propranolol, tamoxifen and trimethoprim were detected at concentrations ranging from 4 to 2370 ng/L.

In the South Wales, UK [86], reported the contamination of the River Taff and the River Ely with PPCPs, illicit drugs and other endocrine disruptors, which was attributed mainly to the extensive discharge of treated wastewater effluent into the rivers. The investigation suggested that the most frequently detected PPCPs represent the compounds that are highly dispensed in the Welsh community. These include: anti-inflammatories/analgesics (tramadol, codeine, paracetamol, naproxen, ibuprofen and diclofenac), antibacterial drugs (erythromycin, trimethoprim and amoxicillin) and antiepileptic drugs (gabapentin and carbamazepine). Some of these PPCPs (e.g. codeine, erythromycin, valsartan, gabapentin and carbamazepine) were found to be ubiquitous and persistent in the aqueous environment. Illicit drugs were also detected in both rivers at low concentrations. The average daily loads of amphetamine, cocaine and its main metabolite benzoylecgonine were reported at 8, 1 and 39 g/day respectively.

[185] also reported PPCPs such as: propranolol, sulfamethoxazole, carbamazepine, indomethacine and diclofenac were frequently detected in wastewater and river water sampled from three WWTPs in England and the River Ouse. Carbamazepine showed the highest concentrations (up to 2336 ng/L) in WWTP influent samples. Interestingly [93], reported as the presence of glucocorticoids (GCs) in the river Thames, in the UK. The total concentrations of 28 GCs ranged between 30 ng/L and 850 ng/L. These concentrations were much higher than those of more extensively studied estrogens especially ethinylestradiol and other steroid hormones. At such concentrations, adverse effects on aquatic organisms are possible. However, Baker and Kasprzyk-Hordern went further to report occurrence of a comprehensive set of drugs of abuse in river water, untreated and treated wastewater in England, UK. They identified the top ten pharmaceuticals with the highest median concentration detected from the WWTPs influent and effluent to be: caffeine (23 778.4 ng/L–1744.2 ng/L), 1,7 dimethylxanthine (20 400.4 ng/L–1219.8 ng/L), nicotine (3919.3 ng/L–85.7 ng/L), codeine (1255.9 ng/L–372.2 ng/L), tramadol (1122.6 ng/L–738.7 ng/L), ephedrine (476.2 ng/L–35.0 ng/L), nortramadol (397.0 ng/L–144.8 ng/L), morphine (371.2 ng/L–59.1 ng/L), dihydrocodeine (226.6 ng/L–118.2 ng/L), and amitriptyline (206.3 ng/L–66.3 ng/L) respectively. Similar high median concentrations of these pharmaceutical compounds were observed in river water samples collected both upstream and downstream of the WWTPs [10].

Furthermore [184], reported the occurrence of pharmaceuticals in samples collected from the River Medway, UK in February 2010. Concentrations in water sampled for upstream sewage effluent and effluent discharge sites were: propranolol (8–35 ng/L), *meso*-biliverdin (3–11 ng/L), thioridazine (6–22 ng/L), carbamazepine (53–265 ng/L), tamoxifen (2–8 ng/L), indomethacine (6–28 ng/L), and meclofenamic acid (28–176 ng/L). The highest concentration of all studied compounds was for diclofenac in the effluent discharge site (543 ng/L). Apart from the water samples analysed, high concentrations of pharmaceuticals were also detected in all solid residue samples in the month of June 2010 with the highest concentrations being: diclofenac (58.7 ng/g), carbamazepine (46.5 ng/g), indomethacine (42.6 ng/g), and meclofenamic acid (37.3 ng/g).

Buser et al. identified clofibric acid concentrations found in various Swiss lakes (the Zurichsee, the Sempachersee and the Greifensee) fell in the range of 1–9 ng/L [22]. Buser et al. also studied the occurrence and fate of diclofenac in Swiss lakes and rivers. The concentrations in the lakes ranged from <1 to 12 ng/L, while the highest concentration (11–310 ng/L) were observed in the river Aabach, one of the major inflows of Lake Greifensee [23]. In 1999, the same research group investigated the presence and behaviour of ibuprofen in surface and wastewater samples. Surface water samples were collected from lakes and rivers in Switzerland and from the North Sea, with wastewater samples collected from the Swiss WWTPs of Gossau, Pfaffikon and Uster. The concentration of ibuprofen in the influents of the WWTPs was up to 3 μg/L while in the river and lakes, ibuprofen was detected at concentrations up to 8 ng/L [24].

Carbamazepine, atenolol, metoprolol, sulfametoxazole, gemfibrozil and propanolol were detected and demonstrated a high degree of persistence in the Hoje River in Sweden, at concentrations ranging from 0.16 to 1.18 μg/L [12]. In a wide survey of more than 100 individual water samples from over 100 European rivers from 27 European countries, Loos et al. identified persistent pharmaceuticals as benzotriazole, caffeine and carbamazepine to be the most frequently detected and at the highest concentration levels [103]. A study in Catalonia, Spain also determined the presence of 11 PPCPs in both surface water (Ebro and Llobregat River) and wastewaters with benzophenone-3 having the highest concentration (7 ng/L) [130]. Another study reported the occurrence and distribution of multi-class pharmaceuticals, their active metabolites and transformation products in the Ebro River basin in Spain. Out of 77 target analytes, the compounds found to be ubiquitous were carbamazepine, clarithromycin, sulfadiazine, propranolol, tamoxifen and salicylic acid. The highest concentration of 1667 ng/L was detected for the carbamazepine metabolite (10,11 epoxi-carbamazepine) in a small tributary, the Zadorra river [104].

