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Review

Abundance, fate, and effects of pharmaceuticals and personal care products in aquatic environments

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ABSTRACT

Pharmaceuticals and personal care products (PPCPs) are found in wastewater, and thus, the environment. In this study, current knowledge about the occurrence and fate of PPCPs in aquatic systems—including wastewater treatment plants (WWTPs) and natural waters around the world—is critically reviewed to inform the state of the science and highlight existing knowledge gaps. Excretion by humans is the primary route of PPCPs entry into municipal wastewater systems, but significant contributions also occur through emissions from hospitals, PPCPs manufacturers, and agriculture. Abundance of PPCPs in raw wastewater is influenced by several factors, including the population density and demography served by WWTPs, presence of hospitals and drugs manufacturers in the sewershed, disease burden of the population served, local regulations, and climatic conditions. Based on the data obtained from WWTPs, analgesics, antibiotics, and stimulants (e.g., caffeine) are the most abundant PPCPs in raw wastewater. In conventional WWTPs, most removal of PPCPs occurs during secondary treatment, and overall removal exceeds 90% for treatable PPCPs. Regardless, the total PPCP mass discharged with effluent by an average WWTP into receiving waters (7.35–20,160 g/day) is still considerable, because potential adverse effects of some PPCPs (such as ibuprofen) on aquatic organisms occur within measured concentrations found in surface waters.

1. Introduction

Pharmaceuticals are primarily used for therapeutic, preventive, and diagnostic purposes, and they play an important role in the health outcome of humans (Fent et al., 2006). The global use of pharmaceuticals and personal care products (PPCPs) has continued to increase in the last decade due to advances in research and development, the growing world population, and increased accessibility to healthcare and pharmaceuticals (Van Boeckel et al., 2014). According to the IQVIA Institute for Human Data Science, 5.8 billion prescriptions were filled in the United States (US) alone in 2018 (The IQVIA Institute). In addition, approximately 100,000 "over the counter" (OTC) medicines and personal care products are sold in pharmacies and convenience stores in the US. Like many other man-made chemicals, PPCPs may be released into the environment at different phases of their lifecycle.

Advances in instrumentation and analytical capabilities have enabled the detection of low concentrations (as low as picograms per liter, pg/L) of several PPCPs in sewage, surface waters, groundwater, drinking water, soil, and aquatic organisms (Cantwell et al., 2017; Arpin-Pont et al., 2016a; Richardson and Ternes, 2018; Christian et al., 2003; Snow et al., 2020). A 2015 survey found that pharmaceuticals have been detected in the natural environment in more than 70 countries, representing all the continents (aus der Beek et al., 2016). In all, more than 600 different pharmaceutical substances have been detected in the environment (aus der Beek et al., 2016). The primary route of PPCPs into the environment is excretion by humans into wastewater systems, persistence during wastewater treatment, and subsequent discharge into the environment with treated wastewater effluent (Brown and Wong, 2018; Subedi and Loganathan, 2016; Kolpin et al., 2002; Watkinson et al., 2009). In addition, environmental exposure of PPCPs

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may also occur through various emissions from hospitals, the pharmaceuticals industry, and agriculture (Richardson and Ternes, 2018; aus der Beek et al., 2016; Van Boeckel et al., 2015; Snow et al., 2016).

Although several review articles on the occurrence of PPCPs in wastewater and the environment have been published, most of the articles focused on specific geographical locations (Liu and Wong, 2013; Balakrishna et al., 2017), environmental media (Arpin-Pont et al., 2016a; Deo, 2014; Sui et al., 2015), drug types/classes (Vieno and Sillanpää, 2014; Kümmerer, 2009), or organism's toxic response (Xin et al., 2021; Corcoran et al., 2010). Only a few reviews exist that compare the abundance, fate, and toxicity of broad classes of PPCPs in different environmental matrices on a global scale. A global review of occurrence of PPCPs in the environment (multiple phases) was published by aus der Beek et al. (2016) but there were no discussions on the fate of PPCPs in wastewater treatment plants (WWTPs) and the impact of detected PPCP on organisms. In contrast, Yang et al. (2017) extensively reviewed the occurrences and removal of PPCPs in drinking water and wastewater, but PPCPs occurrence in wastewater around the world was not discussed. Global-scale information on PPCPs occurrences in wastewater, removal during wastewater treatment, and occurrence and toxicity in the natural environment assembled in one document is useful to WWTP operators, regulators, and other stakeholders.

The objective of this study is to critically review current knowledge about the occurrence and fate of pharmaceuticals in aquatic systems—including WWTPs and natural waters around the world and summarize available information on the known toxicity of highly-detected PPCPs. More so, we aimed to compare the concentrations of PPCPs in WWTP discharges and those found in natural waters to the concentrations of PPCPs causing mortality in laboratory experiments. The article focused on six major classes of PPCPs, including analgesics, antibiotics, psychoactives, antihypertensives, anticholesteremics, and stimulants. These classes of PPCPs were selected because of their consumption volumes, abundance in raw and treated wastewater, and persistence in the environment.

2. Methodology

Selection of PPCPs: Representative compounds were selected from the PPCP classes this study focuses on based on consumption volume, abundance in the environment, and prevalence in the literature. Using these criteria, we selected 13 PPCPs, which constituted the focal point of this review. These PPCPs include two psychoactives (carbamazepine and fluoxetine), one antihypertensive drug (atenolol), non-opioid analgesics (acetaminophen, ibuprofen, naproxen, and diclofenac), one anticholesteremic drug (gemfibrozil), antibiotics (sulfamethoxazole, trimethoprim, tetracycline, and erythromycin), and a stimulant (caffeine). Where relevant, information on other PPCPs outside of these 13 were also included in the manuscript and/or supporting information (SI).

Bibliographic Database: Original and review articles were identified using scientific search engines including Web of Science, Scopus, Science Direct, and Google Scholar. Keywords used in search terms to identify relevant papers are summarized in Table S1. Additional articles were sourced from each relevant article identified with the keywords, using an iterative process. In addition, location-specific searches were performed for Africa and South America (using continents and/or specific country names in the search terms) since these locations have fewer relevant published works. For the toxicity data, studies were prioritized when published after 2010, with a few studies identified between 2000 and 2010 when more recent papers were not identified. Older papers were considered for the sections on occurrence and fate of PPCPs in wastewater and natural waters in order to have sufficient data from all regions of the world.

Data Analysis: Concentrations of PPCPs from different sampling points in WWTPs were used for calculation of stepwise removal efficiencies, which are presented in Section 3. The average concentrations discussed in Section 3.2 were calculated from absolute values reported in the literature. When studies reported concentration ranges instead of absolute values, those concentration ranges were recorded and used for analysis, but were not included in the calculation of average concentrations. In addition, the removal efficiency reported for each WWTP treatment stage was calculated by using PPCP concentrations in the influent and effluent of that specific stage. Most of the studies reviewed adopted the targeted screening approach as against the non-target and suspect screening methods. In addition, the bulk of studies considered for PPCP fate in WWTPs performed 24-hour composite sampling and sampled multiple times over a period of three days to three years (see detailed information in Tables S2 and S3). However, grab sampling was more commonly used in natural water studies (see detailed information in Table S4).

For toxicity data, an exhaustive list of studies included all types of organisms, endpoints, and test durations were compiled. However, toxicity data only using common species (*Daphnia* sp., *Pimephales promelas*, others), common endpoints such as growth, mortality, and reproduction (specifically LC50, lethal concentration at which 50% mortality is observed, and EC50, the half maximal effect concentration data), and test durations of 48–96 h for acute data, and $>$ 96 h for chronic data, were relied upon to make conclusions about PPCP toxicity.

3. Occurrence and fate of PPCPs in wastewater

3.1. Transformation of PPCPs in Humans

PPCPs are designed to interact with biological pathways in target systems during which they undergo enzyme-mediated metabolism (Berkner and Thierbach, 2014; Plósz et al., 2013). During this metabolism, PPCPs are often modified into phase I and phase II metabolites before excretion. Phase I metabolism involves oxidation, reduction, and hydrolysis; while phase II metabolism involves conjugation via the addition of glucuronic acid, sulfate, acetate, or amino acids (Plósz et al., 2013). The resulting metabolites are often released into the environment at higher concentrations than their respective parent compounds. However, some PPCPs are resistant to biochemical transformation, and are excreted without modification (Arnold and McNeill, 2007). Thus, PPCPs may enter the wastewater stream as the unchanged parent compound, as conjugates, or as metabolites (Monteiro and Boxall, 2010). Fluoroquinolones, tetracyclines, penicillin and some beta-blockers (antihypertensives) are commonly excreted unchanged, while analgesics undergo different degrees of metabolism (Monteiro and Boxall, 2010). Understanding the metabolic pathways prior to excretion is important for identifying the PPCP form in the environment.

3.2. Occurrence of PPCPs in wastewater

Prior to 2005, release of PPCPs from formulation facilities was overlooked (Larsson, 2008). However, following the detection of pharmaceuticals at concentrations as high as 31,000,000 ng/L (for ciprofloxacin, an antibiotic) in the effluent of a WWTP (near Hyderabad, India) serving pharmaceutical manufacturers (Larsson et al., 2007), several studies have investigated the contribution of PPCP manufacturers to the environment. A national survey conducted in the United States showed that final effluents from WWTPs that received discharges from PPCP manufacturers could contain 10–1000 times higher concentration of PPCPs than typically found in WWTPs that do not receive inputs from PPCP manufacturers (Phillips et al., 2010). On a global scale, we found that this is also true for several commonly used PPCPs, particularly, antibiotics (Fig. S1). Overall, PPCPs in wastewater is contributed by the sewerage users, including residences, landfills, health facilities, and PPCP producers (Phillips et al., 2010; Chonova et al., 2018; V.Thomas et al., 2007; Nikolaou et al., 2007; Maeng et al., 2016; Masoner et al., 2020).

The occurrence of PPCPs in raw wastewater around the world is

summarized in Fig. 1, and Tables S4 and S5. Analgesics occur at very high concentrations (relative to other pharmaceuticals classes) in municipal wastewater all over the world, with a range of 1.3–1,407,000 ng/L (Table S5). Note that much higher concentrations have been reported in hospital and pharmaceutical industry wastewater (Sim et al., 2010a; Ashfaq et al., 2017). The high values of analgesics found in raw wastewater are not surprising given that analgesics are critically relevant for public health (since most illnesses are associated with pain and inflammation (Hider-Mlynarz et al., 2018)). More so, many analgesics are widely available because they are sold as over-the-counter (OTC) drugs (Heberer, 2002a). They are also often taken at a high daily dose. According to the World Health Organization (WHO), the defined daily dose (DDD) for acetaminophen (paracetamol), ibuprofen and naproxen is 3, 1.2 and 0.5 g/day, respectively (WHOCC). In addition to these three compounds, other analgesics like acetylsalicylic acid (aspirin), diclofenac, and ketoprofen are commonly detected in wastewater (Tables S5 and S6).

Based on the data we obtained, we found that 75% of municipal wastewaters with the 20 highest concentrations of analgesics are in Europe (8 municipal wastewaters) and Africa (7 municipal wastewaters). The highest municipal WWTP influent concentrations reported for acetaminophen that we found include 1,090,000 ng/L (Nzoia Basin, Kenya), 500,000 ng/L (Canada), and 482,687 ng/L (Rhondda Cynon Taf, Wales) (K'oreje et al., 2018; Guerra et al., 2014; Kasprzyk-Hordern et al., 2009). As for the other analgesics detected in municipal wastewater, the highest reported concentrations we found were 1,407,000 ng/L for acetylsalicylic acid (South Korea), 603,000 ng/L for ibuprofen (Seville, Spain), 109,300 ng/L for naproxen (KwaZulu-Natal Province, South Africa), 115,100 ng/L for diclofenac (KwaZulu-Natal Province, South Africa), and 8560 ng/L for ketoprofen (Seville, Spain) (Madikizela and Chimuka, 2017; Santos et al., 2009; Sim et al., 2011).

The median municipal wastewater concentrations of analgesics observed in cities in Asia (540 ng/L) and South America (105 ng/L) were at least an order of magnitude lower than in Australia (8970 ng/L), Africa (8000 ng/L), North America (2485 ng/L), and Europe (1707 ng/L) (Fig. 1 and Table S5). The differences in influent concentrations of analgesics among different cities may be due to monitoring diligence, the population density and demography served by WWTPs, presence of hospitals and drug manufacturers in the sewershed, disease burden of the population served, accessibility to healthcare, and pharmaceutical consumption rates and patterns (Larsson et al., 2007; Hider-Mlynarz et al., 2018; Madikizela and Chimuka, 2017; King and Fomundam, 2010; Sarganas et al., 2015; Majumder et al., 2021). As an example, high consumption rates were hypothesized as the main cause of high

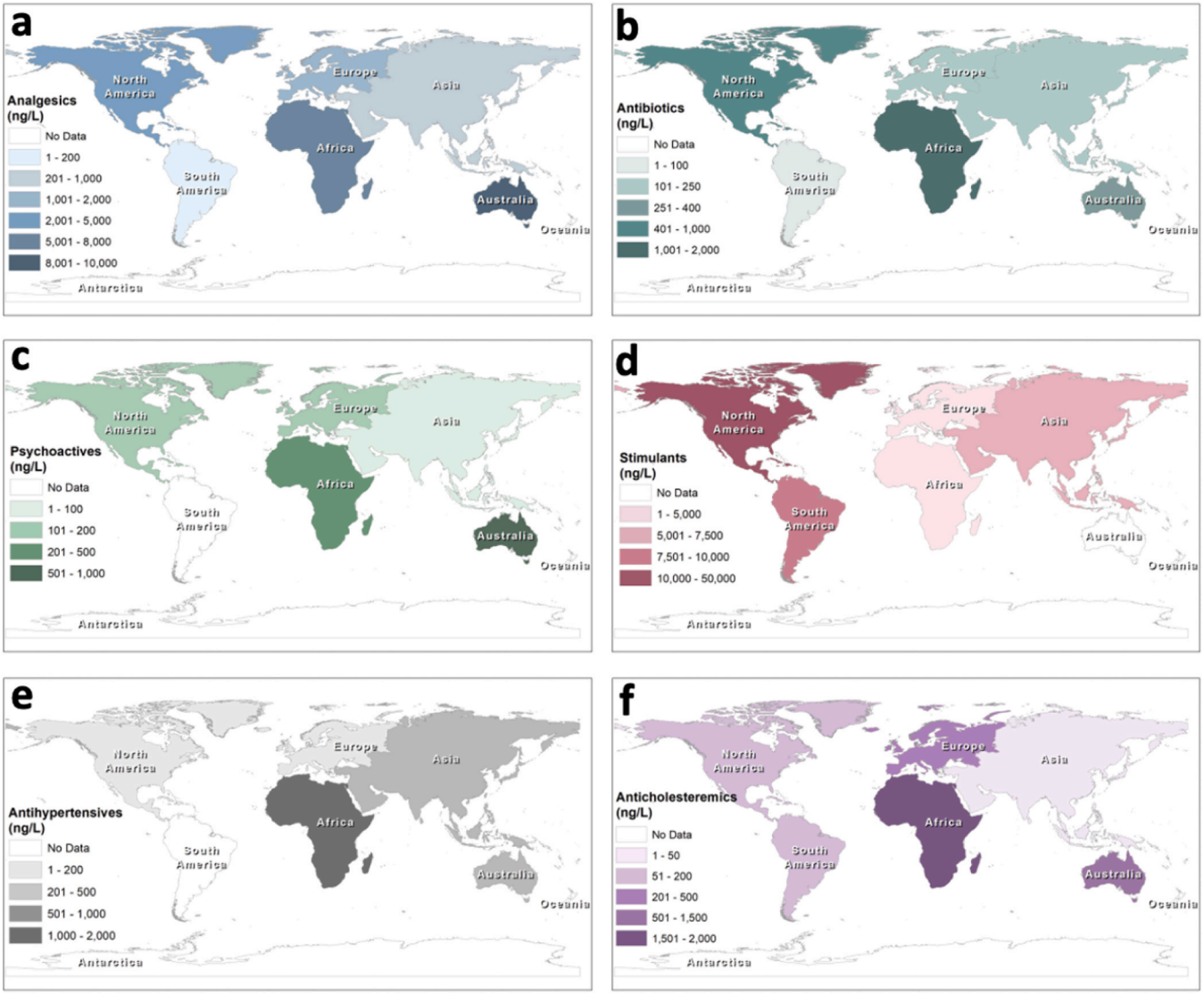

Fig. 1. Median concentration of (a) analgesics, (b) antibiotics, (c) psychoactives, (d) stimulants, (e) antihypertensives, and (f) anticholesteremics reported in raw municipal wastewater different continents.

occurrence of the analgesics and antibiotics in wastewater in KwaZulu-Natal Province, South Africa. However, based on a projected sale of about 577 tons of acetaminophen in 2013 (Matongo et al., 2015a), the calculated DDD/1000 inhabitants/day for the province (~46) is similar to consumption rates of analgesics in Europe (Hider-Mlynarz et al., 2018). The reason for high occurrence of analgesics in the wastewater in KwaZulu-Natal Province of South Africa may thus lie in population density per WWTP, or improper disposal behaviors (Hodes, 2019).

Although most countries classify antibiotics as prescription-only medicines, a non-prescription supply of antibiotics occurs all over the world, and is more rampant in developing countries (Auta et al., 2019; Zapata-Cachafeiro et al., 2019; Horumpende et al., 2018; Chang et al., 2018; Grigoryan et al., 2019; Sakeena et al., 2018). Antibiotics are also widely used in livestock production to prevent and treat diseases, promote growth, and improve productivity (Watanabe et al., 2010; Cromwell et al., 1996). Many antibiotics are poorly absorbed in human or animal guts, and 25–75% of consumed antibiotics are excreted as the unaltered parent compound in feces (Evgenidou et al., 2015). The concentration of antibiotics in raw municipal wastewater around the world is 1–303,500 ng/L (Table S6). Much higher concentrations of antibiotics are present in wastewater from pharmaceuticals manufacturers, landfill leachates, and farms (Zhang et al., 2013; Hou et al., 2016; Borquaye et al.,) (Fig. S1). The most detected antibiotics in raw municipal wastewater are ciprofloxacin, sulfamethoxazole, erythromycin, trimethoprim, and tetracycline. Seventy-five percent of 20 municipal WWTPs with the highest amount of antibiotics in their influent were in India. Raw wastewater in cities in Kenya, Sweden, Australia, and South Africa constituted the remaining 25%. When considering antibiotics in WWTPs serving PPCPs manufacturers, 17 out of the 20 highest concentrations were observed in China.