Calamari et al. reported the detection of therapeutic agents such as atenolol, lincomycin, erythromycin, clarithromycin, bezafibrate and furosemide in the River Po and Lambro, Northern Italy at concentration ranging from 0.1 to 250 ng/L [25]. A study in Portugal revealed the presence of pharmaceutical active compounds (mostly nonsteroidal anti-inflammatory drugs) ranging from 0.050 to 100 μg/L in the influent and up to 50 μg/L in the effluent of 5 WWTPs. Musks were also detected at concentrations of 11.5 μg/L, 0.9 μg/L and 22.6 μg/L in the influent, effluent and sludge respectively [141]. Furthermore [110], monitored seasonal variation of 15 pharmaceuticals during four seasons (February, May, July and November 2010) along a wastewater polluted watercourse, River Rakkolanjoki and Lake Haapajarvi in Eastern Finland. The concentrations ranged from 0 to 556 ng/L. Out of the 15 studied compounds, carbamazepine had the highest concentrations and was not eliminated during any of the seasons.

1.5.2. Sediment and sewage sludge

Several studies have shown that pharmaceuticals consumed in large quantities have been detected in the aqueous environment particularly in sediment. Loffler and Ternes reported the detection of acidic pharmaceuticals and their metabolites (clofibric acid, diclofenac, fenoprofen, gemfibrozil, ibuprofen, 2-hydroxy-

ibuprofen, indomethacin, ketoprofen, and naproxen), antibiotics (clarithromycin, erythromycin, roxithromycin, sulfadiazine, sulfamethazine, sulfamethoxazole and trimethoprim) and parasiticide ivermectin in sediment from the Wickerbach creek, close to Frankfurt, Germany [102]. Martin et al. investigated pharmaceuticals in sewage sludge, compost as well as sediment samples collected from the surface water of Guadiamar River in Seville, Southern Spain. The pharmaceuticals detected in the sediment were naproxen, salicylic acid, propranolol, caffeine and 17α-ethinylestradiol at concentrations of 11.2, 9.49, 3.37, 7.21, and 48.1 μg/kg respectively [108]. A more recent study examined sediment samples collected along four representative Iberian River basins; Llobregat, Ebro, Jucar and Guadalquivir, Spain. The most widely spread and highly concentrated pharmaceuticals were hydrochlorothiazide (3 ng/g), gemfibrozil (6 ng/g), tetracyclines (6 ng/g), codeine (12 ng/g) azithromycin (24 ng/g), and ibuprofen (13 ng/g) [127]. Varga et al. investigated selected acidic pharmaceuticals: ibuprofen, naproxen, ketoprofen and diclofenac in the Danube river water and sediment in Budapest, Hungary. In the river water, ketoprofen was always below the LOQ, while ibuprofen, naproxen and diclofenac were quantified in the range of 8–50, 2–30, 7–90 ng/L. In sediments, only naproxen and diclofenac were found in the range of 2–20 and 5–38 ng/g, respectively [157]. Concentrations of human pharmaceuticals, illicit drugs, and bactericides were reported in Scottish sediments and sludge samples. None of the illicit drugs and metabolites were detected but triclosan (up to 5940 ng/g) and triclocarban (up to 2829 ng/g) were [94]. The study concluded that the drug content of sediment depended on its concentration in the aqueous phase and the total organic carbon content of the sediment.

1.5.3. Biota

Globally, studies have shown that exposure to WWTP effluents containing PPCPs is associated with a range of deleterious effects on the reproduction in aquatic organisms [65]. revealed bioaccumulation of a mixture of estrogenic contaminants in fish tissues, thereby resulting in the induction of vitellogenin and possibly contributing to feminization of wild fish residing in UK rivers. Pojana et al. examined natural and synthetic endocrine-disrupting chemicals (EDCs) in water, sediment and biota of a coastal lagoon in Venice. The result of their study showed that most of the selected compounds were found in water and sediment at concentration ranging from 2.8 to 211 ng/L and 3.1–289 μg/kg dry weight respectively. The compounds detected in the Mediterranean mussel (*Mytilis galloprovincialis*) were 17α-ethinylestradiol and nonylphenol at concentration range 7.2–240 ng/g in dry weight [132]. In another study by Ref. [56]; in which rainbow trout were exposed to pharmaceutical sewage effluents, levonorgestrel was accumulated in fish blood at concentrations of 8.5–12 ng/ml.

Subedi et al. measured galaxolide and tonalide in tilapia and bream fish samples collected from Rhine River, Germany at concentrations of 81 and 5.5 ng/g wet weight respectively [150]. Alvarez-Munoz et al. investigated the presence of pharmaceuticals in oyster, clam and mussel samples collected from the Ebro delta, Spain. The results revealed the most ubiquitous compounds detected were the psychiatric drug venlanfaxine and the antibiotic azithromycin, with the highest concentrations found in mussels (2.7 ng/g) and oysters (3.0 ng/g) [4]. Another Spanish study examined residual pharmaceuticals in pork, veal, lamb and chicken muscle, liver and kidney as well as salmon, sea bass and sole flesh purchased at a local supermarket. The study revealed the most frequently detected analytes were the hormones estrone and 17β-estradiol and the antibacterials florfenicol and pyrimethamine [9].

1.6. North and South America

1.6.1. Wastewater and surface water

In a seminal study, concentrations of pharmaceuticals were reported in Kansas City, US in 1976 in treated wastewater, with clofibric acid present at concentrations ranging from 0.8 to 2 μg/L [50]. In South America, Stumpf et al. detected polar drugs residues in sewage and natural waters in the state of Rio de Janeiro, Brazil. In surface water, clofibric acid, diclofenac and naproxen were frequently detected at low concentrations (0.01–0.06 μg/L) in the major river used for drinking water production [149].

[79] reported estrogenic hormones in effluent from four municipal WWTPs effluent in California, USA, as well as in surface water from a wetland receiving such effluent, namely the Colorado River and the Sacramento River delta. Median concentrations in the wastewater effluents were 1.9 ng/L and - 0.6 ng/L for 17β-estradiol (E2) and 17α-ethinylestradiol (EE2), respectively. Median concentrations in surface water were 0.08 ng/L and > 0.05 ng/L for E2 and EE2.

[92] detected various pharmaceuticals in samples from a network of 139 streams susceptible to contamination (i.e. downstream of urban areas and livestock production) across 30 states during 1999 and 2000. The most frequently detected compounds were coprostanol (fecal steroid), cholesterol (plant and animal steroid), N,N-diethyltoluamide (insect repellent), caffeine (stimulant), triclosan (antimicrobial disinfectant), tri (2-chloroethyl) phosphate (flame retardant), and 4-nonylphenol (nonionic detergent metabolite). Measured concentrations for this study were generally low and rarely exceeded drinking water guidelines, drinking water health advisories, or aquatic life criteria. Boyd et al. investigated the presence of PPCPs in surface water and treated waters of Louisiana, USA and Ontario, Canada. The study revealed that naproxen was detected in Louisiana STP effluent at 81–106 ng/L and in Louisiana (Mississippi River) and Ontario (Detroit River) surface waters at 22–107 ng/L [18]. Another study in Montana, USA, reported detection of sulfamethoxazole, atrazine, carbamazepine, dilantin and diclofenac with maximum concentrations of 490 ng/L, 130 ng/L, 420 ng/L, 22 ng/L and 46 ng/L respectively in ground water [113]. Batt et al. reported the presence of some antibiotics in receiving streams impacted by wastewater discharge in East Aurora and Holland, New York. Ciprofloxacin, sulfamethoxazole and clindamycin (0.043–0.076 μg/L) were detected 100 m from the discharge point [11].

A study of the Mississippi in New Orleans, Louisiana, USA, revealed contamination by PPCPs including: clofibric acid (3–27 ng/L), ibuprofen (<1–34 ng/L), acetaminophen (25–65 ng/L), caffeine (<1–38 ng/L), naproxen (<1–135 ng/L), triclosan (9–26 ng/L), bisphenol A (<1–147 ng/L), carbamazepine (43–114 ng/L), estrone (<1–5 ng/L) and 17β-estradiol (<!-5 ng/L) at the following concentrations [181]. A study of a major receiving river, the Choptank in Maryland, USA, revealed the presence of various antibiotics and hormones at different concentrations in a major agricultural watershed. The most frequently detected antibiotic in the river were sulfamethoxazole and sulfadimethoxine at concentrations ranging from 0.005 to 0.007 μg/L [5].

Wu et al. reported the occurrence of selected pharmaceuticals in an agricultural landscape, western Lake Erie basin in northern Ohio. The results showed that the most frequently detected compounds were caffeine, carbamazepine, ibuprofen and paraxanthine at maximum concentrations of 4.2, 1.2, 2.8 and 1.8 μg/L [169]. Another study examined the distribution and temporal trends of 19 PPCPs including 11 hormones in two WWTPs from Charleston, SC, USA over a period of one year. Acetaminophen, caffeine and ibuprofen showed the highest concentrations in both WWTPs samples, followed by triclosan and triclocarban. In Charleston Harbour surface

water, caffeine, cotinine and acetaminophen were detected in 98.6%, 33.3%, and 22.2% of samples respectively [71] [14]. also reported detection of 32 pharmaceuticals in Lake Michigan water, with 30 detected in the sediment. Among those most frequently detected were: metformin, caffeine, sulfamethoxazole and triclosan.

A study in Cape Cod, Massachusetts, USA, reported most frequently-detected pharmaceuticals including sulfamethoxazole, the anticonvulsant phenytoin, and carbamazepine at maximum concentrations of 113 ng/L, 66 ng/L and 72 ng/L, respectively in well water [142]. Fairbairn et al., also reported the detection of PPCPs (*detection frequencies and median concentration in parentheses*) such as atrazine (99%, 29 ng/L), caffeine (97%, 17 ng/L), metolachlor (88%, 10 ng/L), acetaminophen (88%, 3.3 ng/L), DEET (87%, 16 ng/L) and trimethoprim (72%, 5.9 ng/L) in 68 grab water samples from the Zumbro River watershed, Minnesota, USA at concentrations over a period of one year [47].