High concentrations of antibiotics are common in the wastewater from hospitals and pharmaceutical companies producing antibiotics (Fig. S1), and thus, in WWTPs receiving such waste streams (Larsson et al., 2007; Phillips et al., 2010; Lindberg et al., 2004). Local regulations also play an important role in the extent to which discharges of hospitals and pharmaceutical companies impact the influent of WWTPs. As an example, high occurrence of antibiotics (and other PPCPs) in the raw wastewater of a WWTP in India was attributed to the utility being located in an older area of the city with comparatively relaxed regulations, which may have allowed discharge of inadequately treated wastewater from industries and hospitals (Mohapatra et al., 2016). In addition, high levels of antibiotics in municipal wastewater may indicate widespread bacterial infections. For instance, high levels of antibiotics reported in Nzoia Basin, Kenya are due to the widespread use of combinations of sulfamethoxazole and trimethoprim for treating opportunistic infections occurring in people living with HIV/AIDS, which is prevalent in the region (K'oreje et al., 2018). The concentrations of antibiotics (and other PPCPs) in WWTP influent often exhibits a seasonal pattern, with the lowest concentrations observed in the summer and highest concentrations in the winter (Mohapatra et al., 2016; Golovko et al., 2014). High concentrations of antibiotics in winter months is linked to increased incidences of flu or other ailments that are common in colder seasons (Mohapatra et al., 2016; Coutu et al., 2013), and due to lower biodegradation rates of some antibiotics (LaPara et al., 2001). The median concentration of antibiotics in African wastewaters (1530 ng/L), where several antibiotics are commonly dispensed without prescription (Auta et al., 2019; Horumpende et al., 2018; Akinyandenu and Akinyandenu, 2014; Kalungia et al., 2016), is orders of magnitude higher than the rest of the world (Fig. 1, Table S5).

Like the co-occurrence of high concentrations of trimethoprim and sulfamethoxazole in the Nzoia Basin WWTP (K'oreje et al., 2018), several surveys of raw wastewater reported correlations between the concentrations of trimethoprim and sulfamethoxazole. Both pharmaceuticals are usually prescribed together (ratio 1:5 = trimethoprim: sulfamethoxazole) in a combination product known as Bactrim for the treatment of urinary and respiratory tract infections (Göbel et al., 2007; Ngigi et al., 2019). We observed a moderate correlation ($R^2 \approx 0.5$) between the concentrations of trimethoprim and sulfamethoxazole in the data used for this review (Fig. S2). Differences in the environmental fate of trimethoprim and sulfamethoxazole could lead to low correlation in their concentrations in raw wastewater despite their co-prescription.

Carbamazepine, fluoxetine, amitriptyline, and venlafaxine are the most reported psychoactives in municipal wastewater (Table S6). A few other psychoactives including lorazepam and benzodiazepine were also reported in studies (Čelić et al., 2019; Archer et al., 2017; Santos et al., 2013). Compared to other psychoactives, carbamazepine has a relatively high DDD (that is 1 g, compared to 0.1 g for venlafaxine and 0.02 g for fluoxetine) (WHOCC). Unsurprisingly, several studies performed across the world reported 100% detection frequency for carbamazepine in municipal wastewater influent (Mohapatra et al., 2016; Rivera-Jaimes et al., 2018; Sim et al., 2010b). Psychoactives are present in influents at concentrations up to three orders of magnitude lower than analgesics and antibiotics (Tables S4 and S5). The four highest reported raw wastewater concentrations of psychoactives (carbamazepine) that we found, 31,072 ng/L (United States), 21,600 ng/L (South Korea), 18, 500 ng/L and 17,100 ng/L (both in India) (Sim et al., 2011; Mohapatra et al., 2016; Blair et al., 2013b), were much higher than other reported concentrations (less than 10,000 ng/L). Overall, the median concentrations of various psychoactives reported in wastewaters in Asia (82 ng/L), Europe (129 ng/L), and North America (132 ng/L) were similar, and lower than the other continents (Table S5), except South America, which did not have sufficient studies for this analysis.

Global municipal wastewater influent levels of antihypertensives ranged from 0.26 to 294,700 ng/L (Table S6). The most commonly reported antihypertensives include atenolol, propranolol, metoprolol, valsartan, and sotalol (Balakrishna et al., 2017; Mohapatra et al., 2016; Archer et al., 2017; van Nuijs et al., 2010; Conkle et al., 2008; Bendz et al., 2005; Wang et al., 2018; Subedi and Kannan, 2015; Papageorgiou et al., 2016). The highest raw municipal wastewater concentrations of antihypertensives we found in different continents were for atenolol: 294,700 ng/L in Asia (India), 33,106 ng/L in Europe (Wales), 4790 ng/L in Australia, 3700 ng/L in North America (United States), and 2541 ng/L in Africa (South Africa) (Masoner et al., 2020; Kasprzyk-Hordern et al., 2009; Mohapatra et al., 2016; Archer et al., 2017; Trinh et al., 2011). We were unable to find measured values of atenolol in raw wastewater in South America, and only limited data were available for Africa. Concentrations of metoprolol and propranolol in raw municipal wastewater around the world was 2 – 79,500 ng/L and 0.26–1962 ng/L, respectively (Kasprzyk-Hordern et al., 2009; Mohapatra et al., 2016; Conkle et al., 2008; Wang et al., 2018; Subedi and Kannan, 2015; Kim et al., 2014; Behera et al., 2011). The highest concentrations of other antihypertensives reported in raw wastewater were 8400 ng/L (Portugal), 3573 ng/L (Spain), 169 ng/L (Belgium), and 141 ng/L (United States) for valsartan, sotalol, bisoprolol, and nadolol, respectively, (Masoner et al., 2020; Čelić et al., 2019; Santos et al., 2013; van Nuijs et al., 2010).

Stimulants are widely consumed in tea, coffee, soft drinks, energy drinks, and chocolate products. Caffeine, a typical stimulant, is one of the most consumed substances in the world (Quadra et al., 2020; Fisone et al., 2004). More than 8 billion kg of coffee were consumed globally between 2013 and 2017 (Luz et al., 2017). Several OTC and prescription analgesics, analeptics, appetite suppressants, and cold medicines also contain caffeine to enhance their effects (Buerge et al., 2003). Hence, like analgesics, caffeine is routinely found in raw wastewater at very high concentrations (Fig. 1). In fact, caffeine is often used as a tracer for fecal contamination (sewage spill) in surface water (Buerge et al., 2003). Higher concentrations of caffeine in wastewater influent have been reported in the summer compared to the winter, due to higher consumption of caffeinated beverages during hot summer months (Mohapatra et al., 2016). The highest concentrations of caffeine reported in raw municipal wastewater in different continents were 3,594,000 ng/L in

Asia (Singapore) (Tran et al., 2014), 1,214,375 ng/L in Africa (South Africa) (Archer et al., 2017), 150,413 ng/L in Europe (England) (Baker and Kasprzyk-Hordern, 2013), 130,000 ng/L in North America (United States) (Blair et al., 2013b), and 9310 ng/L in South America (Brazil) (Froehner et al., 2011). The median concentration of stimulants reported in North American municipal wastewater (43,100 ng/L) is an order of magnitude higher than other continents (Table S5).

Clofibric acid—a major metabolite of anticholesteremics such as clofibrate, etofibrate, and etofylline clofibrate—is frequently detected in raw wastewater (Stumpf et al., 1999). The highest concentrations of clofibric acid observed in raw municipal wastewater around the world include 2593 ng/L in Asia (China), 1000 ng/L in South America (Rio de Janeiro, Brazil), 651 ng/L in Europe (England), and 420 ng/L in North America (United States) (Stumpf et al., 1999; Lin et al., 2009; Roberts and Thomas, 2006a; Yu et al., 2013). We did not find studies that reported influent concentrations of clofibric acid in Africa and Australia. Gemfibrozil, another type of anticholesteremic, is also commonly detected at higher concentrations than clofibric acid in municipal wastewater (Čelić et al., 2019; Tran et al., 2014; Yu et al., 2013; Kosma et al., 2010). The highest concentrations of gemfibrozil detected in Europe, North America, Asia, and Australia were 17,055 ng/L (in Spain), 8500 ng/L (in United States), 6861 ng/L (in Singapore), and 3210 ng/L, respectively (Tran et al., 2014; Yu et al., 2013; Rosal et al., 2010a; Al-Rifai et al., 2007). Ockene et al. (2004) reported that the high concentrations of anticholesteremics in winter were consistent with the trend of elevated serum lipids in patients in winter (Golovko et al., 2014). Overall, the levels of anticholesteremics reported in raw municipal wastewater around the world (0.5–17,055 ng/L) is orders of magnitude lower those of analgesics, antibiotics, antihypertensives, and stimulants; but higher than that of psychoactives (Fig. 1, Tables S5 and S6).

3.3. Fate of PPCPs in WWTPs

WWTPs can serve as a sink as well as a pathway for releasing PPCPs into the natural environment (Archer et al., 2017; Zorita et al., 2009; Sui et al., 2010). Investigations of the fate of PPCPs in wastewater has increased in the last two decades as the presence of PPCPs in treated effluent raised concerns regarding their ecotoxicological effects in receiving waterbodies, and unintended exposure of humans (Evgenidou et al., 2015; Tiwari et al., 2017). It is worth noting that WWTPs are designed to remove nutrients, pathogens, and particulate matters from industrial and municipal wastewater, and currently do not specifically target or remove PPCPs (Liu et al., 2017; Guo et al., 2018). However, the concentrations of PPCPs may be decreased to varying degrees in WWTPs depending on the physicochemical properties of PPCPs, the WWTPs' treatment conditions, such as sludge retention time (SRT) and hydraulic retention time (HRT), and climatic conditions, such as precipitation and temperature (Zorita et al., 2009; Sui et al., 2010; Batt et al., 2007; Al Qarni et al., 2016). Therefore, a comprehensive understanding of the removal mechanisms and efficiencies of each treatment process is important and valuable for future efforts to improve WWTPs' removal efficiency of PPCPs. A summary of the removal efficiencies of different wastewater treatment stages for different PPCPs and their classes is provided in Fig. 2 and Table S7.

3.3.1. Primary treatment

Primary sedimentation/clarification, where large, coarse solids with sufficient density are removed by gravitational settling and fat/grease is skimmed from the top of wastewater, is most commonly used as primary treatment (Tchobanoglous et al., 2014). PPCPs may be removed during primary treatment by adsorption to settling particles or absorption into fat/grease floating on wastewater's surface (Carballa et al., 2004; Jelić et al., 2012). In general, traditional primary treatment has a low PPCPs removal efficiency. In fact, negative removal efficiency has been reported for some compounds (Blair et al., 2013b; Tiwari et al., 2017). For instance, Carballa et al. (2004) found that the removal efficiency of primary treatment for several PPCPs, including ibuprofen, naproxen, sulfamethoxazole, and hormones, ranged between 20% and 50%. Traditional primary treatment is also not efficient for removing carbamazepine from wastewater, with efficiency typically below 20% (Blair et al., 2013b; Behera et al., 2011; Sui et al., 2010; Carballa et al., 2004; Roberts et al., 2016). In fact, Behera et al. (2011) and Roberts et al. (2016) reported a removal efficiency of − 11% and − 32.7%,

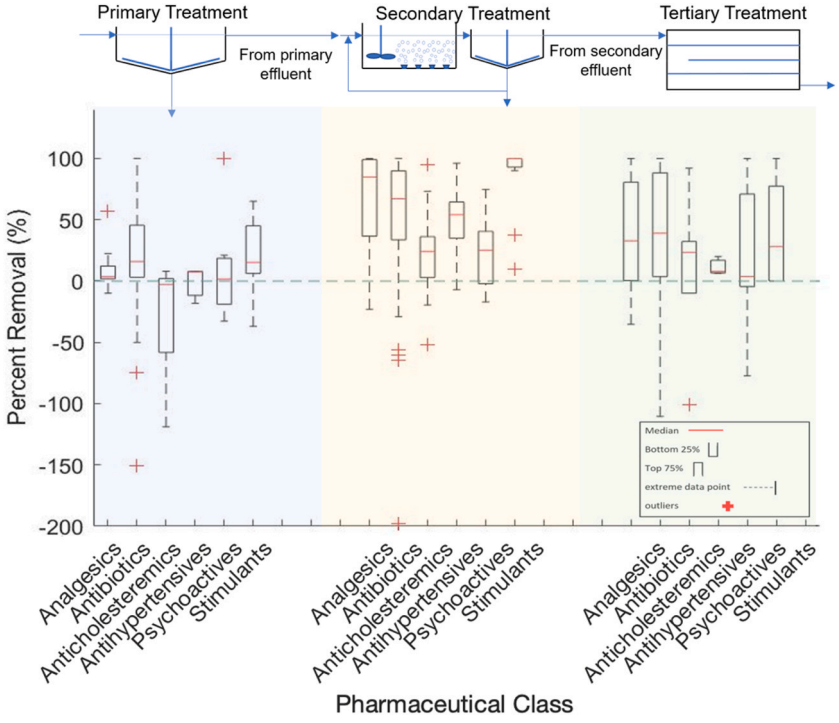

Fig. 2. Removal of different PPCP classes at each wastewater treatment stage.

respectively, for carbamazepine during primary treatment. Negative removal efficiencies after traditional primary treatment were also observed for gemfibrozil (−38%), an anticholesteremic, and atenolol (−20%), an antihypertensive (Blair et al., 2013b; Roberts et al., 2016). These findings show the potential for dissolved PPCP concentrations to increase during primary treatment, for instance, due to desorption from solid phases.

Primary treatment that involves the use of coagulants (known as chemically enhanced primary treatment [CEPT]), is believed to possess a better removal efficiency for PPCPs (relative to traditional primary treatment) (Carballa et al., 2004, 2005). However, information regarding the removal of PPCPs by CEPT is limited, and existing studies do not consistently support the hypothesis that the presence of coagulants enhances PPCPs' removal during primary treatment as enhanced removal would likely be experienced by PPCPs that have high affinity for wastewater solids (low solubility). Zorita et al. (2009) found that 17.4% of ibuprofen was removed with CEPT, but several other studies (such as Carballa et al., 2004; Thomas and Foster, 2005; Behera et al., 2011) reported CEPT removal efficiency of $< 5\%$ for ibuprofen, which was similar to or even lower than removal efficiencies reported for traditional primary treatment. In contrast, the removal of diclofenac increased from $< 10\%$ with traditional primary treatment to 50–70% in the presence of a coagulant (Carballa et al., 2005; Amin et al., 2014).

Commonly used coagulants include aluminum- and iron-based salts (Tchobanoglous et al., 2014; Sillanpää and Matilainen, 2015). More recently, organic polymers, such as polyamine, polyacrylamide, and poly-diallyldimethylammonium chloride (poly-DADMAC), were developed to facilitate primary treatment (Amin et al., 2014; Sillanpää and Matilainen, 2015; Wang et al., 2009). A very limited number of studies have compared the enhancement of PPCPs removal by different types of coagulants. Carballa et al. (2005) found that the removal efficiency of primary treatment for diclofenac reached approximately 70% in the presence of ferric chloride or aluminum sulfate. In comparison, only removal of diclofenac was observed when the coagulant used was aluminum polychloride (Carballa et al., 2005). The same study also found that of all the coagulants tested only ferric chloride promoted the removal of naproxen (Carballa et al., 2005). The use of coagulants is an additional cost to WWTPs, but the potential enhancement in the removal efficiency for PPCPs and other pollutants in wastewater implies that it may be a cost-effective strategy (Amin et al., 2014). Future studies on removal of PPCPs by CEPT need to further investigate the influence of coagulant dosages on the removal efficiency of PPCPs.

The fate of PPCPs during primary treatment is related to their physicochemical properties, such as hydrophobicity and acid dissociation constant (pK_a). Table 1 shows the octanol-water partition coefficients ($\log K_{ow}$), a proxy for hydrophobicity, and the pK_a values for some of the most frequently reported PPCPs. The $\log K_{ow}$ of most of the PPCPs is less than 4, which implies that they will not substantially adsorb to solids in wastewater or interact with grease (Zorita et al., 2009; Yang et al., 2011a). The removal of pharmaceuticals with high $\log K_{ow}$ values, such as diclofenac and fluoxetine, could be limited by their pK_a values, which are lower than the pH of wastewater (pH 6.8–8.3) (Yang et al., 2011a; Popa et al., 2012; Sedlak, 1991). Although the removal of PPCPs can be related to their $\log K_{ow}$ and pK_a, no statistical correlation between removal efficiency of primary treatment and either $\log K_{ow}$ or pK_a was observed. Additional investigations are needed to better understand and optimize removal of PPCPs based on their physicochemical properties. In addition to the physicochemical properties of the compounds, lower temperature generally decreases the removal efficiency of primary treatment for pharmaceuticals, although temperature was not important for the removal of carbamazepine and diazepam (Carballa et al., 2005). Although overall mass is unaffected, precipitation leads to dilution of PPCPs during wastewater treatment, which may decrease degradation kinetics.

3.3.2. Secondary treatment

Secondary treatment is also known as biological treatment. Common secondary treatment technologies in WWTPs include biological oxidation lagoons, rotating biological contact chambers (RBCs) (both of which are common in developing regions), trickling filters (TF), conventional activated sludge (AS), and membrane bioreactors (MBR) (Tchobanoglous et al., 2014; Verlicchi and Zambello, 2015). The removal of PPCPs at this stage depends on biotic degradation, chemical degradation, and adsorption onto sludge media (e.g. flocs) (Blair et al., 2013b; Michael et al., 2013).

Stimulants (89%) and analgesics (69%) are, on average, the most efficiently removed PPCP classes during secondary treatment (Fig. 3). Most widely used analgesics, except diclofenac, are efficiently removed by AS, TF, and MBR (Fig. 3) (Yang et al., 2011a; Radjenović et al., 2009; Wijekoon et al., 2013; Reif et al., 2008). For analgesics, the removal of acetaminophen (92–99%), ibuprofen (50–94%), and naproxen (48–95%) during biological treatment exceeds that of diclofenac (34–51%). The persistence of diclofenac during secondary treatment is mainly due to the chlorine groups in its structure (Tiwari et al., 2017; Joss et al., 2004). Clofibric acid and diazepam, two other chlorinated pharmaceuticals, are also less prone to biodegradation (Cirja et al., 2008). The recalcitrance to biodegradation caused by chlorine groups can be explained by their electron-withdrawing characteristic and electrophilic nature of the oxygen transfer to the reacting molecules (Andreozzi et al., 2006). In addition to the chemical compositions of analgesics, the method of secondary treatment influences analgesics removal. For example, the average removal of acetaminophen by AS, MBR and TF does not differ substantially; however, the removal of ibuprofen and naproxen via TF is lower than via AS (by 40% and 44%, respectively) and MBR (by 38% and 44%, respectively) (Fig. 3).