Metcalfe et al. reported the occurrence of neutral and acidic drugs in the effluents of Canadian STPs. The study showed that lipid regulators such as bezafibrate and gemfibrate were detected in some influent and effluent samples as well as carbamazepine at concentrations as high as 2.3 μg/L [111]. To determine the distribution of acidic and neutral drugs in surface waters near STPs in the lower Great Lake, Metcalfe and colleagues examined surface water collected from Lake Ontario and Lake Erie and STPs effluents. The result shows detection of all the acidic drug analytes except ketoprofen in the effluents. However, ibuprofen and gemfibrozil were detected in STP effluents at concentrations >1 μg/L [112]. Verenitch et al. also reported the presence of acidic drugs and caffeine in municipal wastewaters and receiving water on the west coast of Vancouver Island, British Columbia, Canada. Ibuprofen, naproxen as well as salicylic acid were detected in the samples of STP wastewater and also in surface water samples collected near STP outfalls [159]. Concentrations of pharmaceuticals and s-triazine herbicides were determined in wastewater effluent and surface water sampled from the upper Detroit River, Canada. 15 pharmaceuticals including carbamazepine, cotinine, caffeine, trimethoprim, fluoxetine were detected in the WWTP effluent at concentrations ranging from 1.7 to 1244 ng/L [78].

Gibson et al. investigated reuse of wastewater for irrigation from the Tula Valley in Mexico. The study revealed wastewater used for irrigation to contain pharmaceuticals and potential endocrine disruptors. Ibuprofen (742–1406 ng/L), naproxen (7267–13589 ng/L), and diclofenac (2052–4824 ng/L) were consistently present while other pharmaceuticals such as gemfibrozil, clofibric acid and ketoprofen were below LOD [64].

[53] revealed the presence of ibuprofen in both influent and effluent from WWTPs at Penha and Ilha do Governador, Rio de Janeiro, Brazil. Ibuprofen was detected in all samples analyzed, confirming low removal efficiency of conventional treatment plants. Another study by same author [54] investigated psychiatric pharmaceuticals in Guandu River, Rio de Janeiro, Southern Brazil. The study revealed the presence of benzodiazepines such as bromazepam, clonazepam and diazepam in all samples of surface water at maximum concentrations of 42 ng/L, 198 ng/L, and 335 ng/L respectively. In a comparative study conducted by the Minnesota Pollution Control Agency, DEET, cotinine, lopamidol, bisphenol A, metformin and the steroidal hormone androstenedione were frequently detected in lake water at maximum concentrations of 103, 42, 510, 36, 18 and 5 ng/L. Overall, in surface water, sixteen chemicals including some antidepressants, antibiotics and antihypertensive pharmaceuticals were detected downstream of the WWTPs, while six out of 56 target PPCPs such as Bisphenol A (BPA), carbadox, fluoxetine, sulfamethozine, virginiamycin, methylprednisolone, moxifloxacin and triclosan were detected frequently upstream [55]. Elsewhere [44], reported caffeine to be present in surface water in Barbados at concentrations ranging from 0.1 to 6.9 μg/L.

1.6.2. Sediment and sewage sludge

The occurrence of PPCPs in freshwater sediment has been documented by several authors. Sediment samples collected from rivers (Mississippi, Sauk, South Fork of the Crow and Grindstone), creeks (Center, Okabena) and lakes (Pepin, Superior, Shagawa) in Minnesota, US, revealed a high level of triclocarban in freshwater sediments at concentration up to 822 ng/g [158]. A study conducted by Yang et al. investigated pharmaceuticals and organochlorine pesticides in sediments from the Alafia River in Florida, USA. The most frequently detected compounds were carbamazepine, acetaminophen, diphenhydramine, trimethoprim, caffeine, nicotine, lidocaine and ephedrine at concentrations ranging from 0 to 33 ng/g [177]. Analysis of surface water, sediment and mussel samples collected from San Francisco Bay, California, an urban estuary that receives direct discharge from 40 municipal and industrial wastewater outfalls, revealed the predominant compounds to be: triclocarban in sediment, valsartan in surface water and DEET in mussels at concentrations of 33 ng/g, 92 ng/L and 14 ng/g respectively [91].

1.6.3. Biota

A national pilot study in the US, assessed accumulation of PPCPs in fish sampled from five effluent-dominated rivers receiving direct discharge from wastewater treatment in Illinois, Texas, Florida, Arizona, and Pennsylvania. The study revealed the presence of galaxolide and tonalide in fish fillets at every effluent-dominated site with maximum concentrations ranging from 300 to 2100 ng/L and 21–290 ng/L respectively. The pharmaceuticals detected both in liver and fillets include: diphenhydramine, norfluoxetine, sertraline, diltiazem, carbamazepine, fluoxetine, gemfibrozil, with sertraline the most abundant at a maximum concentration in fillet and liver tissue of 19 and 545 ng/L respectively [134]. The same research group also reported concentrations of diphenhydramine, diltiazem, carbamazepine and norfluoxetine detected in muscle tissues from fish collected in Pecan Creek, Denton County Texas, USA. The concentrations ranged from 0.66 to 1.32, 0.11–0.27, 0.83–1.44, 3.49–5.14 ng/g respectively [135]. Mottaleb et al. used two screening methods to determine 10 extensively used PCPs and 2 alkylphenol surfactants in fish fillets collected from a regional effluent-dominated stream in Texas, USA. Benzophenone, galaxolide, tonalide and triclosan were detected in all environmental samples at concentrations ranging from 37 to 90, 234–970, 26–97 and 17–31 ng/g respectively [117].

Foltz et al. quantified selected nitromusks, antimicrobial agents and antihistamines in edible frozen retail fresh and salt water fish fillets in Maryville, Missouri, USA. The compounds consistently detected were galaxolide, tonalide, triclosan and diphenhydramine at concentrations ranging from 0.163 to 0.892, 0.068–0.904, 0.189–1.182 and 0.942–7.472 ng/g respectively. Musk ketone was not detected in any of the fish studied [59]. A report by Brooks et al. revealed pharmaceutical accumulation in fish of effluent-dominated streams in North Texas, USA. The study showed the selective serotonin reuptake inhibitors (SSRI) fluoxetine and sertraline, in addition to their metabolites norfluoxetine and desmethylsertraline to be detected at concentrations > 0.1 ng/g in all fish tissues examined [20]. Schultz et al. investigated the occurrence and fate of antidepressant pharmaceuticals in surface water, sediment, and native white sucker (*Catostomus commersoni*) samples collected from Boulder Creek, (Colorado) and Fourmile Creek (Iowa). Fluoxetine, sertraline, and their degradates were the principal antidepressants observed in fish brain tissue, typically at low

(0.1–6) ng/g concentrations [143]. Another study investigated the uptake of human pharmaceuticals in bull sharks (*Carcharhinus leucas*) inhabiting the wastewater impacted Caloosahatchee River. Compounds detected in the plasma of Caloosahatchee River sharks were: 17α-ethyinestradiol, citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline and venlafaxine at concentrations ranging from 0.10 to 6.25 [63].

1.7. Asia

1.7.1. Wastewater and surface water

Yamagishi et al., detected musk xylene and musk ketone (synthetic musks) in 100% and 80% respectively of 74 samples from Tama River and Tokyo Bay in Japan [175]. Elsewhere, the levels and distribution of 12 antimicrobials were investigated in water from the Mekong Delta, Vietnam and compared with those in the Tamagawa River, Japan. While a few compounds such as sulfamethoxazole, sulfamethazine, trimethoprim and erythromycin-H_2O were detected in Vietnam at concentrations between 7 and 360 ng/L, while more antimicrobials were found in the Japanese urban river including: sulfamethoxazole, sulfapyridine, trimethoprim, erythromycin-H_2O, azithromycin, clarithromycin, and roxithromycin at concentrations ranging from 4 to 448 ng/L [107]. A study by Ref. [95] investigated the effluent from a WWTP impacted by drug manufacturing in Patancheru, near Hyderabad, India. Extremely high concentrations of pharmaceuticals, such as ciprofloxacin up to 31 mg/L were measured in the effluent. Moreover [57], reported a severe case of contamination of surface, ground and drinking water with pharmaceuticals in the Patancheru industrial area in India. Compounds detected included: 1.2 mg/L of cetrizine and 6.5 mg/L of ciprofloxacin, in addition to several other pharmaceuticals detected at mg/L levels.

Choi et al. examined the concentrations of several pharmaceutical residues in surface water of the Han River, Korea. The concentrations of the target compounds such as cimetidine, caffeine, acetaminophen, and sulfamethoxazole detected in the surface water were 281, 268.7, 34.8 and 26.9 ng/L respectively [34]. Another study [87]; detected several pharmaceuticals including: ibuprofen (nd to 414 ng/L), carbamazepine (nd–595 ng/L), atenolo (nd-690 ng/L), clarithromycin (nd-443 ng/L), mefenamic acid (nd–326 ng/L), erythromycin (nd–137 ng/L), propranolol (nd–40.1 ng/L), indomethacin (nd–33.5 ng/L), fluconazole (nd-111 ng/L), levofloxacin (nd-87.4 ng/L) and ifenprodil (nd-35.4 ng/L) in surface water from the Mankyung River, South Korea. The same research group documented the frequent detection of many pharmaceuticals, hormones, and antibiotics in three major rivers, the Han River, the Nakdong River and the Youngsan River in South Korea [88]. Another study by Sim et al. investigated the occurrence and distribution of pharmaceuticals in influents of WWTPs located near major river basins in Korea. Results showed that non-steroidal anti-inflammatory drugs, caffeine, and carbamazepine were dominant in the influents and the distribution of pharmaceuticals varied with sampling sites and periods [146].

Lin et al. quantified some pharmaceutical residues such as clofibric acid, ibuprofen, carbamazepine, naproxen, ketoprofen, and diclofenac in tap water, groundwater, WWTPs and river water from the Fu-Hsing River in China. None of the target compounds were detected in tap water and groundwater. However, 30 ng/L of naproxen was measured in the river water, while concentrations of ibuprofen, carbamazepine and naproxen reached 30 ng/L, 420 ng/L, and 170 ng/L respectively in WWTP effluent [98]. Xu et al. examined several antibiotics in Victoria Harbour, Hong Kong and the Pearl River in South China. Concentrations were below the limit of quantification in seawater but all of the target compounds except amoxicillin were detected in the Pearl River at concentrations ranging from 11 to 67 ng/L and 66–460 ng/L, respectively [174].