The average removal efficiency of antibiotics during secondary treatment is $58 \pm 28\%$. Overall, MBR is more efficient than AS or TF for removal of commonly used antibiotics from wastewater during secondary treatment (Fig. 3). Sulfamethoxazole is efficiently removed during secondary treatment (Blair et al., 2013b; Watkinson et al., 2007; Drillia et al., 2005). For example, Yang et al. (2011) reported a mean removal of 92% for sulfamethoxazole during secondary treatment, though the mechanism of removal is not well understood. Müller and coworkers postulated the high removal of sulfamethoxazole results mainly from microbial degradation due to its low tendency for adsorption (Müller et al., 2013). Lam et al. (2004) and Kümmerer et al. (2004) also demonstrated that sulfamethoxazole is highly persistent to biodegradation. Although sulfamethoxazole may serve as a source of carbon and nitrogen to microbes when ammonium and fatty acids are depleted, alternative carbon and nitrogen sources are abundant in wastewater, potentially preventing substantial degradation of sulfamethoxazole. The average removal of trimethoprim, an antibiotic typically prescribed with sulfamethoxazole (as discussed earlier) (Göbel et al., 2007; Michael et al., 2013; Clara et al., 2005), is approximately 64% during secondary treatment (Fig. 3). However, the range of reported removal is wide: low removal (13% and 42%) of trimethoprim was reported in two WWTPs in Hong Kong (Li and Zhang, 2011); the highest removal of trimethoprim (94%) reported in an Australian WWTP (Watkinson et al., 2009; Li and Zhang, 2011).

Tetracycline, another frequently detected antibiotic in wastewater (Hou et al., 2016), can be efficiently removed during conventional secondary treatment particularly by biological process via sorption onto sludge (Hou et al., 2016; Kim et al., 2014). For instance, MBR achieved a removal efficiency of 97% in a Canadian WWTP (Kim et al., 2014). Similarly high removal of tetracycline during secondary treatment was reported in Taiwan (66–90%) and in the United States (68–100%) (Lin et al., 2009, 2010; Karthikeyan and Meyer, 2006). In contrast, relatively lower removal efficiencies for tetracycline were reported by Watkinson et al. (2009) in Australia (43%) and by Li and Zhang (2011) in Taiwan (36%) (Watkinson et al., 2009; Li and Zhang, 2011). The complex chemistry of tetracycline favors its binding to solid phases in

Table 1
Physicochemical properties and removal during primary treatment of the most frequently reported pharmaceuticals.

Classification	Pharmaceutical	Molecular Weight (g/mol)	Log K_{ow}	pK_a	% Removal in Primary Treatment	% Average	Standard Deviation	Reference
Analgesics	Acetaminophen	151.2	0.46[a]	9.38[a]	5	3.5	1	(Blair et al., 2013b)
					2			(Gao et al., 2012)
					5			(Behera et al., 2011)
	Diclofenac	296.1	4.51[a]	4.15[a]	21.3	18.5	20	(Thomas and Foster, 2005)
					18.2			(Thomas and Foster, 2005)
					0			(Thomas and Foster, 2005)
					-7			(Sui et al., 2010)
					56.5			(Zorita et al., 2009)
					22			(Behera et al., 2011)
	Ibuprofen	206.3	3.97[a]	4.91[a]	2.1	6.4	6	(Thomas and Foster, 2005)
					2.8			(Thomas and Foster, 2005)
					12.2			(Thomas and Foster, 2005)
					-1.4			(Carballa et al., 2004)
					17.4			(Zorita et al., 2009)
					5			(Behera et al., 2011)
	Naproxen	230.3	3.18[c]	4.2[c]	3.9	3.4	9	(Thomas and Foster, 2005)
					1.7			(Thomas and Foster, 2005)
					3.1			(Thomas and Foster, 2005)
					3			(Blair et al., 2013b)
					-0.3			(Carballa et al., 2004)
					22.4			(Zorita et al., 2009)
					-10			(Behera et al., 2011)
Antibiotics	Erythromycin	733.9	3.06[a]	8.88[a]	9	-1.5	11	(Gulkowska et al., 2008)
					-12			(Göbel et al., 2007)
	Norfloxacin	319.3	0.46[c]	6.34, 8.75[c]	5	15.7	11	(Gulkowska et al., 2008)
					31			(Gao et al., 2012)
					11			(Golet et al., 2003)
	Sulfamethoxazole	253.3	0.89[a]	1.69, 5.7[a]	8	-8	13	(Blair et al., 2013b)
					-29			(Carballa et al., 2004)
					-1			(Gao et al., 2012)
					3			(Behera et al., 2011)
					-13			(Gao et al., 2012)
					-16			(Gulkowska et al., 2008)
	Tetracycline	444.4	-1.3[a]	3.30, 7.68, 9.69[a]	8	54	46	(Gulkowska et al., 2008)
					100			(Gao et al., 2012)
	Trimethoprim	290.3	0.91[a]	7.12[a]	20	8.5	33	(Blair et al., 2013b)
					10			(Behera et al., 2011)
					48			(Gao et al., 2012)
					-44			(Gulkowska et al., 2008)
Anticholesterol	Gemfibrozil	250.3	4.77[c]	4.5[c]	-38	-10	20	(Blair et al., 2013b)
					8			(Sui et al., 2010)
					0			(Behera et al., 2011)
Antihypertension	Atenolol	266.4	0.16[b]	9.6[b]	8	-5.1	13	(Behera et al., 2011)
					-18.2			(Roberts et al., 2016)
	Propranolol	259.3	3.48[b]	9.5[b]	NA	NA	NA	NA
Psychoactives	Carbamazepine	236.3	2.45[a]	13.9[a]	16	-3.4	20	(Blair et al., 2013b)
					14			(Sui et al., 2010)
					-11			(Behera et al., 2011)
					-32.7			(Roberts et al., 2016)
	Fluoxetine	309.3	4.05[b]	10.1[b]	-18	20.4	56	(Blair et al., 2013b)
					99			(Roberts et al., 2016)
					-19.8			(Zorita et al., 2009)
Stimulants	Caffeine	194.2	-0.07[a]	10.4[a]	6.2	12.6	26	(Thomas and Foster, 2005)
					15.3			(Thomas and Foster, 2005)
					23.9			(Thomas and Foster, 2005)
					-2			(Sui et al., 2010)

(*continued on next page*)

Table 1 (*continued*)

Classification	Pharmaceutical	Molecular Weight (g/mol)	Log K_{ow}	pK_a	% Removal in Primary Treatment	% Average	Standard Deviation	Reference
					65			(Subedi and Kannan, 2015)
					-37			(Gao et al., 2012)
					15			(Behera et al., 2011)
					14			(Blair et al., 2013b)

[a]Yang et al., 2011; [b]Roberts et al., 2016; [c]Monteiro and Boxall, 2010. NA means data were not available

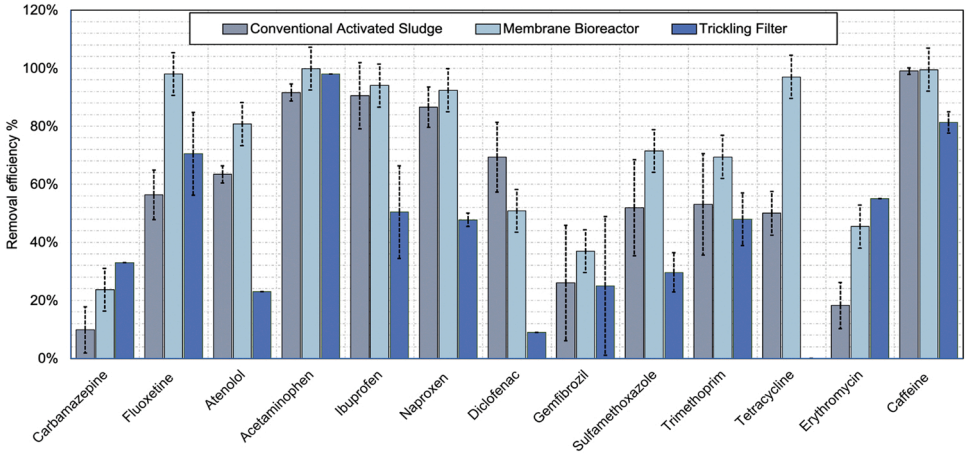

Fig. 3. Removal efficiency of different types of secondary treatment processes for pharmaceuticals and personal care products.

wastewater, making adsorption the major removal mechanism during secondary treatment (Michael et al., 2013; Kim et al., 2005). Tetracycline adsorption has also been observed during primary treatment (Watkinson et al., 2007). Since adsorption is a surface process, a higher concentration of biomass will likely favor the removal of tetracycline during secondary treatment (Kim et al., 2005). Most studies do not include information on biomass concentration (e.g., mixed liquor suspended solids [MLSS]), making it difficult to quantitatively investigate any correlation between biomass concentration in secondary treatment and the adsorption and subsequent removal of tetracycline.

Erythromycin is another antibiotic that is widely detected in wastewater. The removal of erythromycin during secondary treatment varies widely depending on the technology applied. Göbel et al. (2007) reported that the removal efficiency of secondary treatment for erythromycin ranged from < 0% using AS to 90% when SRT was maintained between 60 and 80 days. Radjenović et al. (2009) showed that erythromycin removal efficiency of AS, flat sheet MBR, and hollow fiber MBR was 35.4 ± 50.5%, 43.0 ± 51.5%, and 25.2 ± 108.9%, respectively. Li and Zhang (2011) reported removal of 15% and 26% for AS units in two WWTPs in Hong Kong.

The average removal efficiency for psychoactives during secondary treatment is 29 ± 16%. Biological treatment has limited effects on carbamazepine, the most frequently detected psychoactive in wastewater (Evgenidou et al., 2015), except in studies performed in arid regions under high temperature and intense solar irradiation, both of which improve biodegradation and chemical degradation (Al Qarni et al., 2016). The average removal of carbamazepine during secondary treatment is 13.0 ± 18.6%, with several studies reporting negative removal. For instance, Sui et al. (2010) found − 17% removal for carbamazepine via AS, while Yang et al. (2011a) reported − 8.7% via MBR. Evgenidou et al. (2015) corroborated the finding of negative carbamazepine removal found by both studies. Low removal of carbamazepine during secondary treatment is partly due to its recalcitrance to biodegradation (Brown and Wong, 2018; Subedi and Kannan, 2015; Calero-Díaz et al., 2017). Increases in carbamazepine concentrations during secondary treatment (or a negative removal efficiency) is caused by the conversion of glucuronide conjugates to carbamazepine during biological treatment (Evgenidou et al., 2015; Sui et al., 2010; Jelic et al., 2011). Glucuronide conjugates are formed during the metabolism of carbamazepine and its metabolites after consumption, and then enter wastewater thorough feces (Evgenidou et al., 2015; Sui et al., 2010; Jelic et al., 2011). Unlike carbamazepine, fluoxetine is more efficiently removed during secondary treatment due to its higher biodegradability. Radjenović et al. (2009) reported that MBR removed 98%, and AS removed 33.1% of fluoxetine from primary effluent. Baker and Kasprzyk-Hordern (Baker and Kasprzyk-Hordern, 2013) reported that 51% and 42% of fluoxetine was removed via AS and TF, respectively. Moreover, Fernandez-Fontaina et al. (2016) and Velázquez and Nacheva (2017) observed that improved nitrifying activities could promote the biodegradation of fluoxetine along with other pharmaceuticals (such as mefenamic acid and metoprolol), showing the potential of nitrification-denitrification in AS for PPCPs removal.

The removal efficiency for atenolol, an antihypertensive, is 33–73% using AS (Subedi and Kannan, 2015; Behera et al., 2011; Roberts et al., 2016; Jelic et al., 2011; Lian et al., 2017). Stumpf et al. (1999) found that the removal of atenolol was higher in summer than in winter because of increased microbial activities in summer. Similarly, higher removal of atenolol was reported in two Saudi Arabian WWTPs, due to high temperature and sunlight irradiation (Al Qarni et al., 2016). Radjenović et al. (2009) observed that the removal of atenolol was linked to the ammonia oxidation rate during wastewater treatment. The link between atenolol and ammonia is mainly due to the fact that atenolol is co-metabolized with ammonia by ammonia oxidizing bacteria (AOB) (Xu et al., 2017). MBR achieves an even greater removal for atenolol with efficiencies up to 96% (Radjenović et al., 2009; Jelic et al., 2011; Castiglioni et al., 2006). Propranolol, another common antihypertensive, has a wide range of reported removal efficiencies during secondary treatment. For instance, Radjenović et al. (2009) found that propranolol removal ranged between 0% and 96%. Low and negative propranolol removal efficiencies during secondary treatment were reported for propranolol in other studies (Subedi and Kannan, 2015; Ben et al., 2018). Lower removal of propranolol, relative to atenolol, in

secondary treatment is largely due to propranolol's resistance to degradation and low affinity for sorption (Kim et al., 2014).

The removal efficiency of anticholesteremics during secondary treatment ranges from negative values to more than 90% depending on the compound; the wide range is due to the physiochemical properties of individual compounds. Radjenović et al. (2009) and Jelic et al. (2011) showed that gemfibrozil was poorly removed by AS while MBR was moderately efficient (30–40%). However, other studies including Stumpf et al. (1999) and Behera et al. (2011) reported 34–40% and 91% of gemfibrozil was removed by AS, respectively. More samples need to be analyzed before a conclusive comparison can be made between AS and MBR for removing gemfibrozil. Bezafibrate, another common anticholesteremic, is effectively removed by both AS and MBR (> 90% by both methods) (Radjenović et al., 2009; Clara et al., 2005). In comparison, clofibric acid is highly persistent during secondary treatment, which is due to the combined effects of its chlorination (explained earlier) and its aromatic ring molecular structure (Tiwari et al., 2017; Andreozzi et al., 2006; Kimura et al., 2005).

Many factors play a role in PPCPs removal during secondary treatment, such as biomass concentration, the type of technology used, WWTP operating conditions such as SRT and HRT, and local temperature/sunlight intensity. Several studies reported that the high removal efficiency of some WWTP's secondary treatment for trimethoprim was related to higher SRTs (Göbel et al., 2007; Michael et al., 2013; Radjenović et al., 2009). Diazepam removal efficiency using AS increased from < 10% to approximately 20% with SRT > 100 days (Kreuzinger et al., 2004). Similarly, diclofenac removal increased from < 10% to approximately 50% with SRT > 40 days (Kreuzinger et al., 2004). However, increased SRT does not necessarily lead to a higher removal efficiency for all PPCPs (Göbel et al., 2007; Kreuzinger et al., 2004). For instance, a prolonged SRT negatively impacted the removal of erythromycin and ranitidine in MBR systems (Radjenović et al., 2009). Fluoxetine also had a higher removal with SRT < 20 days compared to SRTs between 20 and 40 days using AS (Suárez et al., 2012). Li and Zhang (2011) demonstrated that longer SRT was unfavorable for the elimination of tetracycline. Since the typical range of SRT for AS is between 3 and 15 days (Tchobanoglous et al., 2014), the removal efficiency for PPCPs using SRT < 40 days is more realistic for most WWTP operating conditions. Higher temperatures and sunlight intensity in the summer and in arid regions improves removal of pharmaceuticals by increasing the chemical and biodegradation rates (LaPara et al., 2001; Al Qarni et al., 2016). However, temperatures above 60 °C could limit the efficiency of secondary treatment by shifting the bacterial communities (LaPara et al., 2001).

3.3.3. Tertiary treatment

Tertiary treatment involves one or multiple treatment steps to further polish secondary effluent before the treated wastewater is discharged into the environment or reclaimed for uses such as irrigation, recreation or potable reuse (Environmental and Pollution Science, 2019). A wide selection of technologies has been employed for tertiary treatment of wastewater, including chlorination, ozonation, advanced oxidation process (AOP), and membrane filtration units. Although several treatment facilities around the world perform (suites of) tertiary treatments, only fifteen studies contained specific information on PPCPs removal efficiency for the tertiary treatment steps (Table 2). Most of these fifteen studies specified irrigation and recreational reuse of final effluent (Blair et al., 2013b; Yang et al., 2011a; Dotan et al., 2016); only one study, Kim et al. (2007), explored the possibility of potable reuse (Blair et al., 2013b; Yang et al., 2011a; Dotan et al., 2016; Kim et al., 2007).

The removal of PPCPs during tertiary treatment varies widely and is associated with complexities arising from: combinations of tertiary treatments, dosage of chemicals or irradiation, contact or reaction time, and the mixtures of PPCPs and metabolites present. Ozonation is a strong oxidation process in which PPCPs are attacked by ozone molecules and/or hydroxyl radicals. Treatment trains that include ozonation achieved mid to high removal efficiency for most PPCPs. For example, more than 50% of ketoprofen, naproxen, and acetaminophen residuals in secondary effluent were removed by ozonation (Nakada et al., 2007a; Rosal et al., 2010b) as compared to the negative and low removal reported when using sand filtration as the tertiary treatment method (Zorita et al., 2009; Sui et al., 2010). Minimal and negative removal of PPCPs by chlorination were reported. In particular, Blair et al. (2013b) reported an over two-fold increase in the concentration of sulfamethoxazole, trimethoprim, and triclosan after chlorination (with sodium hypochlorite) and de-chlorination (with sodium bisulfite). Although no explicit explanation was provided by the authors, the increases in PPCP concentrations during chlorination could be due to reformation of the compounds from their metabolites or conjugates (Blair et al., 2013b; Gao et al., 2012). A major drawback of using chlorination as a tertiary treatment technology for PPCPs is formation of disinfection byproducts (DBPs), some of which may be toxic (Negreira et al., 2015; Bulloch et al., 2012; Guillen et al., 2020; Andrzejczyk et al., 2020).

In comparison, filtration-based tertiary treatment technologies, such as ultrafiltration (UF), nanofiltration (NF), microfiltration (MF), and reverse osmosis (RO), are highly efficient in removing PPCPs from secondary effluent (Table 2). The removal of PPCPs, including ones that had negative removals during chlorination and sand filtration, had over 90% removal with the combination of MF and RO (Sui et al., 2010; Kim et al., 2007). UF uses permeable membranes to remove contaminants with molecular weights between 10^3 and 10^6 Da. UF membranes have pore sizes of 1–50 nm, though some manufacturers make UF systems with a wider pore size range, such as 10–100 nm (Ultrafiltration Membranes,; What Is Ultrafiltration, 2020; Singh and Hankins, 2016; Youcai, 2018). The elimination efficiency of MF and UF for soluble PPCPs with small molecular weights (200–400 Da) is low since the molecular weight cut-off (MWCO) of MF and UF is 10^6 and 10^3 Da, respectively (Sui et al., 2010). On the other hand, NF membranes have a MWCO range from 200 to 500 Da (Park and Snyder, 2020), and RO membranes have pore sizes smaller than 1 nm and can remove molecules smaller than 200 Da (Khulbe et al., 2008). Thus, NF and RO have high removal efficiencies for PPCPs (Sui et al., 2010). The small MWCOs and pore sizes of NF and RO membranes also necessitate the use of MF or UF as pretreatment, to prevent fine colloids and hard scales from forming irreversible fouling on the NF and RO membranes (Cardona et al., 2005; Bhattacharya et al., 2013).

Although advanced filtration tertiary treatment technologies such as ozonation, reverse osmosis, and membrane filtration have high removal efficiencies, they are expensive to set up, and are energy intensive. These factors create barriers for implementation in WWTPs. For wastewater with low turbidity and salinity (i.e. effluent from a conventional WWTP), the energy consumption of UF is 0.2–0.3 kW h/m^3, and approximately 2 kW h/m^3 for RO (Glucina et al., 1998; Kesieme et al., 2013; Gilron, 2016). It is also worth noting that MF, UF and RO are prone to an excess net pressure driving force from fouling and low fluxes. The increased net pressure driving force can lead to higher energy cost and potential membrane defects such as bursting, which would require frequent maintenance (Avlonitis et al., 2003; Ruiz-García et al., 2017).

3.3.4. Overall removal

The overall removal efficiency of PPCPs is dependent on the properties of the compounds, and the configurations and operating conditions of WWTPs. Since the configurations (e.g., some WWTPs are equipped with tertiary treatment) and operating parameters (such as SRT, and pH) vary from plant to plant, it is challenging to equitably compare the removal efficiencies for PPCPs across multiple studies. More so, temperature, which affects primary and secondary treatments and varies spatially and/or temporally, contributes to the spread of overall efficiency observed (LaPara et al., 2001; Al Qarni et al., 2016;

Table 2
The removal rates of pharmaceuticals during various tertiary treatment processes.

Plant/Facility name and Location	Effluent Use	Treatment Process	PPCP Class	PPCP name	Initial Concentration (ng/L)	% Removal in Tertiary Treatment[a]	Reference
The F. Wayne Hill Water Resources Center (Georgia, United States)	Non-potable reuse	Granular media, MF, combined flow to GAC and ozonation	Antibiotics	Sulfamethoxazole	2600*	81	(Yang et al., 2011a)
				Erythromycin	340*	99.3	
				Lincomycin	21*	> 28	
				Ciprofloxacin	620*	98.6	
				Levofloxacin	460*	99.3	
				Tetracycline	160*	> 80	
				Triclosan	470*	> 30	
			Psychoactives	Carbamazepine	230*	99.6	
			Stimulants	Caffeine	80,000*	73.8	
			Analgesics	Acetaminophen	80,000*	NA[b]	
				Ibuprofen	11,000*	> 85	
Arlington County Water Pollution Control Plant (Virginia, United States); City of Alexandria Sanitation Authority (Virginia, United States); Noman M Cole Water Pollution Control Plant (Virginia, United States)	Outfall	Sand filtration + UV	Analgesics	Diclofenac	490	> 99	(Thomas and Foster, 2005)
				Ibuprofen	4700	0–33	
				Ketoprofen	453	8.7–47	
				Naproxen	12,800	18.4–46.7	
			Antibiotics	Triclosan	3300	12.2–56.9	
			Stimulants	Caffeine	43,100	> 99	
Ra'anana/Ben-Gurion airport/ Shafdan/Hod Hasharon/Yeruham, Israel	Non-potable reuse	Sand filtration	Antibiotics	Triclosan	900	50	(Dotan et al., 2016)
		NA		Triclosan	1100	> 99	
		Soil-aquifer treatment		Triclosan	2800	50	
		Sand filtration + UV		Triclosan	900	50	
		Sand filtration		Triclosan	1300	66.7	
Canada	NA	UV	Antihypertensives	Enalapril	NA	2	(Kim et al., 2014)
South Shore Water Reclamation Facility (Wisconsin, United States)	Non-potable reuse	Chlorination	Analgesics	Acetaminophen	5900	-34.5	(Blair et al., 2013b)
				Naproxen	780	73	
				Codeine	15	-61.3	
			Antibiotics	Ofloxacin	980	< 0	
				Sulfamethoxazole	54	-168	
				Trimethoprim	205	-193	
			Anticholesteremics	Gemfibrozil	29	59.5	
			Antiseptics	Triclosan	650	19.2	
			Stimulants	Caffeine	3300	69	
			Antihistamines	Diphenhydramine	35	-145	
			Psychoactives	Carbamazepine	21	-125	
				Fluoxetine	6.1	-237	
Jožef Stefan Institute (Ljubljana, Slovenia)	Laboratory study	UV	Analgesics	Naproxen	NA	15	(Zupanc et al., 2013)
				Diclofenac	NA	17	
				Ibuprofen	NA	2	
				Ketoprofen	NA	18	
			Psychoactives	Carbamazepine	NA	90	
Beijing, China	NA	UF + ozonationSand filtration	Analgesics	Diclofenac	125	> 90	(Sui et al., 2010)
						< 0	
		MF + RO				> 90	
		UF + ozonation	Anticholesteremics	Gemfibrozil	60	80–90	
		Sand filtration				50–80	
		MF + RO				> 90	
		UF + ozonation	Antibiotics	Trimethoprim	400	> 90	
		Sand filtration				80–90	
		MF + RO				> 90	
		UF + ozonation	Psychoactives	Carbamazepine	113	> 90	
		Sand filtration				0–50	
		MF + RO				> 90	
		UF + ozonation	Anticholesteremics	Clofibric acid	26.3	50–80	
		Sand filtration				< 0	
		MF + RO				80–90	
		UF + ozonation		Bezafibrate	56.8	0–50	
		Sand filtration				0–50	
		MF + RO				> 90	
		UF + ozonation	Stimulants	Caffeine	5196	50–80	
		Sand filtration				< 0	
		MF + RO				50 – 80	
Kristianstad, Sweden	Outfall	Sand filtration	Analgesics	Diclofenac	230	-1.3	(Zorita et al., 2009)
				Ibuprofen	6900	30.5	
				Naproxen	4900	11.8	
			Anticholesteremics	Clofibic acid	53.5	24.3	
East Lansing Wastewater Treatment Facility (East Lansing, United States)	Outfall	Chlorination and sand filtration	Analgesics	Acetaminophen	2800	~ 0	(Gao et al., 2012)
			Antibiotics	Chlortetracycline	178	~ 0	
				Oxytetracycline	286	-15	

(continued on next page)

Table 2 (*continued*)

Plant/Facility name and Location	Effluent Use	Treatment Process	PPCP Class	PPCP name	Initial Concentration (ng/L)	% Removal in Tertiary Treatment[a]	Reference
				Sulfadiazine	374	5	
				Sulfamethoxazole	15,639	20	
			Stimulants	Caffeine	41,211	~ 0	
Ulsaan, South Korean	Outfall	UV, DOF and filtration	Analgesics	Acetaminophen	7460	35	(Behera et al., 2011)
				Diclofenac	131	-20	
				Ibuprofen	2265	-10	
				Ketoprofen	202	48	
				Naproxen	2548	-30	
			Antibiotics	Lincomycin	8176	1	
				Sulfamethoxazole	120	15	
				Trimethoprim	205	23	
			Anticholesteremics	Gemfibrozil	222	-10	
			Antihypertensives	Atenolol	7801	20	
			Psychoactives	Carbamazepine	72	-1	
			Stimulants	Caffeine	2349	28	
Canberra, Australia	Outfall	Filtration + chlorination	Antihypertensives	Atenolol	278	3.6–8.7	(Roberts et al., 2016)
				Metoprolol	379	7.8	
				Sotalol	517	-100.5	
			Psychoactives	Carbamazepine	589	-1.5	
				Fluoxetine	51.1	-4.5	
				Sertraline	285	43.8–64.1	
				Venlafaxine	100	19.5–23.5	
			Antihistamines	Diphenhydramine	10.5	30.7–35.9	
Tokyo, Japan	NA	Sand filtration + ozonation	Analgesics	Ibuprofen	785	36.1	(Nakada et al., 2007b)
				Ketoprofen	454	51.9–93.2	
				Naproxen	311	68–99.7	
			Antibiotics	Erythromycin	150	88.7	
				Roxithromycin	27.2	90.9	
				Sulfamethoxazole	104	87.4	
			Psychoactives	Carbamazepine	81.9	8.25	
Jeju Island /South Jeolla, South Korean	Potable and non-potable reuse	RO, NF, RO-UV, NF-UV	Analgesics	Acetaminophen	11,500	> 99	(Kim et al., 2007)
				Diclofenac	10	> 90	
				Hydrocodone	10	90	
				Ibuprofen	5320	> 99	
				Naproxen	262	> 99	
			Antibiotics	Erythromycin	44	> 95	
				Sulfamethoxazole	194	> 99	
				Trimethoprim	21	> 95	
			Antiseptics	Triclosan	42	> 99	
			Psychoactives	Carbamazepine	312	> 95	
			Stimulants	Caffeine	9680	> 99	
Shatin/Stanley Wastewater Treatment Plant (Hong Kong, China)	Outfall	Disinfection	Antibiotics	Cephalexin	440	99	(Li and Zhang, 2011)
				Chlortetracycline	2743	6	
				Erythromycin	2385	24	
				Ofloxacin	1499	39	
				Sulfadiazine	789	4	
				Sulfamethoxazole	619	> 99	
				Tetracycline	1674	13	
				Trimethoprim	2554	40	
Zurich-Werdhölzli Waste Water Treatment Plant (Zurich, Antihypertensives Switzerland)	NA	Flocculation + filtration	Antibiotics	Ciprofloxacin	494	83	(Golet et al., 2003)
				Norfloxacin	433	88	

In some instances, the name of the treatment facility was not available. * Primary effluent concentration. a The removal efficiency represents the amount of PPCPs removed from secondary effluent. Abbreviations found in the table: DOF – Dissolved ozone flotation, GAC – granular activated carbon, MF – microfiltration, NA - not available, NF – nanofiltration, RO – reverse osmosis, UF – ultrafiltration, and UV – ultraviolet light.

Carballa et al., 2005). In this review, the overall removal efficiency was obtained by comparing PPCPs concentrations in primary influent (C_{in}) to final stage effluent (C_{eff}). Data are presented in log form (Eq. 1) to allow for visual comparison among compounds that vary largely in concentration. Tertiary treatment was considered the final stage for WWTPs that have this step. The papers used to determine overall removal are listed in Table S8 and the data are summarized in Fig. 4.

$$\text{Log Removal} = -\log_{10}\left(\frac{C_{eff}}{C_{in}}\right) \quad (1)$$

Analgesics and caffeine have the highest average overall removal efficiency (Fig. 4, Table S8), partially due to their high average wastewater influent concentration. Studies reported more than one-log removal (>90%) for ibuprofen, and over two-log removal (>99%) for acetaminophen and caffeine (Fig. 4a and b). Secondary (biological) treatment accounts for the majority of the removal of acetaminophen and caffeine due to their high bioavailability (Fig. 2, Tables S6-S7) (Tiwari et al., 2017; Yang et al., 2011a). Similarly, ibuprofen and naproxen are efficiently removed via secondary treatment and in the entire treatment process, due to metabolic or co-metabolic biodegradation (Tiwari et al., 2017; Oulton et al., 2010). It is worth noting that despite the high overall removal, residual analgesics and caffeine are present in the final effluent because of their high concentration in raw municipal wastewater. Diclofenac, another popular analgesic, is persistent in most WWTPs (Fig. 4a). Increases in diclofenac concentration in final effluent compared to influent have been reported by multiple studies (Archer et al., 2017; Kermia et al., 2016).

In general, the overall removal efficiencies of WWTPs for antibiotics

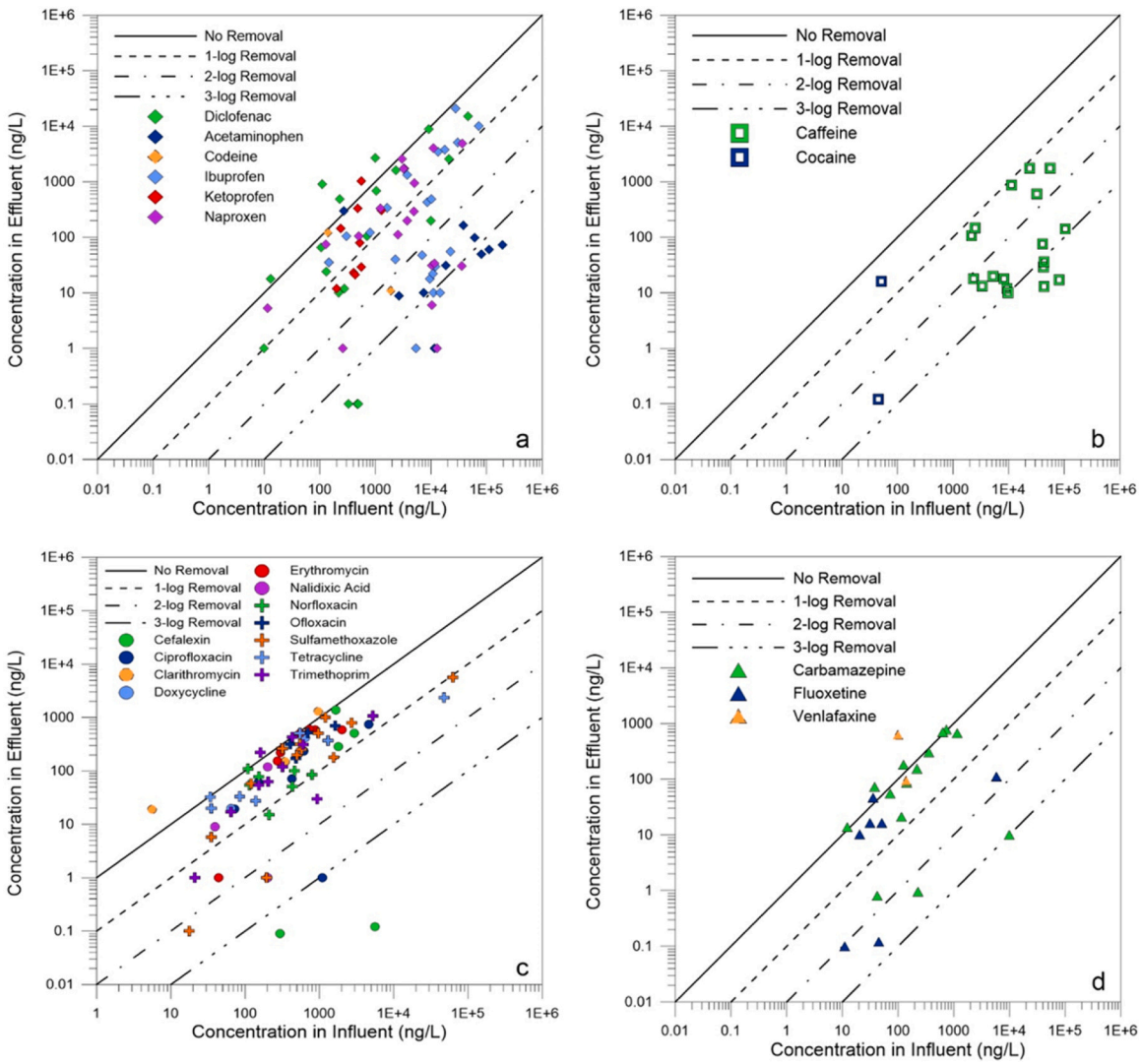

Fig. 4. Overall removal of (a) analgesics, (b) stimulants, (c) antibiotics, and (d) psychoactives during wastewater treatment. The papers reviewed for this figure are listed in Table S4.

are positive (Fig. 4c). Various studies reported overall removal efficiencies over 90% for several antibiotics, including sulfamethoxazole, trimethoprim, and tetracycline (K'oreje et al., 2018; Michael et al., 2013; Gao et al., 2012). The highest overall removal of antibiotics was reported in WWTPs equipped with advanced filtration technologies (such as RO and NF) in the tertiary treatment step (Table 2) (Kim et al., 2007). Dolar et al. (2012) and Michael et al. (2013) reported outstanding removal of antibiotics (up to > 99%) using a combination of MF and RO (Michael et al., 2013; Dolar et al., 2012). Although psychoactives are poorly removed during secondary treatment, overall removal of psychoactives is high (> 90%) for certain tertiary treatment trains (Fig. 4d, Table 2) (Westerhoff et al., 2005; Ikehata et al., 2008). Yang et al. (2011a) showed more than 99% removal of carbamazepine in a WWTP that combined granular activated sludge (GAC) and ozonation as tertiary treatment.

Limited data are available regarding the removal of antibiotics, stimulants, psychoactives and other PPCP classes within WWTPs, especially when compared to the information available for analgesics. In all, we found 11 removal efficiency datasets for anticholesteremics and 6 for antihypertensives (Fig. S7). Limited data makes it difficult to observe global removal patterns for these pharmaceutical classes. It should be noted that each study considered in Fig. 4 provides data that may be specific to the operations of the WWTP(s) studied, which explains the wide range in the overall data for each compound. However, the overall removal efficiency data clearly shows that several WWTPs discharge considerable amounts of PPCPs into receiving waterbodies. For this reason, it is imperative to understand the fate of PPCPs in natural waters as well as the toxic effects they may have on aquatic organisms.