Another study conducted in the urban riverine water of the Pearl River Delta at Guangzhou, South China, revealed the presence of the estrogenic hormone, estrone, at a maximum concentration of 65 ng/L, while acidic pharmaceuticals such as salicylic acid, clofibric acid and ibuprofen were detected in most of the water samples with maximum concentrations of 2098, 248, and 1417 ng/L respectively [131]. In a study of the uptake of antibiotics in irrigation water by plants in Tianjin, China, most of the target analytes including sulfamethoxazole, sulfadoxine, sulfachloropyridazine, choramphenicol, tetracycline, lincomycin, chlortetracycline, ofloxacin, and pefloxacin were detected in vegetables between 0.1 and 532 μg/kg [77]. Luo et al. reported the occurrence and transport of tetracycline, sulfaonamide, quinolone and macrolide antibiotics in the Haihe River Basin, China. The sources of the 12 antibiotics studied were assessed as likely originating from veterinary application in swine farms and fish ponds at concentrations ranging from 0.12 to 47 μg/L [105]. A more recent study in Taihu Lake, China detected eight pharmaceutically active compounds, namely: roxithromycin, erythromycin, ibuprofen, diclofenac, propranolol, carbamazepine, E2, and EE2 in surface water and sediment samples with maximum concentrations in the range of 8.74–118 ng/L and 0.78–42.5 ng/L dry weight respectively [173]. Ma et al. also examined some pharmaceutically active drugs in Dongting Lake, China. The most frequently detected compound was caffeine followed by diclofenac, DEET, mefenamic acid, fluoxetine, ibuprofen, and carbamazepine with mean concentrations between 2.0 and 80.8 ng/L [106].

In Northern Taiwan [48], reported 4 pharmaceutical residues in wastewater STP and in seawater around the effluent discharge area. The pharmaceutical concentrations measured in influent were: clofibric acid (104–109 ng/L), diclofenac (152–185 ng/L), ibuprofen (724–2200 ng/L), and ketoprofen (128–184 ng/L). Corresponding concentrations in effluent were: 95–102 ng/L, 100–131 ng/L, 552–1600 ng/L, and 68–128 ng/L respectively.

1.7.2. Sediment and sewage sludge

Lei et al. studied concentrations of six estrogens including: diethylstilbestrol (DES), estrone (E1), β-estradiol (E2), estriol (E3), 17α-ethynylestradiol (EE2), and β-estradiol 17-valerate (EV) in surface water and sediment sampled from three rivers in Tianjin area, northern China. The concentrations of all six estrogens ranged from 0.98 to 51.6 ng/g in sediment and varied for each river [96]. Yang et al. measured four classes of antibiotics, namely: sulphonamides, macrolides, fluoroquinolones and tetracyclines in sediment of the Pearl River in China. Ofloxacin was detected at the highest concentration of 1560 μg/kg [176]. In another study conducted by Liu and co-workers, high concentrations of chloramphenicol (5.8–47.4 μg/L), oxytetracycline (0.2–5.7 μg/L), and tetracycline (0.7–65.2 μg/L) were observed in the sediment of the Nanming River, Guiyang city, China during summer [99].

Ramaswany et al. studied antiepileptic, antimicrobial and preservative compounds in surface water and sediment from the Kaveri, Tamiraparani, and Vellar rivers in India. The maximum concentrations reported for the antimicrobial triclosan in sediment in the three rivers were 85.3, 46.9 and 32.1 ng/g respectively [133]. A study by Zhou et al. reported the occurrence of 4 classes of commonly used antibiotics including sulphonamides, fluoroquinolones, tetracycline, and macrolides in the sediments of the Yellow River, Hai River and Liao River in Northern China. Higher concentrations were detected for most antibiotics in the Hai River sediment compared to the other rivers. The most frequently detected antibiotics were norfloxacin, ofloxacin, ciprofloxacin and oxytetracycline at concentrations up to 5770, 1290, 653 and 652 ng/g respectively [186]. Another study examined the occurrence of

antibiotics in water, sediments, aquatic plants and animals from Baiyangdian Lake in North China. While sulphonamides were the dominant antibiotics in lake water, quinolones were prominent in sediments at concentrations of 0.86–1563 ng/L and 65.5–1166 μg/kg respectively [97].

1.7.3. Biota

The catastrophic decline in the vulture population in Pakistan has been partially attributed to dietary exposure of vultures to diclofenac-treated livestock. Specifically, the diclofenac concentrations of 0.051–0.643 μg/g were found in the kidneys of all 25 vultures that died of renal failure [121]. Li et al. also detected 13 antibiotics in most of the studied hydrophyte samples (aquatic plants) such as: Salvinia natans (Sal), Hydrocharis dubia (Hyd) and Ceratophyllum demersum (Cer) and four crustacean species including: crab (*Eriocheir sinensis*), river snail (*Viva parus*), shrimps (*Macrobrachium nipponense*) and lobster (*Palinuridae*), 7 fish species: topmouth gudgeon (*Pseudorasbora parva*), loach (*Misgurnus anguillicaudatus*), yellow catfish (*Pelteobagrus fluvidraco*), to mention but a few from Baiyangdian Lake, China. The concentrations of antibiotics in Sal, Cer and Hyd were 1769 μg/kg, 253 μg/kg and 129 μg/kg respectively [97]. Other studies have also reported concentrations of ciprofloxacin in the aquatic plant (*Echinodorus amazonicus*) as high as 795 μg/kg [28,180].