4. Occurrence and fate of PPCPs in natural waters

The total daily mass of PPCPs discharged with effluent after conventional wastewater treatment (estimated using Eq. 2) is 7.35–20,160 g/day. The total mass decreases to 4.8–10,602 g/day when WWTPs apply tertiary/advanced treatment. This suggests a considerable input of PPCPs (which may include persistent compounds) into the environment, including natural waters (Batt et al., 2006). Over the past decade, the literature has confirmed the occurrence of PPCPs in natural waters around the world, including freshwater (such as rivers, streams, lakes), marine and estuary environments, groundwater, and sediments (aus der Beek et al., 2016; Kolpin et al., 2002; Chopra and Kumar, 2018) (Fig. 5 and S9).

$$\text{Total daily PPCP mass discharged} = \sum \left[\text{PPCP}_{\text{effluent}}\right] \times \text{Flow rate} \qquad (2)$$

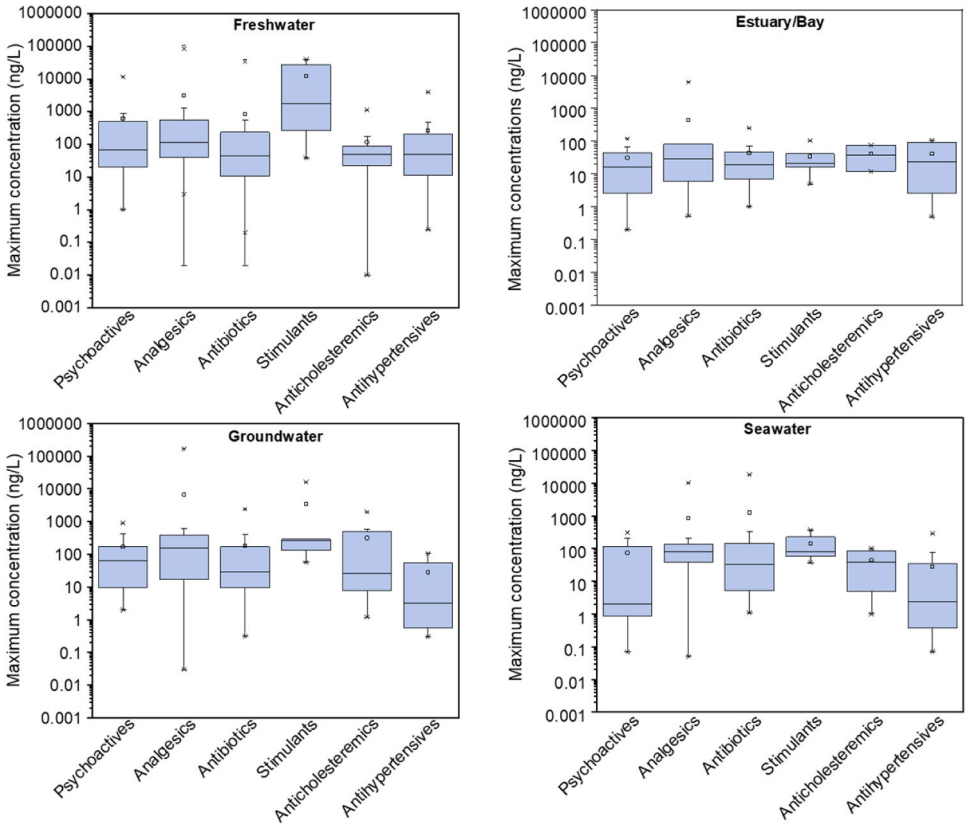

Fig. 5. Maximum concentrations of major PPCP classes in natural waters. The horizontal lines in the boxes represent the median concentrations of the PPCPs. The whiskers (vertical lines above and below the box plots) show the variability of the data outside the upper and lower quartiles while mild and extreme outliers are marked with "□" and "*" respectively.

4.1. Occurrence of PPCPs in freshwater

In general, concentrations of common PPCPs are higher in freshwater than in groundwater and saline waters (Fig. 5). Based on our observations, antibiotics and analgesics are the most frequently detected PPCPs in freshwater. In addition, we observed that PPCPs are more frequently found in rivers than in lakes. The concentrations of PPCPs in freshwater (Table 3 and S8) are generally lower than in raw or treated wastewater due to dilution effects. Analgesics represent the majority of the highest PPCP concentrations reported in Africa, including 107,000 ng/L of acetaminophen in Ngong River, Kenya (K'oreje et al., 2016); 84,600 ng/L of ibuprofen in Msunduzi River, South Africa (Matongo et al., 2015b); 62,000 ng/L of ibuprofen in Umgeni River, South Africa (Matongo et al., 2015a), and 57,160 ng/L of diclofenac in Ogun State, Nigeria (Olaitan et al., 2014). The concentrations of analgesics detected in North American and European freshwaters are generally lower than those observed in Africa despite having similar median analgesic concentrations in municipal wastewater influent (Table S5) (Loos et al., 2009). Overall, we observed higher concentrations of analgesics in freshwaters of developing countries, regardless of population density (Fig. S3). The higher occurrence of PPCPs in freshwaters of developing countries may be attributed to one or more of the following: a high consumption rate, direct municipal sewage discharge due to lack of proper sanitation facilities, inadequate sewage treatment, or discharges/disposal from nearby pharmaceutical factories and PPCP sellers due to weaker regulations (Matongo et al., 2015a, 2015b; Hodes, 2019; Olaitan et al., 2014; Aydin and Talinli, 2013; K'oreje et al., 2012; Rehman et al., 2015; Michael et al., 2019; Rimayi et al., 2019a; Kandie et al., 2020).

Stimulants have been reported at higher concentrations in freshwater than in other aqueous media (Fig. 5). The highest concentration of caffeine in freshwater (144,179 ng/L), based on our literature search, was reported in Asia by Tran et al. (2014). Similar caffeine concentrations of 39,813 ng/L, 33,200 ng/L and 32,400 ng/L were reported in a European waterbody (Loos et al., 2009), Msunduzi River (KwaZulu--Natal, South Africa) (Matongo et al., 2015b), and Atibaia River (Brazil), respectively (Sodré et al., 2007). These concentrations, based on the studies we reviewed, represent the highest caffeine concentrations reported in European, African, and South American freshwaters. High occurrence of caffeine was also reported in Iguaçu River, Brazil (27,000 ng/L) (Ide et al., 2017a; Zhang et al., 2012b), and Ahlat Creek, Turkey (20,427 ng/L) (Aydin and Talinli, 2013). The high concentrations of caffeine in Brazilian rivers is attributed to the widespread consumption of caffeine-containing products coupled with discharge of untreated and/or insufficiently treated wastewater (Sodré et al., 2007). In addition, high concentration of caffeine in Brazilian waters is an indicator of high Loads of untreated domestic sewage and ineffective sanitation Systems (López-Doval et al., 2017; de Souza et al., 2021).

Psychoactive drugs are incompletely metabolized in the body (Calisto and Esteves, 2009; Kosjek et al., 2012), and have low removal in WWTPs (Fig. 4d). Based on the studies we reviewed, the highest concentration of carbamazepine, a common psychoactive, observed in freshwater (11,561 ng/L) was reported in a European river by Loos et al. (2009). Relatively high concentrations of antihypertensives have also been reported globally, particularly in freshwaters of developed countries. Metoprolol was found in Llobregat River (Catalonia, Spain) at concentrations as high as 3960 ng/L (Osorio et al., 2012). Similarly, high concentrations of atenolol were detected in Ebro River, Spain (maximum concentration = 1237 ng/g) (Silva et al., 2011), Mankyung River, South Korea (maximum concentration = 690 ng/g) (Kim et al., 2009), and River Taff, Wales (maximum concentration = 560 ng/g) (Kasprzyk-Hordern et al., 2009). In Eurasia, propranolol and atenolol

Table 3
PPCP concentrations reported in natural waters and sediments.

Class	Compound	Matrix	[a]Concentration range in water (ng/L)	[a]Concentration range in sediment (ng/g)
Antihypertensives	Atenolol	Freshwater	0.25–1237 (Kasprzyk-Hordern et al., 2009; Bendz et al., 2005; Aydin and Talinli, 2013; Osorio et al., 2012; Silva et al., 2011; Beretta et al., 2014; Valdés et al., 2014; Yoon et al., 2010)	0.27–10.4 (Silva et al., 2011; Osorio et al., 2016)
		Estuary/Bay	0.5–38.34 (Cantwell et al., 2017;Alder et al., 2010; Klosterhaus et al., 2013a; Birch et al., 2015)	0.48–9.84 (Beretta et al., 2014)
		Seawater	82–293 (Afonso-Olivares et al., 2013; Krogh et al., 2017; Wille et al., 2010)	
		Groundwater	0.8–106 (Vulliet and Cren-Olivé, 2011; Schaider et al., 2014; Teijon et al., 2010)	
	Metoprolol	Freshwater	0.5–3960 (Kasprzyk-Hordern et al., 2009; Bendz et al., 2005; Osorio et al., 2012; Silva et al., 2011; Kunkel and Radke, 2012; Singh and Suthar, 2021b)	0.04–1.94 (Silva et al., 2011; Osorio et al., 2016)
		Estuary/Bay	1.1–313 (Cantwell et al., 2017)	
		Seawater	0.1–18 (Moreno-González et al., 2015; Magnér et al., 2010; Weigel et al., 2004)	
		Groundwater	0.3–56.3 (Vulliet and Cren-Olivé, 2011; Radjenović et al., 2008)	
Analgesics	Acetaminophen	Freshwater	1–107,000 (Kasprzyk-Hordern et al., 2009; K'oreje et al., 2016; Matongo et al., 2015b; Olaitan et al., 2014; Osorio et al., 2012; Silva et al., 2011; Singh and Suthar, 2021b; Kosjek et al., 2005; Blair et al., 2013a; Wiegel et al., 2004a; Matongo et al., 2015c)	0.03–507.34 (Silva et al., 2011; Osorio et al., 2016; Blair et al., 2013a; Matongo et al., 2015c; Fairbairn et al., 2015; Yang et al., 2015)
		Estuary/Bay	1–916 (Cantwell et al., 2017; Benotti and Brownawell, 2007; Birch et al., 2015; Bean et al., 2018; Mijangos et al., 2018; Sun et al., 2016; Letsinger et al., 2019)	ND – 222 (Silva et al., 2011)
		Seawater	21.5–2379 (Afonso-Olivares et al., 2013; Krogh et al., 2017; Ali et al., 2017; Paíga et al., 2015; Chen et al., 2021)	
		Groundwater	10.3–4689 (Tran et al., 2014; Vulliet and Cren-Olivé, 2011; Fram and Belitz, 2011)	
	Aspirin	Freshwater	< 0.5–22,900 (Kasprzyk-Hordern et al., 2009; Matongo et al., 2015a; Agunbiade and Moodley, 2016; Moldovan, 2006)	
	Codeine	Freshwater	< 1.5–529 (Kasprzyk-Hordern et al., 2009; Osorio et al., 2012; Blair et al., 2013a)	
		Groundwater	0.033–348.3 (Teijon et al., 2010; Fram and Belitz, 2011)	
	Diclofenac	Freshwater	0.42–57,160 (Kasprzyk-Hordern et al., 2009; Bendz et al., 2005; Kermia et al., 2016; K'oreje et al., 2016; Olaitan et al., 2014; Aydin and Talinli, 2013; Osorio et al., 2012; Silva et al., 2011; Chitescu et al., 2015; Valdés et al., 2014; Yoon et al., 2010; Kunkel and Radke, 2012; Kosjek et al., 2005; Wiegel et al., 2004a; David, 2019; Metcalfe et al., 2003; Heberer et al., 2002);	0.16–58.7 (Silva et al., 2011; Osorio et al., 2016; Varga et al., 2010; Zhou and Broodbank, 2014)
		Seawater	4–10,221 (Ali et al., 2017; Metcalfe et al., 2003; Wu et al., 2010)	
		Groundwater	0.184–590 (Heberer, 2002a; Carrara et al., 2008; Vulliet and Cren-Olivé, 2011; Radjenović et al., 2008; Sacher et al., 2001)	
		Estuary	250.8 (Letsinger et al., 2019)	< 0.10–1.06 (Beretta et al., 2014)
	Ibuprofen	Freshwater	1.2–84,600 (Kasprzyk-Hordern et al., 2009; Bendz et al., 2005; Kermia et al., 2016; K'oreje et al., 2016; Matongo et al., 2015b; Aydin and Talinli, 2013; Osorio et al., 2012; Silva et al., 2011; Kim et al., 2009; Yoon et al., 2010; Kunkel and Radke, 2012; Singh and Suthar, 2021b; Kosjek et al., 2005; Matongo et al., 2015c; David, 2019; Metcalfe et al., 2003; Heberer et al., 2002; Roberts and Thomas, 2006b; Wiegel et al., 2004b; Loraine and Pettigrove, 2006; Griffero et al., 2019; Boyd et al., 2003)	0.78–41.41 (Matongo et al., 2015a; Silva et al., 2011; Osorio et al., 2016; Long et al., 2013)
		Estuary/Bay	2.73–6297.14 (Klosterhaus et al., 2013a; Sun et al., 2016; Letsinger et al., 2019)	0.77–15.1 (Beretta et al., 2014)
		Seawater	41–121 (Chen et al., 2021; Metcalfe et al., 2003; Wu et al., 2010; Pintado-Herrera et al., 2013)	0.01–100 (Beretta et al., 2014; Long et al., 2013)
		Groundwater	0.16–166,624 (Eggen et al., 2010; Siemens et al., 2008; Carrara et al., 2008; Nakada et al., 2008; Standley et al., 2008; Gottschall et al., 2012)	
	Indomethacin	Freshwater	1.21–111 (K'oreje et al., 2016; Osorio et al., 2012; Silva et al., 2011; Kim et al., 2009; Chitescu et al., 2015; Wiegel et al., 2004a; David, 2019)	0.28–42.6 (Osorio et al., 2016; Zhou and Broodbank, 2014)
		Estuary		12–164 (Yang et al., 2011b)
	Ketoprofen	Freshwater	0.74–620 (Kasprzyk-Hordern et al., 2009; Bendz et al., 2005; Osorio et al., 2012; Silva et al., 2011; Chitescu et al., 2015; Singh and Suthar, 2021b; Kosjek et al., 2005; Metcalfe et al., 2003; Heberer et al., 2002; Ide et al., 2017b)	1.99–12.54 (Silva et al., 2011; Osorio et al., 2016)
		Seawater	0.05–47 (Paíga et al., 2015; Metcalfe et al., 2003; Togola and Budzinski, 2008)	
		Groundwater	0.9–314 (Carrara et al., 2008; Vulliet and Cren-Olivé, 2011; Radjenović et al., 2008)	
	Mefanamic	Freshwater	0.02–541 (Kasprzyk-Hordern et al., 2009; Osorio et al., 2012; Silva et al., 2011; Kim et al., 2009; David, 2019; Heberer et al., 2002)	12.4–37.3 (Silva et al., 2011; Zhou and Broodbank, 2014)
	Naproxen	Freshwater	< 0.3–12,300 (Bendz et al., 2005; Kermia et al., 2016; Aydin and Talinli, 2013; Osorio et al., 2012; Silva et al., 2011; Ngubane	0.49–20 (Silva et al., 2011; Osorio et al., 2016; Varga et al., 2010)

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Table 3 (*continued*)

Class	Compound	Matrix	[a]Concentration range in water (ng/L)	[a]Concentration range in sediment (ng/g)
			et al., 2019; Chitescu et al., 2015; Yoon et al., 2010; Kunkel and Radke, 2012; Kosjek et al., 2005; Blair et al., 2013a; Chen et al., 2021; Metcalfe et al., 2003; Heberer et al., 2002; Wiegel et al., 2004b; Boyd et al., 2003; Ide et al., 2017b; Na et al., 2019)	
		Seawater	13–160 (Metcalfe et al., 2003; Wu et al., 2010)	
		Estuary/Bay	0.525–8.2 (Klosterhaus et al., 2013a; Sun et al., 2016)	
		Groundwater	0.2–2000 (Carrara et al., 2008; Vulliet and Cren-Olivé, 2011)	
	Salicyclic acid	Freshwater	< 0.3–5170 (Kasprzyk-Hordern et al., 2009; Tran et al., 2014; Ide et al., 2017a; Singh and Suthar, 2021b; Kosjek et al., 2005)	
		Seawater	3–130 (Afsa et al., 2020)	
		Groundwater	ND – 1994 (Tran et al., 2014; Heberer, 2002b)	
	Tramadol	Freshwater	< 30–5970 (Kasprzyk-Hordern et al., 2009; David, 2019)	
Antibiotics	Chloramphenicol	Freshwater	1.06–660 (Kasprzyk-Hordern et al., 2009; K'oreje et al., 2016; Osorio et al., 2012; Chitescu et al., 2015; David, 2019; Chen and Zhou, 2014)	0.7–1138 (Liu et al., 2009; Chen and Zhou, 2014)
		Seawater	400–15,600 (Tahrani et al., 2016)	
	Ciprofloxacin	Freshwater	0.56–13,567 (Batt et al., 2006; Olaitan et al., 2014; Aydin and Talinli, 2013; Osorio et al., 2012; Li et al., 2012; Chitescu et al., 2015; Valdés et al., 2014; Singh and Suthar, 2021b; Kosjek et al., 2005; David, 2019; Chen and Zhou, 2014; Pan et al., 2020; Zheng et al., 2012)	0.1–1290 (Zhou et al., 2011; Osorio et al., 2016; Blair et al., 2013a)
		Seawater	26.12–660 (Chen et al., 2021; Zheng et al., 2012; Na et al., 2011; Wu et al., 2021)	1.13–1.55 (Wu et al., 2021)
		Groundwater	12.3–443 (Heberer et al., 2002; Focazio et al., 2008)	
	Erythromycin	Freshwater	0.02–362.49 (Kasprzyk-Hordern et al., 2009; Matongo et al., 2015a; Matongo et al., 2015b; Aydin and Talinli, 2013; Osorio et al., 2012; Silva et al., 2011; Kim et al., 2009; Li et al., 2012; Singh and Suthar, 2021b; David, 2019; Roberts and Thomas, 2006b; Chen and Zhou, 2014; Zheng et al., 2012)	1.3–385 (Silva et al., 2011; Zhou et al., 2011; Kim and Carlson, 2007; Li et al., 2012; Matongo et al., 2015c; Chen and Zhou, 2014)
		Estuary/Bay	1–29.9 (Zhang et al., 2013a; Liang et al., 2013; Klosterhaus et al., 2013a)	2.29–14 (Liang et al., 2013; Beretta et al., 2014; Klosterhaus et al., 2013b)
		Seawater	1.1–1730 (Chen et al., 2021; Zheng et al., 2012; Minh et al., 2009)	0.276–7.27 (Krogh et al., 2017)
		Groundwater	0.31–2380 (Bartelt-Hunt et al., 2011; Peng et al., 2014; Focazio et al., 2008; López-Serna et al., 2013)	
	Florfenicol	Freshwater	1.6–2840 (Chen and Zhou, 2014; Hanna et al., 2018; Wei et al., 2012)	
		Seawater	2900–18,400 (Tahrani et al., 2016)	
	Tetracycline	Freshwater	5–712.40 (Batt et al., 2006; Osorio et al., 2012; Singh and Suthar, 2021b; Chen and Zhou, 2014; Arikan et al., 2008)	0.1–135 (Liu et al., 2009; Zhou et al., 2011; Kim and Carlson, 2007; Osorio et al., 2016; Chen and Zhou, 2014)
		Estuary/Bay	3–7.37 (Liang et al., 2013; Arikan et al., 2008)	6.62–7.13 (Liang et al., 2013)
		Seawater	13–313 (Minh et al., 2009)	
	Trimethoprim	Freshwater	0.13–13,600 (Kasprzyk-Hordern et al., 2009; Matongo et al., 2015a; Blair et al., 2013b; Bendz et al., 2005; K'oreje et al., 2016; Matongo et al., 2015b; Osorio et al., 2012; Silva et al., 2011; Li et al., 2012; Chitescu et al., 2015; Yoon et al., 2010; Singh and Suthar, 2021b; David, 2019; Roberts and Thomas, 2006b; Zheng et al., 2012; Zhang et al., 2012a)	0.01–9.84 (Silva et al., 2011; Zhou et al., 2011; Osorio et al., 2016; Yang et al., 2015)
		Estuary/Bay	4.1–247.02 (Cantwell et al., 2017; Zhang et al., 2013a; Klosterhaus et al., 2013a; Letsinger et al., 2019)	ND – 18.2 (Klosterhaus et al., 2013b)
		Seawater	1.3–330 (Zhang et al., 2012b; Chen et al., 2021; Zheng et al., 2012; Wu et al., 2021; Minh et al., 2009)	0.23–0.24 (Wu et al., 2021)
	Sulfamethoxazole	Freshwater	0.21–38,850 (K'oreje et al., 2018; Kasprzyk-Hordern et al., 2009; Blair et al., 2013b; Bendz et al., 2005; Batt et al., 2006; Matongo et al., 2015b; Loos et al., 2009; Aydin and Talinli, 2013; Osorio et al., 2012; Li et al., 2012; Chitescu et al., 2015; Yoon et al., 2010; Kunkel and Radke, 2012; Kosjek et al., 2005; Matongo et al., 2015c; Na et al., 2019; Chen and Zhou, 2014; Pan et al., 2020; Zheng et al., 2012; Arikan et al., 2008; Zhang et al., 2012a; Zheng et al., 2011)	0.05–507.3 (Kim and Carlson, 2007; Li et al., 2012; Osorio et al., 2016; Matongo et al., 2015c; Chen and Zhou, 2014)
		Estuary/Bay	2.4–180 (Zhang et al., 2013a; Zheng et al., 2012; Minh et al., 2009; Zhang et al., 2012a)	0.047–0.7 (Klosterhaus et al., 2013b; Arikan et al., 2008)
		Seawater	1.5–212.15 (Zhang et al., 2012b; Zheng et al., 2012; Na et al., 2011; Wu et al., 2021; Minh et al., 2009)	
		Groundwater	0.31–1110 (Peng et al. (2014);Ternes et al. (2007)	
	Norfloxacin	Freshwater	0.2–572 (Osorio et al., 2012; Liang et al., 2013; Pan et al., 2020; Na et al., 2011; Minh et al., 2009)	8.3–5770 (Zhou et al., 2011)
Anticholesteremics	Gemfibrozil	Freshwater	0.25–1114.56 (Blair et al., 2013b; Bendz et al., 2005; Loos et al., 2009; Osorio et al., 2012; Silva et al., 2011; Yoon et al., 2010; David, 2019; Metcalfe et al., 2003; Heberer et al., 2002; Wiegel et al., 2004b; Ide et al., 2017b)	0.07–1.92 (Osorio et al., 2012; Silva et al., 2011)
		Estuary/Bay	12–76.22 (Cantwell et al., 2017; Klosterhaus et al., 2013a)	
		Seawater	1–101 (Chen et al., 2021; Metcalfe et al., 2003; Wu et al., 2010)	
		Groundwater	1.2–1950 (Tran et al., 2014; Carrara et al., 2008; Radjenović et al., 2008; López-Serna et al., 2013)	

(*continued on next page*)

Table 3 (*continued*)

Class	Compound	Matrix	[a]Concentration range in water (ng/L)	[a]Concentration range in sediment (ng/g)
	Clofibric	Freshwater	0.01–450 (Wiegel et al., 2004a; Metcalfe et al., 2003; Heberer, 2002b)	ND – 56.8 (Silva et al., 2011)
Stimulants	Caffeine	Freshwater	11–144,179 (Matongo et al., 2015a; Blair et al., 2013b; Tran et al., 2014; Baker and Kasprzyk-Hordern, 2013; Matongo et al., 2015b; Loos et al., 2009; Aydin and Talinli, 2013; Sodré et al., ; Ide et al., 2017a; Zhang et al., 2012b; Yoon et al., 2010; Griffero et al., 2019; Ide et al., 2017b; Heberer, 2002b)	0.16–22,435 (Blair et al., 2013b; Matongo et al., 2015c; Fairbairn et al., 2015; Yang et al., 2015)
		Estuary/Bay	4.96–152.37 (Cantwell et al., 2017; Klosterhaus et al., 2013a)	0.28–29.7 (Beretta et al., 2014; Klosterhaus et al., 2013b)
		Seawater	37.4–407.6 (Krogh et al., 2017; Afsa et al., 2020)	13.8–55.7 (Krogh et al., 2017)
		Groundwater	56.8–16,249 (Tran et al., 2014; Fram and Belitz, 2011; Nakada et al., 2008; Focazio et al., 2008)	
Psychoactives	Carbamazepine	Freshwater	1–11,581 (Heberer, 2002a; Kasprzyk-Hordern et al., 2009; Bendz et al., 2005; Baker and Kasprzyk-Hordern, 2013; K'oreje et al., 2016; Matongo et al., 2015b; Loos et al., 2009; Liang et al., 2021; Osorio et al., 2012; Silva et al., 2011; Kim et al., 2009; Chitescu et al., 2015; Valdés et al., 2014; Yoon et al., 2010; Kunkel and Radke, 2012; Kosjek et al., 2005; Matongo et al., 2015c; Fairbairn et al., 2015; David, 2019; Na et al., 2019; González Alonso et al., 2010; Ramaswamy et al., 2011; Guruge et al., 2019)	0.03–46.5 (Silva et al., 2011; Osorio et al., 2016; Matongo et al., 2015c; Fairbairn et al., 2015; Yang et al., 2015; Zhou and Broodbank, 2014)
		Estuary/Bay	0.2–117.6 (Cantwell et al., 2017; Birch et al., 2015; Klosterhaus et al., 2013b)	ND – 4.81 (Beretta et al., 2014)
		Seawater	0.02–310 (Chen et al., 2021; Metcalfe et al., 2003)	1.38–47.9 (Krogh et al., 2017)
		Groundwater	2–900 (Tran et al., 2014; Eggen et al., 2010; Sacher et al., 2001; Focazio et al., 2008; Huntscha et al., 2012; Lapen et al., 2008)	

[a] Minimum concentration is the lowest concentration detected (reported). ND = not detected

were detected in concentrations as high as 561 and 122 ng/L, respectively, in Büyükcekmece Lake, Turkey (Aydin and Talinli, 2013).

PPCP concentrations in freshwater are influenced by higher temperatures, which enhance chemical and biological degradation of compounds in water. Thus, seasonal variations are observed in the concentration of PPCPs in surface waters (Ebele et al., 2017; Kay et al., 2017; Lindholm-Lehto et al., 2016; Fekadu et al., 2019; Singh and Suthar, 2021a). PPCP degradation may also be promoted by solar radiation (Georgaki et al., 2014; Li et al., 2015; Rubasinghege et al., 2018). Overall, the concentrations of PPCPs in freshwater are higher during the winter compared to spring and summer due to lower temperatures and sunlight intensity (Azzouz and Ballesteros, 2013; Daneshvar et al., 2010; Kot-Wasik et al., 2016; Veach and Bernot, 2011). Seasonal influenza outbreak also correlates with increased concentration of PPCPs, such as antivirals and analgesics, in the environment (Azuma et al., 2012; Ghosh Gopal et al., 2010; Leknes et al., 2012; Söderström et al., 2009).

4.2. Occurrence of PPCPs in estuary and marine waters

Studies on the occurrence of PPCPs in estuary and marine waters are limited compared to freshwater. Major classes of PPCPs reported in saline waters include antibiotics, analgesics, antihypertensives, anticholesteremics, stimulants, and psychoactives (Table 3). In general, higher concentrations of PPCPs occur in rivers than in estuaries and bays. PPCP concentrations are the lowest in the open ocean due to dilution effects, sorption to sediments, transformation, and decrease in anthropogenic pressure (Alygizakis et al., 2016; Arpin-Pont et al., 2016b; Desbiolles et al., 2018; Ngubane et al., 2019; Wille et al., 2011; Zhang et al., 2013b). The highest concentrations of major PPCP classes detected in saline waters are 10,221 ng/L for analgesics (diclofenac in Al-Arbaeen Lagoon, Saudi Arabia), 18,400 ng/L for antibiotics (florfenicol in Hergla, Tunisia), 407.6 ng/L for stimulants (caffeine in Mahdia, Tunisia), 310 ng/L for psychoactives (carbamazepine in Hamilton Harbour, Canada), and 313 ng/L for antihypertensives (metoprolol in Narragansett Bay, USA) (Table 3). These concentrations are 2–700 times lower than the respective concentrations reported in freshwater (Table 3 and S8).

Similar to freshwaters, the concentrations of PPCPs in marine water also vary seasonally (due to environmental factors and tourist activities during summer seasons). Environmental factors such as precipitation, temperature, and sunlight affect the degradation, sorption, and concentration of the PPCPs in the marine environment (Čelić et al., 2019; Alygizakis et al., 2016; Moreno-González et al., 2015; Pavlidou et al., 2014; Rodríguez-Navas et al., 2013; Zhao et al., 2017; Mezzelani et al., 2018). Precipitation induces seasonal variability in PPCP concentrations in marine waters due to dilution effects. Although, high precipitation rate could also result in combined sewer overflow in treatment plants, leading to increased direct release of PPCPs into natural waters (Benotti and Brownawell, 2007). High concentrations of PPCPs are more likely to occur in regions where there is low water exchange with the open sea, and conversely, low concentrations of PPCPs are more likely to occur in regions with high exchange.

4.3. Occurrence and concentrations of pharmaceuticals in groundwater

Analgesics and antibiotics are the most frequently detected PPCPs in groundwater. Most of the studies on PPCP occurrence in groundwater were performed in Europe, North America, and South America. The occurrence of PPCPs in groundwater was attributed to direct and indirect impact of wastewater and septic systems, contributions from surface waters, and contamination from agricultural activities. Groundwater contamination by PPCPs may occur via leachate percolation from municipal landfills, groundwater recharge from treated wastewater, and inappropriate disposal of industrial and hospital wastes (Jones et al., 2001; Migliorini, 2002; Paíga and Delerue-Matos, 2016; Scheytt et al., 2001). PPCPs in groundwater may also originate from leaking underground sewer lines, agricultural runoff, and seepage from biosolids applied on croplands (Watanabe et al., 2010; Bexfield et al., 2019; Burkholder et al., 2007; Kot-Wasik et al., 2007; Musolff et al., 2007; Roehrdanz et al., 2017).

While the concentrations of PPCPs in freshwater are generally much higher (Fig. 6), high concentrations of certain PPCPs, such as acetaminophen (4689 ng/L, found in Singapore (Tran et al., 2014)), ibuprofen (166,624 ng/L, found in Norway (Eggen et al., 2010)), naproxen (2000 ng/L, found in Mexico (Siemens et al., 2008)), erythromycin (2380 ng/L, found in Nebraska, USA (Bartelt-Hunt et al., 2011)), sulfamethoxazole (1110 ng/L, found in the United States (Barnes et al., 2008)), gemfibrozil (1950 ng/L, found in Ontario, Canada (Carrara et al., 2008)), and caffeine (16,249 ng/L, found in Singapore (Tran et al., 2014)), have been detected in groundwaters around the world.

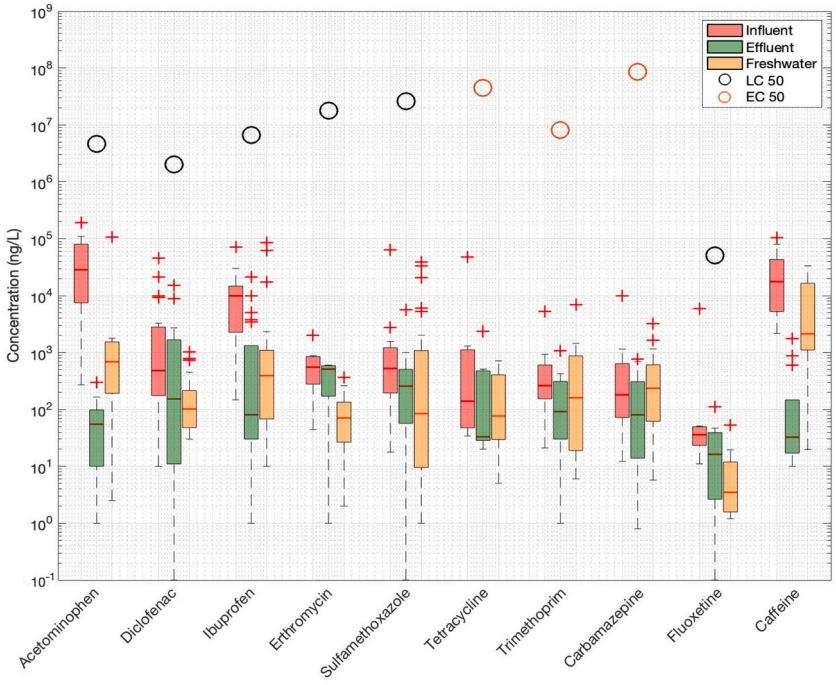

Fig. 6. Global average concentrations of ten common PCPPs in wastewater treatment plant influent, effluent, and freshwater and their toxicity (LC50/EC50) values. The toxicity value of caffeine is higher than the scale of this figure. The horizontal lines in the boxes represent the median percent removal. The whiskers (vertical dash lines above and below the box plots) show the variability of the data outside the upper and lower quartiles while extreme outliers are marked with "+".

Compared to surface waters, groundwater is characterized by reduced redox activities and photodegradation. Consequently, contamination by PPCPs may be persistent and difficult to remove (Peng et al., 2014). Carbamazepine and sulfamethoxazole were detected at higher frequencies (70% and 66%, respectively) in groundwater samples collected from the Rhône–Alpes region (France) than in surface waters in the same region (61% and 37%, respectively) (Vulliet and Cren-Olivé, 2011). In a similar study carried out along Ebro River (Catalonia, Spain), sulfamethoxazole was detected at a higher frequency (~73%) in groundwater compared to surface water (~48%) (García-Galán et al., 2010). Boy-Roura et al. (2018) found 11 antibiotics in groundwater samples collected from the Alt Empordà region (Catalonia, Spain) and only 5 antibiotics in surface water samples collected within the same study area. The antibiotics found in groundwater but absent in surface water include pipemidic acid, oxolinic acid, flumequine, azithromycin, ofloxacin, and danofloxacin. This finding is important for understanding how PPCPs behave in different environmental media and indicate that once in groundwater, PPCPs may degrade more slowly than in surface waters.

4.4. *Occurrence and concentrations of pharmaceuticals in sediments*

Studies investigating PPCP concentrations in sediments were predominantly performed in Europe, South America, Asia, and North America. In the studies we reviewed, the highest concentrations of PPCPs found in sediments are for: acetaminophen (222 ng/g) (Silva et al., 2011), chloramphenicol (1138 ng/g) (Liu et al., 2009), ciprofloxacin (1290 ng/g) (Zhou et al., 2011), sulfamethoxazole (507 ng/g) (Matongo et al., 2015a), norfloxacin (5770 ng/g) (Zhou et al., 2011), and caffeine (22,435 ng/g) (Matongo et al., 2015a) (Table 3). The highest concentrations of PPCPs in sediments were generally found in Asia (Zhou et al., 2011) and Africa (Matongo et al., 2015a).

Sediments can act as sinks or as secondary sources of PPCPs in freshwater and marine systems. Sediments are regarded as sinks when the concentrations of PPCPs in sediments are higher than those in the water column (Kim and Carlson, 2007). Physiochemical properties of marine waters, such as salinity, pH, and natural organic matter content, influence the adsorption of PPCPs to suspended solids (which may eventually form sediment) (Gaw et al., 2014). For instance, erythromycin ($pK_a = 8.9$) is predominantly cationic at pH 7, and non-ionized in seawater (pH ~ 8). The non-ionized species of erythromycin has a larger log K_{ow}, which facilitates adsorption to sediment (Baker, 1997; Liang et al., 2013; Wunder et al., 2011). Organic carbon acts as sorption sites; hence, high organic carbon content also increases accumulation of PPCPs in sediments (Burgess et al., 2001; Yang et al., 2010; Pintado-Herrera et al., 2017). Carbamazepine, acetaminophen, trimethoprim, tetracycline, ciprofloxacin, and diazepam were all detected at higher frequencies in estuarine sediments of a Mediterranean coastal wetland as compared to the aqueous phase (Vazquez-Roig et al., 2012). After accumulation, sediments may act as a source for PPCPs to be released back into the water column or as a pathway for entry into bottom-feeding aquatic organisms (Ebele et al., 2017; Gaw et al., 2014).

Like water samples, PPCPs are often detected at higher concentrations in sediments near the potential source. Venkatesan et al. (2012) detected triclosan, triclocarban, and their transformation products in sediments close to a WWTP in Minnesota, USA. They observed that the concentration of triclosan and triclocarban in sediments collected downstream of a WWTP were higher than concentrations upstream. Overall, sediments act as a sink for many PPCPs and these PPCPs can re-enter the water column, especially during major storm events or bioturbidation. The literature demonstrates that PPCPs are found worldwide in all aqueous-based environmental compartments, including surface water, groundwater, fresh and marine environments, estuaries, and bays as well as in sediment (Table 3). The ubiquitous nature of PPCPs is a concern, especially since many PPCPs show the potential for toxicity to aquatic organisms.