Liu et al. also reported steroid estrogens at concentrations up to 11.3 ng/g dry weight in wild fish species such as crucian carp, carp, and silvery minnow from Dianchi Lake in Southern China. Liver displayed highest estrogen accumulation, followed by gills and muscle [100]. Following a study of fluoroquinolones in the aquaculture environment of the Pearl River Delta, South China, He et al. reported the accumulation of fluoroquinolones in *Siganus fuscescens* from Hailing island, *Sparus microcephalus* from Dapeng'ao and *Lutianus argentimaculatus* from Hailing island, at concentrations of 255, 133 and 5 ng/g wet weight respectively, with concentrations higher in liver than in muscle tissue. ~Concentrations of norfloxacin were higher than those of ciprofloxacin and enrofloxacinin in both tissues [69].

1.8. Australia

1.8.1. Wastewater and surface water

Data exists demonstrating the presence of numerous pharmaceuticals in effluents, river systems, marine sediments and sewage sludge in Australia as well as New Zealand. During a national survey of trace organic contaminants in Australian rivers, the most commonly detected contaminants were pharmaceuticals such as: salicylic acid, paracetamol, carbamazepine, and caffeine at maximum concentrations of 1530 ng/L, 7150 ng/L, 682 ng/L and 3770 ng/L respectively [144]. A study by Ref. [162] reported the occurrence of antibiotics in three hospital effluents, five WWTPs, six rivers and a drinking water catchment within watersheds of South-East Queensland, Australia. The results of the study showed high concentrations of antibiotics in the hospital effluent (up to 14.5 μg/L). Concentrations of target antibiotics in the studied WWTP influent and effluent were up to 64 μg/L and 3.4 μg/L respectively, while river water samples contained up to 2 μg/L of target analytes. Interestingly, none of the studied antibiotics were detected in drinking water.

[179] detected the antimicrobial triclosan in wastewaters and biosolids from Australia WWTPs. Concentrations of triclosan ranged from 23 to 434 ng/L and 0.09–16.79 mg/kg for the WWTP effluents and biosolids respectively. Triclosan at concentrations up to 75 ng/L was detected in surface waters (outfall, upstream, and downstream) from five rivers receiving effluent discharge from the investigated WWTPs. Costanzo et al. reported detection of six antibiotics entering local waterways of South East Queensland. Among the antibiotics investigated, cephalexin had the highest concentration of 2000 ng/L being the second most prescribed antibiotic in Australia [39].

1.9. Sediment and sewage sludge

Few studies have been conducted in Australia in terms of monitoring pharmaceuticals in sediments [168]. investigated isotopic exchangeability to measure the available fraction of carbamazepine in river sediment collected from Mackreath Creek and Scott Creek in South Australia. The study demonstrated isotopic exchangeability as a relatively quick and simple alternative to batch desorption techniques for the assessment of the available fraction of the carbamazepine in sediments following their release into aquatic ecosystems [168]. Another study reported the detection of emerging contaminants including pharmaceuticals in the estuarine-receiving environment around Auckland, New Zealand. 21 out of 46 targeted pharmaceuticals were quantified in one or more estuarine sediments with concentrations ranging from 0.2 to 7.7 ng/g. The highest concentrations were detected for acetaminophen (7.7 ng/g) and naproxen (5.5 ng/g) [148].

1.10. Africa

1.10.1. Wastewater and surface water

Currently, very little is known about the occurrence, fate and behaviour of PPCPs in the African freshwater aquatic environment. In most developing countries in Africa, where the waste disposal system is basically through landfill, it is important to monitor the presence of PPCPs, since some of these PPCPs are not easily degradable either through biodegradation or photodegradation. Moreover, they can contaminate groundwater which constitutes a major water supply for a large proportion of the population in arid regions of Africa.

Antimalarial drugs such as artemether and lumefantrine, that are widely used in Africa for the treatment of the malaria parasite, as well as amoxicillin were detected at concentrations ranging from 3 to 32 μg/L in Tanzania [115]. A study in South Africa reported the presence of pharmaceuticals such as erythromycin, chloramphenicol, nalidixic acid, tetracycline, sulfamethoxazole, acetaminophen, atenolol, diclofenac, ibuprofen, caffeine and others in Umgeni surface water and in a dam along the Umgeni River used for water supply in KwaZulu-Natal South Africa. There was 100% occurrence of the analytes studied in wastewater, with caffeine displaying the highest average concentration at 61 ± 5 μg/L and nalidixic acid being the most abundant antibiotic at 31 ± 3 μg/L. The waste treatment process reduced the influent concentrations by 43–94% before discharge except for atenolol removal (for which reduction was only 15%). Analyte concentrations were generally much lower in the surface water (<10 μg/L), except acetaminophen (16 μg/L) and atenolol (39 μg/L) [1]. A more recent study reported residues of pharmaceuticals in wastewater from Msunduzi River, KwaZulu-Natal, South Africa. Results revealed ibuprofen to display the highest concentrations at 117 μg/L and 85 μg/L in wastewater and surface water respectively. Concentrations of antibiotics in surface water were generally lower (>10 μg/L) but up to 34.5 μg/L in wastewater [109]. In Kenya [84], investigated 10 classes of pharmaceutically active ingredients (PAIs) in Nairobi River. Analgesics, anti-inflammatory and antiepileptic agents were the most prevalent PAIs at about 30–35 μg/L, followed by antibiotics/antimalarial drugs at up to 25–30 μg/L, while antivirals were detected at up to 10–15 μg/L. Another study reported the occurrence of antibiotics and antivirals in the Nairobi River Basin, Kenya. The maximum concentrations in river water for sulfamethoxazole, trimethoprim,

ciprofloxacin, lamivudine, nevirapine, and zidovudine were 13.8, 2.6, 0.5, 5.4, 4.8, and 7.7 μg/L respectively [118].