5. Ecotoxicity of PPCPs in natural waters

PPCPs and their metabolites have been found in waterbodies, and many PPCPs exhibit ecotoxicity effects (Chopra and Kumar, 2018; Celiz et al., 2009). Furthermore, research found PPCPs in aquatic organism

tissues, and in some cases, concentrations were higher in tissues than in the surrounding environment (Li et al., 2012; Ramirez et al., 2009; Subedi et al., 2012; Wang and Gardinali, 2012). Table 4 provides examples of PPCPs and their concentrations found in treated effluent from WWTPs and waterbodies from North America. International data were used when North American data were not available. The PPCP concentrations found in the environment are then compared to toxicity values, specifically for mortality (LC50 and EC50). The majority of the studies summarized in Table 4 represent laboratory experiments with PPCPs. Multiple studies are summarized to provide a range of toxicity data for each PPCP and more details on the toxicity studies are found in Table S10 in the SI.

PPCP concentrations in treated WWTP effluents and other waterbodies were on average one to six orders of magnitude lower than the reported LC50 concentrations for fish, invertebrates, amphibians, algae, and rotifers (Table 4). Toxicity studies in the laboratory did not show mortality or any adverse effects at such low environmental concentrations. The data suggest that mortality from PPCPs may not be observed in aquatic populations due to the low exposure concentrations in the environment. It is more likely that sub-lethal effects to aquatic organisms may occur in the environment with low PPCP concentrations. These sub-lethal effects can include changes in behavior and reproductive effects, feminization, and reduction in activity that causes reduced feeding and body weight (Corcoran et al., 2010; Chopra and Kumar, 2018; Brodin et al., 2014). Treated effluent PPCP concentrations are higher than concentrations found in other waterbodies such as lakes and rivers; and therefore, exposure to treated effluent or effluent-discharge locations in natural waters is more likely to result in both mortality and sub-lethal effects. Additionally, factors influencing toxicity include the type of species, PPCP type, and the long-term exposure and bioaccumulation of PPCPs. The following text discusses bioaccumulation and sub-lethal effects observed in aquatic organisms exposed to PPCPs.

As reported in Corcoran et al. (2010), a commonly found PPCP in the environment, ibuprofen, has been observed to impact reproduction (1–100 μg/L), impair ion regulation (>1000 μg/L), and cause cardio abnormalities (>10 μg/L) in various fish species. In fact, sub-lethal adverse effects of ibuprofen on reproductive and cardiological health were observed to occur within measured concentrations found in effluent (at 0.37–85 μg/L). Since environmental concentrations are typically at 0.1–185 μg/L (Table 4); this demonstrates that sub-lethal toxicity effects are possible at environmental concentrations.

For fluoxetine, adverse sub-lethal effects observed in multiple freshwater fish species at various concentrations included decreases in the following behaviors: territorial aggression at 6 μg/L (*Thalassoma bifasciatum*), ability to catch prey at 23–100 μg/L (*Pimephales promelas*), and feeding rates at 51–170 μg/L (*P. promelas*) (Corcoran et al., 2010). Decreases in growth were also observed at 51 – 53 μg/L (*P. promelas*) (Corcoran et al., 2010). Fluoxetine at 51 μg/L was found to be the lowest observable effect concentration (LOEC) for *P. promelas* (Corcoran et al., 2010). Increases in estradiol levels at 0.1 – 0.5 μg/L (*Oryzias latipes*) and development abnormalities at 0.1–5 μg/L (*Oryzias latipes*) (Corcoran et al., 2010) were also observed. However, fluoxetine effluent concentrations (0.01–0.841 μg/L) and surface water concentrations (0.002–0.1 μg/L) (Corcoran et al., 2010) (Table 4) are one to three orders of magnitude lower than the fluoxetine concentration expected to cause mortality (6.6–8.3 mg/L; Table 4). Therefore, mortality to fish species from fluoxetine is unlikely due to its extremely low concentrations; however, sub-lethal effects from fluoxetine may be likely. For example, at levels that are currently observed at the high end of surface water concentrations and at levels found in effluent, fluoxetine may cause changes to estradiol levels and increase developmental abnormalities.

Similar trends were noted for diclofenac, erythromycin, acetominophen, propranolol, sulfamethoxazole, tetracycline, and trimethoprim (Table 4). Concentrations of these PPCPs causing mortality in laboratory experiments were orders of magnitude higher than the concentrations found in the environment, indicating that mortality in the environment is unlikely, though sub-lethal effects may be possible. Fig. 6 shows the toxicity data from Fig. 4 and compares to global PPCP concentrations in WWTP influent and effluent, and in freshwater. This figure clearly demonstrates that mortality data (LC50 and EC50) is orders of magnitude larger than PPCP concentrations entering and leaving the WWTP and entering the natural environment. However, it should be noted that sub-lethal concentrations are not displayed on this figure, and some concentrations are in the same range as PPCP concentrations in WWTP effluent.

There is some uncertainty associated with these data that should be considered. For example, overall the toxicity studies are performed in controlled laboratory settings, and as such do not take into consideration long-term exposure or a mixture of chemicals that might represent environmental exposure more accurately. It has been shown that combinations of PPCPs may cause a greater adverse effect compared to individual impacts of the PPCPs (Deblonde and Hartemann, 2013). However, synergistic toxicity effects are not the only outcome with combinations of PPCPs, additive and antagonistic effects are also possible (Jonker et al., 2005). Additionally, the laboratory studies do not account for chronic exposures to PPCPs at low doses throughout an organism's life. The majority of studies summarized in Table 4 involved exposures lasting less than a month. Organism life cycles for fish, invertebrates, and amphibians are much longer. Because of these complexities, tools, such as risk assessments, that use predictive modeling have been developed to consider these additional factors.

Various studies conducted risk assessments on PPCPs to rank the most toxic and bioaccumulative compounds (Ortiz de García et al., 2017; Guo et al., 2016). For example, Ortiz de García et al. (2017) found that out of 49 compounds tested, PPCPs with the highest potential to impact aquatic organisms include compounds belonging to specific classes: hormones, antidepressants, fragrances, antibiotics, blood lipid regulators, and angiotensin receptor blockers. Specifically, antibiotics such as clarithromycin and ciprofloxacin, and the antidepressants paroxetine and sertraline had the highest rankings for potential effects to aquatic organisms. To determine the pharmaceuticals with the highest risk, Ortiz de García et al. (2017) developed a ranking for potential impacts on organisms based on parameters such as ecotoxicity, bioaccumulation, physical chemical properties, and degradation rates. Studies such as these offer an approach that considers a broader range of variables than solely using traditional laboratory data. A similar risk-based prioritization study by Guo et al. (2016) had similar findings; the study identified 16 compounds with the potential for high risk to aquatic organisms. Specifically, the compounds belonged to the following classes: antidepressants, analgesics, anti-diabetic drugs, antibiotics, anti-obesity drugs, and estrogen drugs (Guo et al., 2016). The highest ranked compounds with the potential for chronic effects included diclofenac, atorvastatin, estradiol, omeprazole, and mesalazine (Guo et al., 2016). PPCPs receiving the highest rankings with the potential for acute effects included orlistat, carbamazepine, and a carbamazepine metabolite (Guo et al., 2016). This is concerning because these classes of PPCPs are the most commonly found in treated wastewater effluent.

Similar to how physicochemical properties of a PPCP influence removal and degradation in a WWTP, physicochemical properties also affect environmental fate and partitioning. For example, PPCPs that resist environmental degradation have the potential to bioaccumulate in aquatic organisms, and may be considered toxic (Deblonde and Hartemann, 2013). Bioaccumulation, along with persistence, and toxicity (PBT), are three metrics commonly used to determine if chemicals build up in the environment over time, and if exposed populations have higher risks associated with these chemicals. A commonly used criteria to determine the bioaccumulation potential is an octanol-water partition coefficient ($\log K_{ow}$) > 3 (OECD, 2008). A high $\log K_{ow}$ also indicates the potential for persistence (Zenker et al., 2014). Previous work detected (out of a database containing nearly 4000 PPCPs), 275 compounds in the

Table 4
PPCP concentrations in aquatic environments and concentrations at which toxicity is observed.

Compound	Median or Range (maximum) Concentrations (μg/L)[a] in the Environment		Environmental Concentrations Reference	Observed Toxicity (Range, mg/L)[b]	Length of Exposure	Toxicity Reference
	Treated effluent	Waterbodies				
Acetaminophen	–	(0.04)	(Krogh et al., 2017)	LC10: 1.35–2.39;	1–42 days	(Du et al., 2016; Oliveira et al.,
Acetaminophen	–	0–0.06	(Cantwell et al., 2017	LC50: 4.59 – 8.96; EC50:		2016; Sung et al., 2014; Kim et al.,
Acetaminophen	–	0–0.002.5	Blair et al. (2013b)	1.88;		2012; Galus et al., 2013)
				EC50: 2.83 – 56.84		
				(109.6 in ref. Lin et al.		
				(2010))		
Atenolol	–	0–0.002	Klosterhaus et al. (2013a)	EC50 for embryotoxicity	3–7 days	(Diniz et al., 2015; Muhammet Ali
Atenolol	–	0.001–0.038	(Cantwell et al., 2017)	was 66.46		et al.,)
Caffeine	–	0.015–0.041	(Klosterhaus et al., 2013a)	EC50: 395	48–96 h	(Aguirre-Martínez et al., 2015; Di
Caffeine	–	0.005–0.104	(Cantwell et al., 2017)	LC50: 5280		Lorenzo et al., 2019)
Carbamazepine	–	0.0002–0.063	(Cantwell et al., 2017)	EC50: 0.066–86.5	1–42 days	(Galus et al., 2013;
Carbamazepine	–	0.005–0.044	(Klosterhaus et al., 2013a)			Aguirre-Martínez et al., 2015; van
Carbamazepine		0.31–0.65	(Metcalfe et al., 2003)			den Brandhof and Montforts,
						2010; Melvin et al., 2014)
Diclofenac	0.4 (2.3)	< LOQ (0.6)	(Ashton et al., 2004)	LC50: 2–6;	3–21 days	(Du et al., 2016; Oliveira et al.,
Diclofenac	0.3 (0.6)	<LOQ	(Roberts and Thomas, 2006a)	EC50: 5.3–123		2016; van den Brandhof and
Diclofenac	0.81–33.9	0.006–1.8	(Corcoran et al., 2010)			Montforts, 2010)
Diclofenac	–	29–256	(Teijon et al., 2010; Wiegel et al.,			
			2004b)			
Erthromycin	–	<LOQ (0.1)	(Thomas and Hilton, 2004)	LC50: 17.7–27.5; EC50:	1–7 days	(Isidori et al., 2005; Kiryu and
Erthromycin	<LOQ (1.8)	<LOQ (1.0)	(Ashton et al., 2004)	0.22–22.5; LD50:		Moffitt, 2002)
Erythromycin	0.01–10.4 μg/L	–	(Kasprzyk-Hordern et al., 2009;	350–1041 mg/ kg		
	(range)		Lin et al., 2009; Nakada et al.,			
			2007b; Snyder et al., 2007; Xu			
			et al., 2007)			
Erythromycin	–	0.0024 (0.012)	(Klosterhaus et al., 2013a)			
Fluoxetine	0.2 (0.3)	0.01 (0.1)	(Roberts and Thomas, 2006a)	LC50: 0.2–0.8; 15.2 mg/	2 days; 10	(Brooks et al., 2003)
Fluoxetine	0.01–0.1	0.002–0.04	(Boucard and Gravell, 2006)	kg	days for	
Fluoxetine	0.099–0.841	0.012–0.030	(Corcoran et al., 2010)		15.2 mg/kg	
Ibuprofen	3.1 (27.3)	0.8 (5.0)	(Ashton et al., 2004)	LC50: 6.6–8.3; various	3–21 days	(Corcoran et al., 2010; Du et al.,
Ibuprofen	3.0 (4.2)	0.3 (2.4)	(Roberts and Thomas, 2006a)	adverse effects observed		2016; Sung et al., 2014; Du et al.,
Ibuprofen	0.37–85	0.1–2.7	(Corcoran et al., 2010)	at 1–1000 μg/L		2016; Sung et al., 2014)
Ibuprofen	–	8–185	(Teijon et al., 2010; Ferguson			
			et al., 2013)			
Ibuprofen	–	0.064 (0.79)	(Klosterhaus et al., 2013a;			
			Metcalfe et al., 2003; Loraine and			
			Pettigrove, 2006)			
Gemfibrozil	–	0.012–0.038	(Klosterhaus et al., 2013a)	LC50 4.9–6.7	48–96 h	(Fabbri et al., 2017)
Gemfibrozil	–	0–0.0762	(Cantwell et al., 2017)			
Gemfibrozil	–	0.004–0.019	(Blair et al., 2013b)			
Gemfibrozil	–	0.066 (0.112)	(Metcalfe et al., 2003)			
		0.012 (0.007)				
Naproxen	–	0–0.008	(Klosterhaus et al., 2013a)	EC50: 0.03–741.3	1–47 days	(Melvin et al., 2014; Kwak et al.,
Naproxen	–	0–0.015	(Blair et al., 2013b)			2018; Li et al., 2016)
Naproxen	–	0.022–0.107	(Boyd et al., 2003)			
Naproxen	–	0.201 (0.551)	(Metcalfe et al., 2003)			
		0.094 (0.139)				
Paracetamol	< 0.02	–	(Roberts and Thomas, 2006a)	LC50: 26.6 – > 160;	96 h	(Kim et al., 2007)
Paracetamol	NA	0.6	(Bound and Voulvoulis, 2006)			
Propanolol	0.08 (0.3)	0.03 (0.2)	(Ashton et al., 2004)	LC50: 1.2–1.7;	2 days; for L/	(Stanley et al., 1780)
Propanolol	0.3 (0.4)	0.06 (0.1)	(Roberts and Thomas, 2006a)	EC50: 1.4–1.7; LOEC:	EC50; 21 days	
Propanolol	0.01–0.29	0.012–0.59	(Corcoran et al., 2010)	0.4–0.8	for LOEC	
Sulfamethoxazole	<LOQ (0.1)	<LOQ	(Ashton et al., 2004)	LC50: 26.3–35.4 mg/L;	1–7 days	(Melvin et al., 2014; Isidori et al.,
Sulfamethoxazole	–	0.006–0.01	(Blair et al., 2013b)	EC50: 0.13–25.2		2005)
Sulfamethoxazole	–	0.043–0.45	(Batt et al., 2006)			
Sulfamethoxazole	–	0.002–0.067	(Klosterhaus et al., 2013a)			
Sulfamethoxazole	–	0–0.047	(Cantwell et al., 2017)			
Sulfamethoxazole	–	43.467–43.592	[390]			
Tetracycline	–	1.0	(Watts et al., 1984)	EC50: 44.8	21 days	(Hui-zhu, 2008; Wollenberger
Tetracycline	–	0–0.005	(Arikan et al., 2008)			et al., 2000)
Trimethoprim	0.07 (1.3)	<LOQ (0.04)	(Ashton et al., 2004)	EC50: 8.1–100	3–21 days	(De Liguoro et al., 2012; Kolar
Trimethoprim	0.27 (0.32)	0.01 (0.02)	(Roberts and Thomas, 2006a)			et al., 2014)
Trimethoprim	–	0–0.004	(Klosterhaus et al., 2013a)			
Trimethoprim	–	0–0.017	(Cantwell et al., 2017)			
Trimethoprim	–	0–0.006	(Blair et al., 2013b)			

Toxicity values are for various organisms including but not limited to fish, invertebrates, amphibians, algae, and rotifers. Specific study details such as the species are presented in depth in Table S9 in the SI. The first four columns are modified from WHO 2011 (Pharmaceuticals in Drinking-Water World Health Organization, 2011). [a] – median and maximum value reported when available. Data are also reported as the range of concentrations measured; = /when the median/maximum values were not available. Concentrations for the toxicity studies are reported in mg/L unless otherwise noted. EC50 – half maximal effect concentration; LC50 – concentration at which a 50% mortality is observed; LOEC – lowest observed effect concentration; LOQ – limit of quantification; A "–" symbol indicates data is not available.

environment. Of those, 92 were rated as potentially bioaccumulative and 121 were rated as persistent (Howard and Muir, 2011). These findings applied to numerous hormones, antibiotics, and commonly detected analgesics such as diclofenac, ibuprofen, naproxen, fluoxetine, and norfluoxetine (Howard and Muir, 2011).

In addition, bioaccumulation can be assessed by the bioaccumulation factor (BAF), the ratio of the chemical in an organism to the concentration in the environment, or by using a bioconcentration factor (BCF), defined as the accumulation of a compound in an organism relative to the concentration in the water. BCFs are equivalent to BAFs but exclude dietary intake (Puckowski et al., 2016). Examples of PPCP bioaccumulation are found in Table 5 and in Table S11. Table 5 depicts the range of possible BCF and BAF values based on species or tissue type. Regulatory bioacccumulation assessments consider compounds to be highly accumulative at BCF values > 5000 (Arnot, 2006). For example, fluoxetine has a BCF of 7–3000 depending on the organism (Table 5). However, the majority of fluoxetine BCF values presented in Table 5 are lower than 1000 which indicates an overall low potential for bioaccumulation. Diclofenac BCF values are 0.3–2732 for *Oncorhynchus mykiss* livers (rainbow trout) (Schwaiger et al., 2004), and this large range also encompasses diclofenac BCF values for other species (Table 5). The highest diclofenac BCF value of 2732 indicates the potential to bioaccumulate, though the entire BCF range for diclofeanc suggests bioaccumulation is species and/or tissue specific. The log K_{ow} for diclofenac is 4–4.5 (Database of Experimental Octanol-water,; Avdeef et al., 1998). A log $K_{ow} > 3$ indicates the potential for bioaccumulation; therefore, both the BCF and log K_{ow} for diclofenac indicate the potential for accumulation in aquatic organisms.

Moreover, these BCF and log K_{ow} values do not consider PPCP metabolites. Recent research has shown that diclofenac is transformed into various oxidation products and conjugates in two aquatic invertebrates, *Gammarus pulex* and *Hyalella azteca* (Fu et al., 2020). The BCFs of the metabolites were found to be 25 – 100 times greater than the BCFs of the parent compounds (Fu et al., 2020). However, toxicity of PPCP metabolites will also be species specific and the overall persistence, bioaccummulation, and toxicity (PBT) may be very different from the parent compound (Fu et al., 2020). In these instances, using both a PBT assessment and computational tools may need to be combined to understand metabolite toxicity. Computational tools have been used to determine and rank the PBT for over 1200 PPCP ingredients (Sangion and Gramatica, 2016), and serve as a useful technique to quickly prioritize PPCPs based on their ranking. Three examples of computational tools include the quantitative structure-activity relationship (QSAR) model (Khan et al., 2019), the EPA's ecological structure activity relationships (ECOSAR) model (US EPA,), and the REPA's persistence, bioaccummulation, and toxicity (PBT) profiler (Development,). Computational tools may also be especially useful for understanding toxicity in the PBT assessment, for chemical mixtures.

Table 5
Bioconcentration factor (BCF) and bioaccumulation factor (BAF) values for various pharmaceuticals.

Compound	BCF	BAF	Organism	Reference
Caffeine	2.0	–	*Gambusia holbrooki* (Mosquitofish)	(Wang and Gardinali, 2013)
Carbamazepine	0 – 0.9	–	Fish	(Valdés et al., 2014
Carbamazepine	3.2	–	Freshwater snails	(Du et al., 2015)
Carbamazepine		2.2	Microalga	(Vernouillet et al., 2010)
Carbamazepine		12.6	*Thamnocephalus platyurus* (Freshwater crustacean)	(Vernouillet et al., 2010)
Carbamazapine	–	241	Snail	(Na et al., 2013)
Carbamazapine	–	210	*Cyprinus carpio* (Common carp)	(Na et al., 2013)
Carbamazapine	–	132	Lake anchovy	(Na et al., 2013)
Carbamazapine	–	133	*Carassius carassius* (Crucian carp)	(Na et al., 2013)
Carbamazapine	–	3.4	White shrimp	(Na et al., 2013)
Carbamazapine	–	265	Yellow catfish	(Na et al., 2013)
Carbamazapine	0.4 – 0.3-		*Oncorhynchus mykiss* (Rainbow trout)	(Lahti et al., 2011)
Carbamazepine	1.4		*Gambusia holbrooki* (Mosquitofish)	(Wang and Gardinali, 2013)
Ciprofloxacin	–	66,300	Aquatic plant	(Li et al., 2012
Ciprofloxacin	–	3262	Fish	(Gao et al., 2012)
Diazepam	–	927	*Cyprinus carpio* (Common carp)	(Muir et al., 2017)
Diclofenac	12 – > 2500 (liver)	–	*Oncorhynchus mykiss* (rainbow trout)	(Schwaiger et al., 2004)
Diclofenac	10–180	–	*Mytilus edulis* (Baltic Sea blue mussel)	(Ericson et al., 2010)
Diclofenac		4.2-	Fish	(Tanoue et al., 2014)
Diclofenac	4.9–5.7		*Oncorhynchus mykiss* (Rainbow trout)	(Lahti et al., 2011)
Diclofenac	12–2732 (liver); 5–971 (kidney); 3–763 (gills); 0.3–69 (muscle)		*Oncorhynchus mykiss* (Rainbow trout)	(Schwaiger et al., 2004)
Fluoxetine	74–80	–	*Oryzias latipes* (Japanese medaka)	(Paterson and Metcalfe, 2008)
Fluoxetine	–	185,900	Amphipod crustacean	(Meredith-Williams et al., 2012)
Fluoxetine	8.8–260	–	Fish	(Zenker et al., 2014)
Fluoxetine	200–800	–	Marine Mussel	(Franzellitti et al., 2014)
Fluoxetine	3000	–	Freshwater snails	(Du et al., 2015)
Fluoxetine	138–345	–	*Salvelinus fontinalis* (Brook trout)	(Lajeunesse et al., 2011)
Fluoxetine	–	386–906	*Carassius auratus* (Goldfish)	(Muir et al., 2017)
Fluoxetine	–	3000	*Lasmigona costata* (freshwater mussel)	(de Solla et al., 2016)
Ibuprofen	28		*Gambusia holbrooki* (Mosquitofish)	(Wang and Gardinali, 2013)
Ibuprofen	19	–	Fish	(Tanoue et al., 2014)
Ibuprofen	3.3–4.3	–	*Oncorhynchus mykiss* (Rainbow trout)	(Lahti et al., 2011)
Naproxen	1.4–1.6	–	*Oncorhynchus mykiss* (Rainbow trout)	(Lahti et al., 2011)
Norfluoxetine	117	–	*Oryzias latipes* (Japanese medaka)	(Paterson and Metcalfe, 2008)
Nonfluoxetine	8.8–60	–	Fish	(Zenker et al., 2014)
Norfluoxetine	510	–	Freshwater snails	(Du et al., 2015)
Norfloxacin	–	2120	Aquatic plant	(Li et al., 2012)
Propranolol	0.16	–	Fish	(Ding et al., 2015)
Propranolol	40.9–103.4	–	*Scenedesmus obliquus* (algae)	(Ding et al., 2015)
Propranolol		0.05–0.52	Daphnia	(Ding et al., 2015)
Propranolol	10–180	–	*Mytilus edulis* (Baltic Sea blue mussel)	(Ericson et al., 2010)
Propranolol	–	2782	Fish	(Liu et al., 2014)

The - symbol indicates the data were not available. Genus and species name provided when available.

The above examples demonstrate that the PBT of PPCPs can vary widely based on the class or individual PPCP, and that factors other than only toxicity should be assessed for understanding how these chemicals impact aquatic organisms. Both the chemical structure and the PBT should be considered when assessing environmental toxicity of PPCPs. Other factors to consider include the test organism used, if the organism is exposed to an environmentally relevant concentration, and the physicochemical properties of the PPCPs. Overall, data indicate that chemicals from the following classes: hormones, antidepressants, antibiotics, analgesics, anticholesteremics, anti-diabetics, anti-obesity, and angiotensin receptor blockers, have the highest potential to impact aquatic organisms (Ortiz de García et al., 2017; Guo et al., 2016).

6. PPCPs in wastewater of healthcare facilities and regulations

Hospital wastewaters contain contaminants such as radionuclides, organic solvents, pathogenic bacteria, disinfectants, and pharmaceuticals (Verlicchi et al., 2010; Carraro et al., 2018); and are an important source of PPCPs entering WWTPs and the environment (Fig. S1) (Majumder et al., 2021; Santos et al., 2013). To decrease discharge of contaminants from hospitals to the environment, the WHO recommends pre-treatment of hazardous liquids, use of dedicated sewerage, and minimum treatment and removal requirements (Chartier, 2014). Despite the recommendations, wastewater from healthcare facilities is often regarded as similar to municipal wastewater and discharged into public drainage systems (Al Aukidy et al., 2018). Hospital wastewater is also discharged directly into the environment without pre-treatment in several developing countries with weak waste regulations and/or poor waste management infrastructures (Majumder et al., 2021; Al Aukidy et al., 2018; Ekhaise and Omavwoya, 2008; Khan et al., 2020). Conventional wastewater treated via activated sludge is not efficient for removing PPCPs, hence, on-site treatment of hospital wastewater, rather than combining it with municipal wastewater, has been long considered (Majumder et al., 2021; Casas et al., 2015; Verlicchi et al., 2015). On-site treatment of hospital wastewater is in use in several countries, including China, Japan, Germany, The Netherlands, Switzerland, Denmark, Brazil, India, Ethiopia, and Greece (Majumder et al., 2021; Casas et al., 2015; Verlicchi et al., 2015; Rodriguez-Mozaz et al., 2018).

Effluents from PPCPs manufacturers and landfills are classified and treated as industrial waste in most countries, but regulation of hospital waste varies widely across the world (Carraro et al., 2018; Al Aukidy et al., 2018; Verlicchi et al., 2015; Rodriguez-Mozaz et al., 2018). The European Directive n. 91 of 21 May 1991 on urban wastewater treatment aims to protect the environment from the adverse effects of wastewater discharges (European Union, 1991). Later European Union directives—European Directive n. 98 of 19 November 2008 (2008/98/CEE) (European Union, 2008a) and the European Decision n. 532 of 3 May 2000 (2000/532/CEE) (European Union, 3, 2000) —require that some hospital liquid waste (including PPCPs) must be treated as a waste product, and collected and disposed of as such. There are however no specific guidelines for hospital wastewater, leaving member states of the European Union to determine their own management of hospital wastewater (Carraro et al., 2018). In European countries where hospital wastewater is not classified as domestic wastewater, pretreatment is required before discharge into the municipal wastewater stream (Carraro et al., 2018). In addition to national wastewater regulations, the classification of hospital wastewater as domestic wastewater in Europe, at times, depend on hospital size and local regulations (Carraro et al., 2018). Apart from the selected European countries, China and Vietnam also have specific regulations for hospital wastewater (Al Aukidy et al., 2018; Yu et al., 2013).

In the United States, discharges into municipal wastewater stream by healthcare facilities (indirect dischargers) are subject to regulations by local sewer authorities, as required by the Clean Water Act (CWA) (Carraro et al., 2018). Hospitals that discharge directly into natural waters (direct dischargers) are regulated by the EPA through national discharge standards (Effluent Guidelines). It should be noted that PPCPs are not included in the pollutants limited in hospital wastes. Hospitals often must install a separate WWTP to meet the direct discharge limitations. Similarly, constituents in discharges from PPCPs manufacturing facilities are regulated under the CWA. Direct monitoring of PPCPs in waste streams of hospitals and PPCP manufacturers is not required, but chemical oxygen demand (COD) and nitrogen are good surrogates since the removal of PPCPs in wastewater is mainly via co-metabolism (LaPara et al., 2001; Casas et al., 2015; Yu et al., 2013). More so, specific PPCPs are being considered for legislation in different countries (Rodriguez-Mozaz et al., 2018). For instance, diclofenac, erythromycin, clarithromycin, and azithromycin have been added to the “watch list” of priority substances under the European Union’s Water Framework Directive (European Union, 2008b). Similarly, the US EPA added a number of PPCPs, including erythromycin, to the Drinking Water Contaminant Candidate List (USEPA, 2016).

Methods commonly used to treat hospital wastewater include AS, MBR, constructed wetlands, moving bed bioreactor (MBBR), chlorination, advanced oxidation, filtration, and adsorption methods (including with engineered nanomaterials) (Khan et al., 2020; Verlicchi et al., 2015; Rodriguez-Mozaz et al., 2018; Adeleye et al., 2016; de Franco et al., 2018; Song et al., 2017). As discussed earlier, biological treatment does not provide a sufficient elimination of persistent PPCPs, and additional advanced steps are needed (Rodriguez-Mozaz et al., 2018). Although physical treatment methods such as activated carbon adsorption, microfiltration, reverse osmosis, and nanofiltration may effectively remove PPCPs, the waste generated (including spent adsorbent with the removed PPCPs, concentrate) may end up in landfills, from where they may reenter WWTPs or the environment. Therefore, chemical treatments that lead to complete degradation of PPCPs are more suitable for hospital wastewater and other waste streams with high concentrations of PPCPs.

7. Conclusions, perspectives, and recommendations

WWTPs typically do not target removal of constituents of emerging concern such as PPCPs. However, the mass of several PPCPs may decrease during normal wastewater treatment, due to the physicochemical properties of the PPCPs and the WWTPs’ treatment conditions, such as SRT and HRT, or because advanced treatments have been implemented. In conventional treatment, the highest removal of PPCPs occurs during secondary treatment due to microbial degradation and adsorption to biomass (although chemically enhanced primary treatment may enhance the removal of PPCPs with high affinity for solids). The average removal efficiency for most PPCPs is similar for AS, TF and MBR, except for a few pharmaceuticals such as naproxen and atenolol (where TF removal efficiency is much lower) and erythromycin (where the removal efficiency of AS is lower). In general, MBR is more efficient than AS and TF units for removal of commonly used antibiotics. If the concentration of some PPCPs in wastewater effluents are regulated in the future, the removal efficiency of secondary treatment technologies for different compounds may play a role in the technology adopted when building new WWTPs or retrofitting existing plants.

In developing countries, relatively high concentrations of analgesics, antibiotics, and stimulants are detected in surface waters. This agrees with the occurrence of these PPCPs at high concentrations in WWTPs in several developing countries. The highest concentrations of psychoactives and anticholesteremics in surface waters were, however, reported in developed countries, probably due to lower consumption in developing economies. High occurrence of PPCPs in the natural aquatic system of cities in developing countries is due to lack of proper sanitation facilities, inefficient sewage treatment, effluent discharges from pharmaceutical factories, and weaker environmental protection laws. Developing countries often lack access to efficient WWTPs or when in use, are not able to implement tertiary treatments.

Despite the high removal of several PPCPs by WWTPs in developed

countries, and additional removal using tertiary treatments, a substantial amount of PPCPs still enter receiving waters due large effluent volume. Overall, the global concentrations of PPCPs currently detected in WWTP effluents and natural waters are below the mortality threshold of commonly used PPCPs. However, the observed concentrations of a few PPCPs are in the range that sub-lethal effects are observed (Gutiérrez-Noya et al., 2021). In addition, studies on occurrence and risks of PPCPs need to consider the metabolites and transformation products of PPCPs, and not just the parent compounds. More so, more PPCPs would be discharged into the environment as human population and accessibility to healthcare continue to grow.

There are numerous studies on PPCPs' occurrence in wastewater; but for the most part, WWTPs can still be regarded as "black boxes" with respect to PPCPs fate. The role of key wastewater treatment biochemical processes (such as nitrification) in the removal of PPCPs has only been identified for a couple of PPCPs. Also, the kinetics and mechanisms of PPCPs transformations, the intermediates formed, the microorganisms or enzymes involved in transformation, and the interactions among PPCPs and their metabolites are mostly unknown and need to be systematically investigated. A comprehensive understanding of these processes is important and valuable for future efforts to improve WWTPs' removal efficiency of PPCPs. The widespread differences in the configurations and operation conditions of WWTPs further complicate mechanistic study of PPCPs' fate in real world scenarios. Thus, researchers may have to rely on pilot-scale studies performed with simulated or real wastewater under controlled conditions to enhance our understanding of the fate and transformations of PPCPs in WWTPs.

In this review, we observed inadequacies in terms of data availability and in terms of data quality. For instance, while there was abundance of studies performed in developing countries in North America and Europe, wastewaters and natural waters in Africa and South America are highly under-monitored for PPCPs. The geographical lopsidedness of surveys makes it more difficult to fairly compare occurrence of PPCPs in the environmental on a global scale and future efforts should focus on these understudied locations. Data quality inadequacies (e.g., related to analytical approach, sampling mode, and QA/QC reporting) also abound in a lot of existing PPCP survey studies that should be addressed by future works, to advance our knowledge of the abundance and fate of PPCPs in the environment:

Analysis approach: The benefits of using non-target and suspect screening methods for comprehensive monitoring of environmental pollutants, including PPCPs, has been demonstrated (K'oreje et al., 2012; Eggen et al., 2010; Singer et al., 2016; Vergeynst et al., 2015; Chitescu et al., 2015). However, at least 95% of the studies that analyzed PPCPs in wastewater (before and after treatment) and in natural waters employed the targeted analysis approach. Based on the studies reviewed, selection of compounds in targeted studies was influenced by PPCPs prescription rate, sales and consumption databases, frequency of detection by previous studies, existing analytical methods (such as EPA Method 1694), compound risk quotients, and priority lists of government agencies. Selection of compounds and sampling mode were also been dependent on availability of high resolution instruments in developing countries, as well as availability of analytical methods and reference standards (Rimayi et al., 2019b). Overall, targeted approaches allow for low detection limits and reliable quantification but could also underestimate the PPCP loads in wastewater and natural waters. There is need for future studies to employ suspect and non-target approaches and integrative monitoring in order to more accurately identify and quantify PPCPs in engineered and natural environments (Murrell and Dorman, 2020; Pinasseau et al., 2019; Gago-Ferrero et al., 2018; Branchet et al., 2021).

Sampling mode: We observed a stark difference in sample collection mode between studies focused on wastewater and those that investigated PPCPs in natural waters. While most of the studies analyzing PPCPs in wastewater employed 24-hour composite sampling (Tables S2 and S3), grab sampling was more common for samples collected from the natural environment (Table S4). Although composite sampling is widely regarded as being more thorough than grab sampling, flow variations should determine the sampling mode/frequency (Ort et al., 2010). As noted by a previous review of 87 peer-reviewed articles that sampled for PPCPs (Ort et al., 2010), sampling errors or inadequacies arising from sampling mode can lead to overinterpretation of data and wrong conclusions. Researchers are referred to the step-by-step Sampling Guide proposed by Ort et al. (2010) as a tool for sampling mode planning for future studies. In general, more guidelines are needed for proper monitoring of PPCPs in natural waters, where there are challenges due to dilution effects, hydrodynamics, and logistics (Branchet et al., 2021).

QA/QC reporting: As also noted by previous studies, the bulk of peer-reviewed articles do not report sufficient information to judge the quality of measured data (Ort et al., 2010; Miège et al., 2009). For instance, less than 60% of the studies that analyzed PPCPs in wastewater and natural waters (reviewed in this work) reported QA/QC parameters such as percent recovery, limit of detection (LOD), and limit of quantification (LOQ). Furthermore, only a handful of papers reported determination of method detection or reporting limit (MDL or MRL), or used QA/QC samples such as matrix spike, method blank, field duplicate, etc. Not only is it important for proper QA/QC procedures to be followed in ensuring the integrity of the data obtained and reported, but the procedures should be clearly documented during manuscript/report preparation.

Lastly, thorough characterization of the wastewater or natural matrix being analyzed could offer additional insights into removal mechanisms and make it easier to compare across studies. For instance, reporting biomass concentration (e.g., mixed liquor suspended solids [MLSS]) makes it easier to draw any correlations between biomass concentration in wastewater and the removal of recalcitrant PPCPs, which may be preferably removed via adsorption to biomass.

CRediT authorship contribution statement

Adeyemi S. Adeleye: Conceptualization; Methodology; Supervision; Writing – original draft; Writing – review & editing. **Jie Xue**: Data curation; Investigation; Validation. **Yixin Zhao**: Formal analysis; Investigation; Visualization; Roles/Writing - original draft; Writing - review & editing. **Alicia A. Taylor**: Methodology; Supervision; Validation; Roles/Writing - original draft; Writing - review & editing. **Jenny E. Zenobio**: Formal analysis; Methodology. **Yian Sun**: Formal analysis; Investigation; Visualization; Roles/Writing - original draft; Writing - review & editing. **Ziwei Han**: Formal analysis; Methodology. **Omobayo A. Salawu**: Formal analysis; Investigation; Visualization; Roles/Writing - original draft; Writing - review & editing. **Yurong Zhu**: Data curation; Investigation; Validation.

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.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jhazmat.2021.127284.

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