Olaitan et al. reported the detection of pharmaceutical compounds in surface and groundwater samples collected from an irrigation canal and several wells in a pharmaceutical industrial area of Sango Ota, Ogun State, Nigeria. The average concentrations of the targeted pharmaceuticals such as diclofenac, chloroquine, paracetamol and ciprofloxacin were 17 μg/L, 5 μg/L, 3 μg/L and 1 μg/L, respectively [122]. To augment the limited database on the occurrence of pharmaceutical compounds in the Nigerian environment, a monitoring campaign was conducted in Lagos. Pharmaceutical residues in wastewater impacted surface waters and sewage sludge were quantified using LC-MS/MS. For the surface water, ibuprofen showed the highest concentrations up to 8.8 μg/L, while diclofenac was more abundant in sewage sludge with concentrations up to 1100 μg/kg dry weight [123].

1.10.2. Sediment and sewage sludge

Aspirin, diclofenac, ketoprofen and ibuprofen were measured in sediment samples collected from Msunduzi River, kwazulu-Natal, South Africa. The highest concentrations in sediment were observed for aspirin (212–427 ng/g). The concentrations of diclofenac, ketoprofen, and ibuprofen detected in sediment were between 57 and 309, 7–57 and 5–11 ng/g respectively [2]. Matongo et al. also detected ibuprofen in sediment from the Msunduzi River, KwaZulu-Natal, South Africa at concentrations as high as 659 ng/g [109].

2. Summary, research gaps and future perspectives

PPCPs are a group of emerging contaminants with physicochemical characteristics that distinguish them from other contaminants (e.g. persistent organic pollutants). Pharmaceuticals are structurally designed to maximise their biological activity at low concentrations and developed to produce a prolonged action. These properties highlight the risks associated with the inadvertent presence of PPCPs in the environment. This review highlights that aquatic organisms are continuously exposed to PPCPs throughout their life cycle and there is mounting evidence that the unintended presence of these contaminants in the aquatic environment may exert detrimental impacts on aquatic life. To date, little is known about the impacts of their environmental presence on humans. The major point source of PPCPs into the aquatic environment is WWTPs, alongside other sources such as agricultural runoff, PPCP manufacturing sites, and aquaculture. Evidence suggests that WWTPs are not completely capable of removing PPCPs during treatment processes. Therefore, treated effluents discharged into receiving water bodies may still contain substantial PPCP residues and there is a clear need for the development of advanced WWTP technologies to more efficiently remove/degrade PPCPs.

Despite the recent advances in analytical techniques that allow sensitive multi-residue analysis of several PPCPs in different environmental matrices, and clearly demonstrate the unintended environmental presence of such chemicals, this literature review reveals gaps in the current state-of-knowledge about this emerging class of environmental contaminants.

It is apparent from this review that more studies of PPCPs are required to characterise their environmental presence in developing countries, as there are currently far fewer data for Africa, Asia and South America compared to the Europe and North America. Moreover, while sorption to sediment particles was suggested to play a role in determining the fate of PPCPs in the freshwater aquatic environment, there are no detailed studies addressing the behaviour and dynamics of PPCPs in freshwater systems, or how sediment may act as a sink for these contaminants or source of PPCPs for bottom-feeding aquatic biota.

Currently, very little is known about the levels of PPCPs in biota in general. Few studies have investigated PPCP residues in fish, birds and mammals. There is also a lack of information on the potential trophic magnification of these compounds or the influence of prenatal exposure on the possible transfer of PPCPs to birds' eggs and other nascent wildlife.

It is also imperative to further the current understanding of the toxicological implications of chronic exposure to complex mixtures of PPCPs at sub-therapeutic levels in both target and non-target organisms. More research is also needed to characterise the influence of such exposure on the status of public health in contaminated areas (e.g. impacts on malarial resistance in Africa or fertility/fecundability in areas contaminated with estrogenic hormones).

Although data exist about the presence of PPCPs in the freshwater aquatic environment, there appear gaps in knowledge about the seasonal variability in concentrations of commonly and consistently detected PPCPs in the aquatic environment [184]. highlighted seasonal variations in concentrations of some pharmaceuticals in water samples collected between December 2009 and 2010 from the river Medway, Kent, UK, with the highest concentrations detected in June. Further investigation is needed to provide more detailed definition of seasonal variations of PPCPs in various environmental compartments. Another important area that has to be properly addressed is the bioaccumulation of PPCPs in aquatic organisms such as: algae, crustaceans, and fish. Initial investigations of this issue [37,163,166] highlight its importance and further study of the potential bioaccumulation by aquatic biota is warranted, including its implications for human exposure via consumption of contaminated fish/shellfish.

Finally, future research on PPCPs should not focus only on the parent (intact) compounds but also on their potential degradation products/metabolites in various matrices. This is of importance because such degradation products/metabolites formed under various environmental conditions (temperature, pressure, UV light … etc) or by non-target organisms may differ from those formed under human physiological conditions. Consequently, this may produce more toxic/bioaccumulative compounds than the parent PPCPs.

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